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Autoimmune extraintestinal manifestations of *Helicobacter pylori* infection: A bundle of conflicts

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Abstract

It has been well-known that several microorganisms that have an effect on particular areas of the body might additionally have systemic sequelae. In the last ten years, various studies have been performed on the relationship between *Helicobacter pylori* infection and a variety of extra digestive illnesses including immunological, hematological, neurological disorders and different pathologies. It has been recommended that complicated interactions between bacterial and host genetic factors, as well as environmental factors, play considerable roles in determining different clinical outcomes. Although, there are conflicting and controversy data in some diseases, in the light of literature, it is currently accepted; that the presence or absence of *H. pylori* infection might influence the chance of developing of many autoimmune diseases. Treatment of *H. pylori* infection has been reported to be effective in some diseases like Schoenlein-Henoch purpura, ITP, psoriasis and chronic autoimmune urticaria. This review focuses the possible role of *H. pylori* infections in various autoimmune diseases taking into account the recent literature.

Key words: *Helicobacter pylori*, extraintestinal manifestations, autoimmune diseases

Introduction

H*elicobacter pylori* chronically infects more than half of the world's population and, one of the most frequent causes of gastrointestinal infections and it is estimated that the pathogen has co-evolved with its human host for at least 30.000 years (1-5). *H. pylori* infection fulfills each of Koch's postulates as an infectious agent inflicting chronic active gastritis and ulcer. It is related with a wide spectrum of gastrointestinal diseases, as well as gastroduodenal ulcers, mucosaassociated lymphatic tissue lymphoma (MALToma), and gastric adenocarcinoma.

It is well-known that several microorganisms have an effect on particular region of the body might additionally have systemic sequelae like Campylobacter species *Streptococcus pneumonia* infections.

In the last decade, various studies have been performed on the relationship between *H. pylori* infection and a variety of extra digestive illnesses, including immunological, hematological, neurological disorders and different pathologies (Table 1). More recently, numerous publications have supported a role for *H. pylori* infection in causing a variety of extraintestinal manifestations like allergic, chronic inflammatory and autoimmune diseases. It has been recommended that complicated interactions between bacterial and host genetic factors, as well as environmental factors, play considerable roles in determining different clinical outcomes among different subjects (1).

This review focuses the possible role of *H. pylori* infections in different autoimmune diseases by a systemic approach.

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Helicobacter pylori, infections and possible pathophysiological mechanisms

The agent is a Gram-negative spiral shaped bacterium that has the unique ability to colonize the human gastric mucosa in spite of acid pH of the stomach. Virulence factors like urease enzyme and flagella are present in all infectious strains and are required for colonization of the gastric mucosa. The other major virulence factors associated with pathogenicity are: cytotoxin-associated gene A (CagA) and Vacuolating cytotoxin A (VacA) toxins (1). The *cagA* and *s1/m1 vacA* alleles have associated with a higher degree of gastric mucosal inflammation (6).

H. pylori infection is one of the most common bacterial infections worldwide and its prevalence has been estimated to extend from 40 to 80% and it changes widely by geographic region, age, race, ethnicity, and socioeconomic factors (1-3). Gastroduodenal ulceration and carcinogenesis are exclusive results of this infection.

Diversity in the clinic result of *H. pylori*-induced pathologies are multifactorial, involving a complex interplay between host immune responses and the pathogen virulence factors (1).

Several mechanisms have been suggested in an effort to clarify the extraintestinal manifestations of *H. pylori* infections. One of them is; gastric vascular permeability increases during atrophic gastritis due to infection and might cause increased exposure to alimentary antigens.

In addition, the gastric infection causes releasing of inflammatory mediators and molecular mimicry to systemic circulation. For example, antigastric autoantibodies have been found in more frequently in patients infected with *H. pylori* (7).

After the gastric colonization by *H. pylori*, production of large amounts of various proinflammatory substances, like interleukins, eicosanoids, and several proteins of the acute phase occur (8). This inflammatory response may cause the development of Ag-Ab complexes or cross-reactive antibodies due to molecular mimicry and may result in damage to other organs.

Also, it has been suggested that *H. pylori* induces a remarkable development similar to that seen in the molecular mimicry between *Streptococcus pyogenes* antigens and host proteins, resulting in both humoral and cell mediated immunologic reactions and eventually causing rheumatic fever, arthritis and rheumatic heart disease (7).

Table 1. Extraintestinal manifestations with a proven or suspected pathophysiological role in *H. pylori* infection.

Affected system	Clinical manifestations
Cardiovascular system	Stroke, atherosclerotic heart disease, hypertension, Primary Raynaud phenomena
Central Nervous system	Alzheimer's disease, Parkinson's disease, migraine
Immune system	Rheumatoid arthritis, Immune thrombocytopenic purpura, Raynaud's phenomenon, Sjogren's syndrome, diabetes mellitus
Endocrine system	Autoimmune thyropathies, obesity
Respiratory system	Bronchial asthma, Lung cancer
Hematologic system	Iron deficiency anemia, Cobalamin deficiency
Hepato-biliary diseases	Hepatocellular carcinoma, Cholangiocellular carcinoma, Gallstone formation
Skin	Chronic urticaria, Schoenlein-Henoch purpura, Atopic dermatitis, angioedema, rosacea, psoriasis, alopecia areata, Sjögren Syndrome
Others	Extragastric MALT-lymphoma, Growth retardation, preeclampsia, hyperemesis gravidarum, glaucoma, oral ulcers, urethritis, inflammatory bowel diseases, glaucoma.

H. pylori infections bring out a remarkable immunomodulation, which are activated by chronic inflammation (9). Chronic infection results in a mainly Th1 response, resulting in the production of IL-2 and IFN-gamma as well as other inflammatory cytokines like TNF-α, IL-6, IL-10, and IL-8. (10). This chronic infection due to *H. pylori* can also cause anarchic growth and proliferation of CD5+ B lymphocytes that produce poly- and auto-reactive IgM and IgG3 antibodies (11). Several studies have reported that Toll-like receptors (TLR) and Treg cells play roles in the immune pathogenesis of *H. pylori* infection and it is suggested in an experimental study there might be an interplay between TLR signaling and Treg cells which is significant for restricting *H. pylori* colonization and suppressing the inflammatory response (12).

H. pylori have an ability of immunomodulatory effect. The immunomodulatory features of the bacterium reprogram the immune system towards immunological

tolerance and help the bacteria in setting up a persistent infection (13). As a result, the products of the local immune responses could migrate to extra-gastric region and this might clarify the association between *H. pylori* infection and the diversity of extra gastric diseases, as well as autoimmune disorders (14).

In contrast, some epidemiological data suggests a protective effect of *H. pylori* infection against the development of various sicknesses with an autoimmune component. The proposed mechanism for this effect may define as *H. pylori*'s ability to induce immune tolerance and restrict inflammatory processes (15).

In view of these data, researchers have investigated the role of *H. pylori* as a pathogenic determinant for idiopathic extraintestinal diseases, in case of immune dysregulation.

This paper reviews current literature on the role of *H. pylori* infection within the pathological process of extraintestinal diseases taking into account the recent literature.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disorder that causes irreversible joint deformities and functional impairment. As with many other connective tissue disorders, the etiopathology of RA is not clearly understood. A report from Turkey, Yula E. et al. (2016) researched active *H. pylori* infection rate and CagA virulence marker positivity in patients with various autoimmune diseases, including RA and SLE, and they suggested that in a similar manner to the some literature their first results recommended that active *H. pylori* infection rates are higher in patients with autoimmune diseases when compared with their routine laboratory data (16). Similarly, in a recent study, El-Hewala ASI, et al. (2015) was to assess the effect of *H. pylori* treatment on disease activity in patients with rheumatoid arthritis and the authors suggested that *H. pylori* treatment may induce a significant improvement of the disease activity over two months (17). On the other hand, a study of 1815 Japanese RA patients, 49.3% were reported to have *H. pylori* antibodies, which was lower compared with the healthy Japanese subjects (18).

There are few data in the literature on this topic and the possible effect of *H. pylori* infection in the pathogenesis of RA remains controversial.

Parkinson's disease

Parkinson's disease is a chronic, progressive and degenerative disorder of the central nervous system and in most people is idiopathic. Recently, some studies have advised that chronic *H. pylori* infection may worsen the neurodegenerative process in Parkinson's disease. Tan et al. (2015) reported in a large cross-sectional study showed a link between *H. pylori* and worse Parkinson's disease motor severity (19). In addition, it has been suggested that eradication of *H. pylori* infection improves levodopa action, clinical symptoms and quality of life in patients with Parkinson's disease (20). Interestingly, Blaecher C, et al. (2013) declared that frequency of *Helicobacter suis* is significantly higher in patients with idiopathic parkinsonism than healthy subjects (21).

An another exciting assumption is that in case of *H. pylori* infection is not controlled by the immune system or not eradicated, *H. pylori* may causes the development of Parkinson's disease by damaging dopaminergic cells in central nervous system. (22).

Multiple sclerosis

Multiple sclerosis (MS) is a multifactorial, complex, chronic inflammatory and neurodegenerative disease of the central nervous system. Gavalas E. et al (2015), reported that *H. pylori* infection appears to be more frequent in MS patients (23). A recent report indicated the presence of immunomodulating features of "Sydney Strain-1 antigen" administration in an experimental model of MS, recommending the possible role of *H. pylori* infection in the mechanism of the disease (24). Long Y, et al. showed *H. pylori* seropositivity in patients with MS, though it did not differ considerably when compared with controls (25). In contrast, a recent meta-analysis reported that *H. pylori* infection and MS are negatively correlated, particularly in Western countries (26). These conflicting findings among the aforementioned reports may be due to ethnicity, and methodological dissimilarity.

Cardiovascular Disease

Cardiovascular disease, including coronary artery disease, peripheral artery disease and stroke are the leading causes of mortality and morbidity globally. The possible effect of *H. pylori* infection in the pathogenesis of cardiovascular disorders remains controversial. Many

epidemiological researches have been performed to detect association between ischemic heart disease, lipid abnormalities and the pathogen (27). Recently, it has been reported that *H. pylori* may be present at the level of the carotid plaques. Because of the some strains elicit a strong local inflammatory response, particularly *cagA* gene positive strains; the presence of the bacteria may contribute to plaque instability and to the development of ischemic stroke (28). Despite of these studies, whether the association is still unclear. A study from Japanese population examined possible relationships between *H. pylori* infection and risk of death from coronary heart disease and stroke in a large prospective cohort study (29). They suggested that there is no link between *H. pylori* infection and coronary heart disease and stroke mortality risk. In contrast, Sagar V. et al. (2016) researched the prevalence and association of *H. pylori* infection in patients of ischemic cerebrovascular stroke and they suggested there is link between *H. pylori* infection and acute cerebral ischemia (28). But they found no considerably association between *H. pylori* seropositivity and carotid plaque instability. In a recent work from Korea, the authors investigated the relationship of current *H. pylori* infection with lipid profile and cardiovascular disease and its eradication effect (30). In a similar manner to the literature, they have declared that the current infection with the pathogen had a positive association with high LDL, low HDL, and cardiovascular disease. They also reported that successful *H. pylori* eradication decreased the risk of high LDL and low HDL. However, eradication of the bacteria did not reduce the risk of cardiovascular disease.

Skin diseases

Autoimmune based dermatological pathologies are characterized by dysregulation of the immune system that causes loss of self-tolerance to dermal antigens. Many studies have been reported an association between idiopathic chronic urticaria, acne rosacea, alopecia areata and *H. pylori* infection (31-33). Treatment of *H. pylori* infection has been reported to be effective in some patients with psoriasis, Schoenlein-Henoch purpura chronic autoimmune urticaria and alopecia areata (11). Some studies declared higher prevalence of *H. pylori* infection in patients with systemic sclerosis, than in healthy individuals (34). Despite that, there is conflicting data about the association of *H. pylori* infection with scleroderma, Behçet's disease and autoimmune bullous diseases.

One of the most researched skin diseases is immune thrombocytopenic purpura (ITP). Several reports have recommended a pathological link between ITP and *H. pylori* infection. Clinical experiences have described a spontaneous resolution of ITP symptoms in approximately half of chronic ITP patients taking after treatment against *H. pylori* infection (35). Also, a randomized controlled trial suggested that, *H. pylori* eradication plays significant role in the management of *H. pylori* infected chronic ITP children and adolescents (36).

It is well known that the prevalence of eczema is increasing, particularly in developed countries where the *H. pylori* seroprevelance is relatively low. The reported risk factors linked with increased prevalence of eczema include higher level of family education, higher socioeconomic status, smaller family size and urban environment. Opposite of these conditions is known as risk factors for higher prevalence of *H. pylori* positivity. Similarly, in a recent work, Ali AM et al., reported that *H. pylori* infection is associated with childhood eczema in genetically predisposed atopic children and likewise a considerable inverse correlation between atopic dermatitis and positive *H. pylori* serology (37). In addition, a meta-analysis provides evidence that *H. pylori* infection is inversely associated with atopy (38).

Recent studies proposed a potential relationship between rosacea, psoriasis and *H. pylori*. Information from the literature involving the H. *pylori* infection in psoriasis are not clear; on the other hand, a recent study has recommended that *H. pylori* seems able to affect the clinical severity of psoriasis (39). However, several researches reported that the prevalence of *H. pylori* infection was considerably higher in patients with rosacea (40).

Migraine

Migraine is a common, multifactorial, disabling, an episodic, hereditary neurovascular headache disorder (41). The well-known vascular theory of migraine is that migraine headache is caused by the dilatation of blood vessels, while the aura of migraine resulted from vasoconstriction. It has been reported that C-reactive

protein, which can increase blood-brain barrier permeability, and some pro-inflammatory cytokine levels rise in migraineurs (42, 43), and likewise it has been suggested that single nucleotide polymorphisms in TNF-α and IL-1 are associated with migraine may relevant to the etiology of the disease (44). Due to the high levels of IL-17, the cytokine most strongly associated with autoimmune disorders, it has been suspected that migraine may also be associated with autoimmune disorders (45).

Several studies presented a positive correlation between *H. pylori* infection and migraine headache. It has been proposed that the pathogenic role of the bacterium in migraine, in light of a relationship between the host immune response against the *H. pylori* and the chronic release of vasoactive substances. The proposed factors of the relationship between migraine and *H. pylori* infection included inflammation, nitric oxide imbalance, oxidative stress, or virulence of *cagA*-positive strains (46, 47). Similarly, in a recent study, it is reported that mean of *H. pylori* IgM antibody in migrainous patients showed a significant difference with a healthy control group (48). Nowadays, Mann, NS. et al. reported a meta-analysis about the possible relationship between *H. pylori* and migraine (49). They reported that 1084 cases of migraine associated with *H. pylori* and in some studies elimination of the bacteria resulted in amelioration of migraine symptoms.

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disease which several causes have been suggested like relationship with known pathogens. Most of the infectious hypotheses are proposed by the alteration of the blood-brain barrier and the stimulation of neuroinflammation in the central nervous system that may play a role, particularly in the decrease of amyloid peptide clearance (50,51). Some bacterial or viral pathogens have been incriminated, including *Chlamydia pneumonia*, *H. pylori* and Herpes simplex virus-1 (52).

Although, the direct laboratory evidence is lacking, *H. pylori* infection has been reported to be related to a high risk of Alzheimer's disease. In a recent study, researchers investigated the effect of *H. pylori* infection on tau phosphorylation due to abnormal hyperphosphorylation of microtubule-associated protein tau is involved in the pathogenesis of Alzheimer's disease (53). The authors, Xiu-Lian W. et al. reported evidence supporting the role of *H. pylori* infection in Alzheimer's disease-like tau pathology and they suggested that *H. pylori* eradication may be useful in the prevention of tauopathy.

Vitamin and mineral deficiency

It is reported that *H. pylori* infection was associated with an enhanced rate of iron deficiency anemia, cobalamin (vitamin B12), folic acid, alpha-tocopherol, beta-carotene and vitamin C deficiency (54). One of the suspected mechanisms for these deficiencies is that *H. pylori*-induced gastritis leads to a functional inhibition of the parietal cells and causes hypochlorhydria. Thus, higher gastric pH causes iron malabsorption and also have a major role in the development of vitamin deficiencies like folate, vitamin B12 and vitamin A.

Diabetes mellitus

It is suggested that *H. pylori* infection may associated with insulin resistance, diabetes mellitus and metabolic syndrome. However, the relationship between *H. pylori* infection and type 2 diabetes mellitus is controversial, as some studies revealed a higher prevalence of infection in diabetic patients while others reported there is no significant difference (55-57). Some studies from Asia have reported on an relationship between *H. pylori* infection with insulin resistance in normal-weight individuals. Recently, Nasif WA. et al. (2016), reported that infection with *H. pylori* in type 2 diabetes mellitus was higher when compared to non-diabetic population and seems no link with glycemic control (58); Likewise, they proposed that diabetes seems to be associated with increased oxidative stress in *H. pylori* infection and they reported that significantly raised serum Oxidized low-density lipoprotein (Ox-LDL) levels in diabetes patients with positive *H. pylori* infection, proposing hypothesis that high serum level of Ox-LDL levels in diabetes patients with positive *H. pylori* infection considered as a risk factor for atherosclerotic vascular disease. One recent study has shown obese patients do not provide evidence for an enhanced insulin resistance state associated with gastric *H. pylori* infection, but they suggested that the presence of the bacterium in gastric biopsies is associated with an adverse lipid profile (59). In addition, it was suggested that eradication rate of *H.*

pylori is significantly lower in patients with obese non-diabetic than healthy subjects (60).

Oral pathologies and Sjögren Syndrome

Several studies indicated that *H. pylori* can be isolated from the oral cavity, salivary secretions and dental plaque. The presence of the pathogen in some oral lesions like burning, halitosis and lingual dorsum hyperplasia has been reported with high frequency (61). Alireza Monsef Esfahani et al. (2015) reported that *H. pylori* infection plays important role in the pathogenesis of Sjögren Syndrome a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands (62).

Recurrent aphthous stomatitis is one of the common oral mucosal diseases with unknown etiology. Gülseren D. et al. (2016) researched possible link between recurrent aphthous stomatitis, and periodontal disease and *H. pylori* infection in a cross-sectional study and they suggested that *H. pylori* might have played an etiological role in recurrent aphthous stomatitis and might have caused periodontal disease and eradicating *H. pylori* may be useful to prevent the disease (63).

Obesity

In developed countries, the prevalence of overweight and obese individuals has substantially increased, but the prevalence of *H. pylori* has decreased. It has been speculated that decreasing prevalence of *H. pylori* might represent a risk or contributing factor to the endemic of obesity in western countries. But, the relationship between gastric *H. pylori* infection and body mass index (BMI) is controversial. While several cross-sectional studies have reported a link between *H. pylori* infection with BMI, others did not find an association (64). Arslan E, et al. has shown an increased prevalence of gastric *H. pylori* infection in obese individuals when compared to normal-weight counterparts (65). Interestingly, Lender N. et al., reported that the prevalence of gastric *H. pylori* colonization in various countries is inversely related to the prevalence of obesity (64).

Bronchial asthma and chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is considered the fourth leading cause of death worldwide. Controversial results of *H. pylori* seroprevalence have been achieved in patients with bronchial asthma, sarcoidosis, pulmonary tuberculosis, cystic fibrosis, chronic bronchitis and lung cancer (66). For example, a recent systematic review has reported that there is a relationship between *H. pylori* infection and extra-gastric diseases like bronchiectasis, asthma, COPD, lung cancer, and lung tuberculosis (67). It is well known that *H. pylori* prevalence in developed countries has been declining simultaneously with increases in childhood asthma and other allergic diseases. Thus, several studies have linked these phenomena. Lim JH et al. (2016) have declared an inverse association between *H. pylori* infection and asthma among young adult, and they proposed that the underlying immune mechanism induced by *H. pylori* infection may affect allergic reactions associated with asthma in young adults due to its low prevalence (15). Also, they supposed that, *H. pylori* infection may inhibit development of asthma in some way in young adults due to effects on the immune system. On the other hand, den Hollander WJ et al. reported that colonization of a European child with a CagA negative strains at age 6 was associated with an increased prevalence of asthma, but they declared no link for non-European children (68). We think that the underlying mechanisms for the relationship between asthma and *H. pylori* infection requires further research like the other diseases.

Inflammatory bowel diseases (Crohn's disease, ulcerative colitis)

Interestingly, some epidemiological data suggest a protecting effect of *H. pylori* infection against the development of autoimmune diseases and, additionally, there are laboratory data illustrating *H. pylori*'s ability to induce immune tolerance and limit inflammatory responses (69). Inflammatory bowel disease is an important growing health problem, globally. In last decades, a lot of developing countries have experienced a spectacular climb in the incidence of the disease. Recently, a meta-analysis indicated a significant negative link between *H. pylori* infection and inflammatory bowel diseases that supports a possible protective profit of *H. pylori* infection against the development of the disease (69). The researchers also reported that further prospective studies determining the role of *H. pylori* and its eradication in the evolvement of inflammatory bowel

diseases are required by taking into account the role of confounders like environmental factors.

Conclusion

The distinctive ability of *H. pylori* to inveterately infect the gastric tissue to activate inflammation and host immunological response recommends its role in various autoimmune diseases. Although there are conflicting and controversy data in some diseases, in the light of mentioned reports, it is currently accepted; that the presence or absence of *H. pylori* infection might influence the chance of developing of many autoimmune diseases. Despite extensive medical advancement many questions still remain unanswered and, further studies analyzing the supposed causality of the observed relationship between *H. pylori* infection and extra-intestinal diseases are clearly in need. We think that, if such causality is confirmed, this could have a great effect on clinical practice as it will probably goes to the recommendation of *H. pylori* screening and eradication in various diseases as a clinical standard therapy.

Although, lots amount of studies are required to address the role of *H. pylori* in pathogenesis of various autoimmune diseases, some reports give a hope that eradication of the bacteria could be a cure or to reduce the severity of some diseases.

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References

1. Yula E, Nagiyev T, Kaya OA, Inci M, Celik MM, Köksal F. Detection of primary clarithromycin resistance of *Helicobacter pylori* and association between cagA (+) status and clinical outcome. *Folia Microbiol* 2013; 58: 141-146.
2. Nagiyev T, Yula E, Abayli B, Koksal F. Prevalence and genotypes of *Helicobacter pylori* in gastric biopsy specimens from patients with gastroduodenal pathologies in the Cukurova Region of Turkey. *J Clin Microbiol* 2009; 47: 4150-4153.
3. Nagiyev T, Köksal F, Abaylı B, Yula E. [Comparison of culture and GlmM-PCR Methods for detecting *Helicobacter pylori* in antral and corpus biopsy specimens in patients with gastroduodenal disorders]. *Turkiye Klinikleri J Med Sci* 2010; 30: 919-924.
4. Yula E, Nağiyev T, Köksal F, [Comparation of two different primer sets used for detection *Helicobacter pylori* DNA by polymerase chain reaction assay in gastric tissues], *Turkiye Klinikleri J Med Sci* 2010; 30: 1166-1170.
5. Moodley Y, Linz B, Yamaoka Y, Windsor HM, Breurec S, Wu JY, Maady A, et al. The peopling of the Pacific from a bacterial perspective. *Science* 2009, 323: 527-530.
6. Miernyk K, Morris J, Bruden D, McMahon B, Hurlburt D, Sacco F, et al. Characterization of *Helicobacter pylori* cagA and vacA genotypes among Alaskans and their correlation with clinical disease. *J Clin Microbiol* 2011; 49: 3114-3121.
7. Hernando-Harder AC, Booken N, Goerdt S, Singer MV, Harder H. *Helicobacter pylori* infection and dermatology diseases. *Eur J Dermatol* 2009; 19: 431-444.
8. Negrini R, Savio A, Poiesi C, Appelmelk BJ, Buffoli F, Paterlini A, et al. Antigenic mimicry between *Helicobacter pylori* and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology* 1996; 111: 655-665.
9. Fae KC, Diefenbach da Silva D, Bilate AM, Tanaka AC, Pomerantzeff PMA, Kiss MH, et al. PDIA3, HSPA5 and vimentin, proteins identified by 2-DE in the valvular tissue, are the target antigens of peripheral and heart infiltrating T cells from chronic rheumatic heart disease patients. *J Autoimmun* 2008; 31: 136-141.
10. Kim SY, Lee YC, Kim HK, Blaser MJ. *Helicobacter pylori* CagA transfection of gastric epithelial cells induces interleukin-8. *Cell Microbiol* 2006; 8: 97-106.
11. Eli Magen, Jorge-Shmuel Delgado. *Helicobacter pylori* and skin autoimmune diseases. *World J Gastroenterol* 2014; 20: 1510-1516.
12. Gong Y, Tao L, Jing L, Liu D, Hu S, Liu W, et al. (2016) Association of TLR4 and Treg in *Helicobacter pylori* colonization and inflammation in mice. *PLoS ONE* 11(2): e0149629.
13. Müller A, Oertli M, Arnold IC. *H. pylori* exploits and manipulates innate and adaptive immune cell signaling pathways to establish persistent infection. *Cell Communication and Signaling* 2011; 9: 25.
14. Ram M, Barzilai O, Shapira Y, et al. *Helicobacter pylori* serology in autoimmune diseases-fact or fiction? *Clin Chem Lab Med* 2013; 51: 1075–1082.
15. Lim JH, Kim N, Lim SH, Kwon JW, Shin CM, Chang YS, Kim JS, Jung HC, Cho SH. Inverse Relationship Between *Helicobacter pylori* Infection and Asthma Among Adults Younger than 40 Years: A Cross-Sectional Study. *Medicine (Baltimore)*. 2016; 95(8): e2609.
16. Yula E, Tok YT, Kalkan T, Gökmen AA, Balık R, Baran N, Sener AG et al. Comparison of active *Helicobacter pylori* infection rate and CagA virulence marker positivity in patients with various autoimmune diseases; first results. *Turk J Immunol* 2016; 4 (Suppl 1): 70.
17. El-Hewala ASI, Khamis SS, Soliman SG, Alsharaki DR, Abd El-Raof Salman MM. Study of the effect of treatment of *Helicobacter pylori* on rheumatoid arthritis activity. *Menoufia Med J* 2015; 28: 319-324.
18. Tanaka E, Singh G, Saito A, Syouji A, Yamada T, Urano W, et al. Prevalence of *Helicobacter pylori* infection and risk of upper gastrointestinal ulcer in patients with rheumatoid arthritis in Japan. *Mod Rheumatol* 2005;15: 340-345.
19. Tan AH, Mahadeva S, Marras C, Thalha AM, Kiew CK,

Yeat CM, et al. *Helicobacter pylori* infection is associated with worse severity of Parkinson's disease. *Parkinsonism related disorders* 2015; 21: 221-225.

20. Hashim H, Azmin S, Razlan H, Yahya NW, Tan HJ, Manaf MR, et al. Eradication of *Helicobacter pylori* infection improves levodopa action, clinical symptoms and quality of life in patients with Parkinson's disease. *PLoS One* 2014; 9: e112330.

21. Blaecher C, Smet A, Flahou B, Pasmans F, Ducatelle R, Taylor D, et al. Significantly higher frequency of *Helicobacter suis* in patients with idiopathic parkinsonism than in control patients. *Aliment Pharmacol Ther* 2013; 38: 1347-1353.

22. Dobbs RJ, Dobbs SM, Weller C, Charlett A, Bjarnason IT, Curry A, et al. Helicobacter hypothesis for idiopathic parkinsonism: before and beyond. *Helicobacter* 2008; 13: 309-322.

23. Gavalas E, Kountouras J, Boziki M, Zavos C, Polyzos SA, Vlachaki E, et al. Relationship between *Helicobacter pylori* infection and multiple sclerosis. *Ann Gastroenterol* 2015; 28: 353-356.

24. Boziki M, Grigoriadis N, Deretzi G, Lagoudaki R, Lourbopoulos A, Panayotopoulou E et al. *Helicobacter pylori* immunomodulative properties in a mouse model of multiple sclerosis. *Immunogastroenterology*. 2012; 1: 34-39.

25. Long Y, Gao C, Qiu W, Hu X, Shu Y, Peng F, Lu Z. *Helicobacter pylori* infection in neuromyelitis optica and multiple sclerosis. *Neuroimmunomodulation* 2013; 20: 107-112.

26. Gang Yaoa, Ping Wangc, Xiang-Dan Luo, Ting-Min Yu, Robert A. Harris, Xing-Mei Zhang. Meta-analysis of association between *Helicobacter pylori* infection and multiple sclerosis. *Neuroscience Letters*. 2016; 620: 1-7.

27. A Gasbarrinia, F Franceschia, A Armuzzib, V Ojettib, M Candellib, E Sanz Torreb, A De Lorenzoc, et al. Extradigestive manifestations of *Helicobacter pylori* gastric infection. *Gut* 1999; 45: I9-I12.

28. Sagar V, Zafar KS, Kumar G. A study of *Helicobacter pylori* infection in patients of ischemic cerebro vascular stroke. *Int J Res Med Sci* 2016; 4: 589-592.

29. Lin Y, Obata Y, Kikuchi S, Tamakoshi, Iso H, JACC Study Group. *Helicobacter pylori* infection and risk of death from cardiovascular disease among the Japanese Population: a Nested Case-Control Study within the JACC Study. *Journal of Atherosclerosis and Thrombosis* 2015; 22: 1-7.

30. Nam SY, Ryu KH, Park BJ, Park S. Effects of *Helicobacter pylori* infection and its eradication on lipid profiles and cardiovascular diseases. *Helicobacter* 2015; 20: 125-132.

31. Tebbe B, Geilen CC, Schulzke JD, Bojarski C, Radenhausen M, Orfanos CE. *Helicobacter pylori* infection and chronic urticaria. *J Am Acad Dermatol* 1996; 34:685-686.

32. Sharma VK, Lynn A, Kaminski M, Vasudeva R, Howden CW. A study of the prevalence of *Helicobacter pylori* infection and other markers of upper gastrointestinal tract disease in patients with rosacea. *Am J Gastroenterol* 1998; 93: 220-222.

33. Tosti A, Pretolani S, Figura N, Polini M, Cameli N, Cariani G, et al. *Helicobacter pylori* and skin diseases. *Gastroenterology International* 1997; 10: 37-39.

34. Danese S, Zoli A, Cremonini F, Gasbarrini A. High prevalence of *Helicobacter pylori* type I virulent strains in patients with systemic sclerosis. *J Rheumatol* 2000; 27: 1568-1569.

35. Frydman GH, Davis N, Beck PL, Fox JG. *Helicobacter pylori* eradication in patients with immune thrombocytopenic purpura: A review and the role of biogeography. *Helicobacter* 2015; 20: 239-251.

36. Brito HSH, Braga JAP, Loggetto SR, Machado RS, Granato CFH, Kawakami K. *Helicobacter pylori* infection and immune thrombocytopenic purpura in children and adolescents: A randomized controlled trial. *Platelets* 2015; 26(4): 336-341.

37. Ali AM, Ayman MN, Mahmoud MA. Helicobacter pylori Infection and its Potential Role in Childhood Eczema. *J Immunol Tech Infect Dis* 2016, 5:1.

38. B. Taye, F. Enquselassie, A. Tsegaye, G. Medhin, G. Davey, A. Venn. Is *Helicobacter pylori* infection inversely associated with atopy? A systematic review and meta-analysis. *Clinical and Experimental Allergy* 2015: 45; 882–890.

39. Campanati, A., Ganzetti, G., Martina, E., Giannoni, M., Gesuita, R., Bendia, E., Giuliodori, K., Sandroni, L. and Offidani, A. (2015), *Helicobacter pylori* infection in psoriasis: results of a clinical study and review of the literature. *Int J Dermatol* 54: e109–e114.

40. AG Gravina, A Federico, E Ruocco, A Lo Schiavo, M Masarone, C Tuccillo et al. *Helicobacter pylori* infection but not small intestinal bacterial overgrowth may play a pathogenic role in rosacea. *United European Gastroenterol J* 2015; 3: 17-24.

41. Burstein R, Noseda R, Borsook D. Migraine: Multiple Processes, Complex Pathophysiology. *Journal of Neuroscience* 2015: 35: 6619-6629.

42. Anderson G, Maes M. Melatonin: a natural homeostatic regulator - interactions with immune inflammation and trytophan catabolite pathways in the modulation of migraine and endometriosis. *Journal of Natural Products Research Updates* 2015; 1: 7-17.

43. Tanik N, Celikbilek A, Metin A, Gocmen AY, Inan LE. Retinol-binding protein-4 and hs-CRP levels in patients with migraine. *Neurol Sci.October* 2015; 36: 1823-1827.

44. Yilmaz IA, Ozge A, Erdal ME, Edgünlü TG, Cakmak SE, Yalin OO. Cytokine polymorphism in patients with migraine: some suggestive clues of migraine and inflammation. *Pain Med* 2010; 11: 492-497.

45. La Mantia L, Prone V. Headache in multiple sclerosis and autoimmune disorders. *Neurol Sci* 2015; 36: 75-78.

46. Gasbarrini A, Gabrielli M, Fiore G, Candelli M, Bartolozzi F, De LA, et al. Association between *Helicobacter pylori* cytotoxic type I CagA-positive strains and migraine with aura. Cephalalgia. 2000; 20: 561-565.

47. Faraji F, Zarinfar N, Zanjani AT, Morteza A. The effect of *Helicobacter pylori* eradication on migraine: a randomized, double blind, controlled trial. *Pain Physician* 2012; 15: 495-498.

48. Behnaz Ansari, Keivan Basiri, Rokhsareh Meamar, Ahmad Chitsaz, Shahrzad Nematollahi. Association of *Helicobacter pylori* antibodies and severity of migraine attack. *Iran J Neurol* 2015; 14: 125-129.

49. Mann NS, Singh S. *Helicobacter Pylori* and Migraine: systematic evaluation of 1084 cases with meta-analysis. *International Medical Journal* 2015; 22: 65-66.

50. Roubaud Baudron C , Varon C , Mégraud F , Salles N. Alzheimer's disease and *Helicobacter pylori* infection: a possible link? Geriatrie et Psychologie Neuropsychiatrie du Vieillissement 2016; 14: 86-94.
51. Judith Miklossy, Patrick L. McGeer. Common mechanisms involved in Alzheimer's disease and type 2 diabetes: a key role of chronic bacterial infection and inflammation. *Aging* 2016; 8: 575-588.
52. Vitale G, Barbaro F, Ianiro G, et al. Nutritional aspects of *Helicobacter pylori* infection. *Minerva Gastroenterol Dietol* 2011; 4: 369-377.
53. Wang XL, Zeng J, Yang Y, Xiong Y, Zhang ZH, Qiu M, Yan X et al. *Helicobacter pylori* filtrate induces Alzheimer-like tau hyperphosphorylation by activating glycogen synthase kinase-3β. *Journal of Alzheimer's Disease* 2015; 43: 153-165.
54. Faldu KG, Shah JS, Patel SS. Anti-Viral Agents in Neurodegenerative Disorders: New Paradigm for Targeting Alzheimer's Disease. *Recent Pat Antiinfect Drug Discov* 2015; 10: 76-83.
55. Devrajani BR, Shah SZ, Soomro AA, Devrajani T. Type 2 diabetes mellitus: a risk factor for *Helicobacter pylori* infection: A hospital based case-control study. *Int J Diabetes Dev Ctries* 2010; 30: 22-26.
56. Bener A, Micallef R, Afifi M, Derbala M, Al-Mulla HM, Usmani MA. Association between type 2 diabetes mellitus and *Helicobacter pylori* infection. *Turk J Gastroenterol*. 2007; 18: 225-229.
57. Anastasios R, Goritsas C, Papamihail C, Trigidou R, Garzonis P, Ferti A. *Helicobacter pylori* infection in diabetic patients: prevalence and endoscopic findings. *Eur J Intern Med* 2002; 13: 376.
58. Nasif WA, Mukhtar MH, Eldein MMH, Ashgar SS. Oxidative DNA damage and oxidized low density lipoprotein in Type II diabetes mellitus among patients with *Helicobacter pylori* infection. *Diabetol Metab Syndr* 2016; 8: 34.
59. Gerig R, Ernst B, Wilms B, Thurnheer M, Schultes B. Gastric *Helicobacter pylori* infection is associated with adverse metabolic traits in severely obese subjects. *Obesity* 2013; 21: 535-537.
60. Abdullahi M, Annibale B, Capoccia D, Tari R, Lahner E, Osborn J, Leonetti F, Severi C. The eradication of *Helicobacter pylori* is affected by body mass index (BMI). *Obes Surg* 2008; 18: 1450-1454.
61. Adler I, Denninghoff VC, Alvarez MI, Avagnina A, Yoshida R, Elsner B. *Helicobacter pylori* associated with glossitis and halitosis. *Helicobacter* 2005; 10: 312-317.
62. Esfahani AM, Irani S, Sabeti S, Zerehpoush FB. The Possible Role of *Helicobacter pylori* in the Development of Sjogren's Syndrome and Chronic Sialadenitis. *Avicenna J Dent Res* 2015; 7: e23212.
63. Gülseren D, Karaduman A, Kutsal D, Nohutcu RM. The relationship between recurrent aphthous stomatitis, and periodontal disease and *Helicobacter pylori* infection. Clinical Oral Investigations. 2016. In press. DOI: 10.1007/s00784-015-1704-0
64. Lender N, Talley, Enck P, Haag S, Zipfel S, Morrison M, GJ Holtmann NJ. Review article: associations between *Helicobacter pylori* and obesity - an ecological study. *Aliment Pharmacol Ther* 2014; 40: 24-31.
65. Arslan E, Atilgan H, Yavaşoğlu I. The prevalence of *Helicobacter pylori* in obese subjects. *Eur J Intern Med* 2009; 20: 695– 697.
66. Adriani A, Repici A, Hickman I, Pellicano R. *Helicobacter pylori* infection and respiratory diseases: actual data and directions for future studies. *Minerva Med* 2014; 105: 1-8.
67. Malfertheiner MV, Kandulski A, Schreiber J, Malfertheiner P. *Helicobacter pylori* infection and the respiratory system: A systematic review of the literature. *Digestion* 2011; 84: 212-220.
68. den Hollander WJ, Sonnenschein-van der Voort AM, Holster IL, de Jongste JC, Jaddoe VW, Hofman A, et al. *Helicobacter pylori* in children with asthmatic conditions at school age, and their mothers. *Aliment Pharmacol Ther* 2016, Mar 1. doi: 10.1111/apt.13572.
69. Rokkas T, Gisbert JP, Niv Y, O'Morain C. The association between *Helicobacter pylori* infection and inflammatory bowel disease based on meta-analysis. *United European Gastroenterology J* 2015; 3: 539-550.

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