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TOPIC HIGHLIGHT

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Metabolic consequences of *Helicobacter pylori* infection and eradication

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Abstract

Helicobacter pylori (*H. pylori*) is still the most prevalent infection of the world. Colonization of the stomach by this agent will invariably induce chronic gastritis which is a low-grade inflammatory state leading to local complications (peptic ulcer, gastric cancer, lymphoma) and remote manifestations. While *H. pylori* does not enter circulation, these extragastric manifestations are probably mediated by the cytokines and acute phase proteins produced by the inflammed mucosa. The epidemiologic link between the *H. pylori* infection and metabolic changes is inconstant and controversial. Growth delay was described mainly in low-income regions with high prevalence of the infection, where probably other nutritional and social factors contribute to it. The timely eradication of the infection will lead to a more healthy development of the young population, along with preventing peptic ulcers and gastric cancer An increase of total, low density lipoprotein and high density liporotein cholesterol levels in some infected people creates an atherogenic lipid profile which could promote atherosclerosis with its complications, myocardial infarction, stroke and peripheral vascular disease. Well designed and adequately powered long-term studies are required to see whether eradication of the infection will prevent these conditions. In case of glucose metabolism, the most consistent association was found between *H. pylori* and insulin resistance: again, proof that eradication prevents this common metabolic disturbance is expected. The results of eradication with standard regimens in diabetics are significantly worse than in non-diabetic patients, thus, more active regimens must be found to obtain better results. Successful eradication itself led to an increase of body mass index and cholesterol levels in some populations, while in others no such changes were encountered. Uncertainities of the metabolic consequences of *H. pylori* infection must be clarified in the future.

Key words: Diabetes mellitus; Cytokines; Glucose homeostasis; Growth; *Helicobacter pylori*; Interleukins; Lipid metabolism; Metabolic syndrome

Core tip: Although *Helicobacter pylori* (*H. pylori*) in considered the main cause of peptic ulcer, gastric cancer and mucosa-associated lymphoid tissue lymphoma, the infection could induce many extragastric manifestations: among them, the metabolic disturbances are less well debated. Growth-as expression of general metabolism-could be delayed especially in low income-high infection prevalence regions and this can be restored by timely eradication of the infection. *H. pylori* infection may be associated with increased total and low density lipoprotein cholesterol and decrease of high density liporotein, creating an atherogenic lipid profile and promoting atherosclerosis. *H. pylori* is consistently associated with insulin resistance. In the future, larg-scale studies are needed to clarify if eradication of *H. pylori* will result in restoration of normal growth, decrease of atherosclerotic disease, type 2 diabetes mellitus and metabolic syndrome.

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INTRODUCTION

If it is not cleared shortly after being acquired, *Helicobacter pylori* (*H. pylori*) infection invariably leads to a chronic, low-grade inflammation (CLGI) of the gastric mucosa. The inflammation could by limited to the antrum, angulus or extended to corporeal mucosa (pangastritis), according to the phenotype of the host. Inflammation is classically defined as a complex biological response of the tissues to pathogens, damaged cells and irritants[1,2]. Common factors to chronic gastritis, atherosclerosis, metabolic syndrome, obesity and type 2 diabetes are increased levels of tissue and circulatory cytokines produced by different cell types and secreted into the circulation, where they regulate metabolic processes through local, central and peripheral actions[3]. Classical acute inflammation differs in many ways from chronic low-grade inflammation. The cardinal signs of inflammation described by Aulus Cornelius Celsus (30 BC-38 AD) and Claudius Galen (AD 129-200) (calor = heat, dolor = pain, rubor = redness, tumor = swelling + functio laesa = loss of function), all are lacking in CLGI, which does not led to pus, abscess, granuloma, serous fluid formation or sepsis. Acute inflammation, if unresolved, could led to chronic process with an outcome affecting the rest of patient's lifetime: this is the case of chronic gastritis and its complications, as peptic ulcer disease, gastric cancer and the manifold extragastric manifestations. Additionaly, CLGIs can influence the overall health status far from the site of inflammation[3].

CLGI the gastric mucosa caused by *H. pylori* could lead to some metabolic disturbances which have much in common with other similar states, creating pathogenetic interfaces. The pro-inflammatory cytokines released will have different metabolic effects which could influence the outcome and complications of these states, as outlined below.

ACUTE PHASE PROTEIN AND CYTOKINE PROFILE IN *H. PYLORI*-INDUCED CHRONIC GASTRITIS

Colonisation of the gastric mucosa with *H. pylori* inevitably results in chronic-active or inactive-gastritis: this creates a CLGI state (see above). While *H. pylori* does not enter the circulation, the remote effects of the infection are probably induced by circulating cytokines, acute phase proteins and other mediators. *H. pylori* itself was not isolated from atherosclerotic lesions, but its DNA was found in coronary plaques obtained from 46 patients undergoing bypass sugery, suggesting a direct involvement of bacteria in plaque progression[4]. Virulence factors of *H. pylori* induce the recruitment of immunologically active cells, which release cytokines, tumor necrosis factor (TNF) α, interferons (IFNs) that can act remotely from the natural habitat of *H. pylori*. Their specific roles are summarized below.

Acute phase proteins

C-reactive protein (CRP) is synthetised in liver upon interleukin 6 (IL-6) and TNF α stimulation and in adipocytes by TNF α and resistin. CRP increases the production of intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractive protein-1 (MCP-1) by the endothelial cells and these molecules are involved in atherogenesis[3]. Elevated levels of CRP are associated with obesity, diabetes, coronary heart disease, smoking and sedentarism. CRP levels determined by high-sensitivity assay showed mild and variable increases in *H. pylori* infection. In a recent meta-analysis of 10 retrospective case-control studies, a positive association was found between $CagA^+$ status and ischemic heart disease (OR = 1.87, 95%CI: 1.46-2.40) and cerebrovascular disease (OR = 2.43, 95%CI: 1.89-3.13)[5]. In coronary heart disease patients infected with $CagA^+$ strain, a positive correlation was found between severity of vascular changes and CRP levels[6]. These results were confirmed by a later meta-analysis of 4241 cases, and anti-CagA antibodies were found inside coronary plaques, suggesting that in a subset of patients with coronary heart disease, the immune response to CagA antigen mediated plaque instability, leading to angina[6]. Further studies are needed to shed light on the role of CRP on this process.

Cytokines

CLGI states are characterized by mild, two- to three-fold increase in plasma concentrations of several cytokines. Up to now, 35 cytokines have been described: most of them, have pro-inflammatory and some anti-inflammatory action. In case of human gastric mucosa, elevated levels of IL-1β, IL- 6, IL-8, IL-10, and IL-17 were described: their selected features and actions are presented in Table 1[7-12]. The ILs could excite their pathogenic effect with increased tissue and plasma levels, or with genetic changes resulting modified gene products. Thus, recent meta-analyses showed that IL-8 gene -251 T/A polymorphism increased the risk of peptic ulcer but not that of gastric cancer[7,8]. In another study, no association of IL-1β 511 C/T polymorphism and risk of duodenal ulcer was found and the T allele state was even protective against the disease[9]. It is not known whether or not these polymorphisms have any role in the extragastric manifestations of the infection. Much of IL studies have been performed *in vitro*, so that their *in vivo* importance is less clear. INFγ was also found to be increased both in *H. pylori* induced gastritis, diabetes and metabolic syndrome. Some ILs are envisaged as therapeutic targets in the future.

Table 1 Profile of cytokines involved in *Helicobacter pylori* infection

Cytokine	Cellular origin	Role in gastric mucosa	Implications in metabolic processes
IL-1β	Mucosal and circulating monocytes, mast cells, epidermic and endothelial cells	Proinflammatory molecule, its expression is increased in the infected gastric mucosa. Mast cells stimulated by VacA toxin also produce IL-1β. Certain polymorphisms of IL-1β gene might promote atrophic gastritis and adenocarcinoma[2,9]	IL-1β *in vitro* induces distruction of pancreatic β cells, in insulin-sensitive organs produces inflammation and insulin resistance. It is increased in type 2 DM and mediates thrombotic complications[3]
IL-6	Monocytes, epithelial and endothelial cells	Innate immune recognition of *H. pylori* is mediated by TLR4 and induces increased expression of IL-6, IL-8, IL-10,IL-12[2]	IL-6 is increased in diabetes mellitus and *in vitro* downregulates adiponectin mRNA expression[3]
IL-8	Monocytes, fibroblasts, epithelial and endothelial cells	Secreted upon stimulation by IL-1β and TNF α, Il-8 induces polymorph neutrophil infiltration. *H. pylori*-infected gastric mucosa and gastric carcinoma cells express increased levels of IL-8. Recruited leucocytes phagocytose opsonized bacteria and produce reactive oxygen and nitrogen species[2,10]	Circulating monocyte IL-8, and TNF α levels are increased in type 2 DM with peripheral vascular disease[3]
IL-10	Th2 cells	Antiinflammatory cytokine but IL-10 gene polymorphism could reduce its production and enhance the risk of gastric cancer[2]	Idem as IL-8
IL-17	Th17 cells	IL-17 regulates the Th2 response to *H. pylori* and has anti-inflammatory effect[11]	Unknown
TNF α	Macrophages, T cell, natural killer cells	Elevated production TNF α and/or polymorphism of its gene (308 G > A) increase the risk of atrophic gastritis and distal gastric cancer. TNF α inhibits acid secretion[1,2]	Elevated levels in diabetes, obesity and metabolic syndrome alters insulin sensitivity, decreases glucose-transporter 4 and supresses adiponectin, increases the expression of *IL-6* and *MCP1* genes, promoting atherosclerosis[3]
IFNγ	Th1 cells	INFγ expressed in higher proportion of *H. pylori*-infected persons than those uninfected, inducing expression of IL-1β, IL-6, IL-8 and TNF α	Serum IF is increased in autoimmune type 1 diabetes. Polymorphism of IFγ is implicated in the pathogenesis of proliferative retinopathy is Type 1 and 2 DM. INFγ is increased in metabolic syndrome[3]

DM: Diabetes mellitus; *H. pylori*: *Helicobacter pylori*; IFN: Interferon; MCP-1: Monocyte chemotactic protein-1; TLR: Toll like receptor; IL: Interleukin; TNF: Tumor necrosis factor.

TNF α promotes inflammation and endothelial activation

Chronically elevated levels are detrimental to both gastric mucosa and glucose metabolism. TNF α alters insulin sensitivity, decreases glucose-4-transporter expression, suppresses adiponectin production and increases the expression of genes encoding other pro-inflammatory cytokines and proteins promoting atherosclerosis[3]. Tip-α is a new virulence factor of *H. pylori* which induces increased expression of TNF α, IL-1β and IL-8 in gastric epithelial cell lines and cancer cells[10]. This factor possesses DNA-binding activity and exerts its action by binding to nuclear factor κB. The role of this factor in the pathogenesis of gastric and extragastric actions of *H. pylori* must be investigated further[12].

GROWTH, STATURE AND *H. PYLORI*

In most individuals-regardless to geographic region-*H. pylori* infection is acquired during early childhood. In the first two decades of life, growth is an expression of general metabolism. Chronic inflammation of the gastric mucosa could be associated with disturbances of growth and stature; however, the published results are controversial and the results obtained in paediatric and adult populations are discordant[13-24].

Children

In a Peruvian paediatric population, that short stature was related with low nutrient and socioeconomic status intake rather than *H. pylori* infection[14]. In an uncontrolled French study, 426 children were examined endoscopically and *H. pylori* was detected in 18.1%, but the prevalence of infection was 55% in of children investigated for short stature[15]. In a Scottish study, 554 schoolchildren from Edinburgh were investigated and the growth in height between 7 and 11 years was diminshed in infected cases, but this was confined largely to girls[16]. In schoolchildren aged 3 to 14 years in Italy, 16.3% of infected children were below of 25th percentile for height compared with only 7.8% in *H. pylori* negative children, especially in those older than 8.5 years, suggesting that once acquired, the infection takes several years before to affect growth[17]. In another Italian study, the prevalence of anti-CagA IgG antibody was not different in normal and short children, suggesting *H. pylori* plays no role in short stature[18].

In a cross-sectional populational survey of 3315 German boys 5 to 7 years old, those infected were smaller than those *H. pylori* negative[19]. Other authors found a growth delay around the time of puberty in *H. pylori* positive children in Turkey and China[20,21]. In lower-middle class Columbian children aged 12 to 60 mo the growth velocity monitored for 2.5 years was lower in cases of new *H. pylori* infection, as determined by ^{13}C-UBT[22]. In another Turkish study, a positive association was found between recurrent abdominal pain, *H. pylori* infection and

growth delay[23]. Finally, in the most recent study, *H. pylori* infection in Columbian Andean children was found to impair growth velocity as compared to uninfected children, followed-up between 2004 and 2010. The results were not adjusted for socioenvironmental factors[24].

The mechanisms of growth retardation associated with *H. pylori* infection are hypothetical. The role of dyspeptic symptoms is uncertain, because they appear only in a fraction of infected children and no assocation was found between these variables. The infection could result in low energy intake and malnutrition; however, these could preceed its aquirement, especially under low economic standards. Finally, the low grade inflammation of gastric mucosa induces the release of cytokines which in turn affect growth: in this respect, the role of IL-8 IgA autoantibodies was assumed and in children with inflammatory bowel disease, serum levels of TNF α may be associated with growth failure[10,25]. No such studies were performed in *H. pylori* infected and healthy children.

A long-term follow up study in Columbia showed that in children who were always negative and those who received successful eradication treatment, grew significantly faster than those infected with *H. pylori* even after adjusting for covariates[26].

In a large cohort of 1222 Chinese children, *H. pylori* infection was associated with growth retardation and low serum acetylated ghrelin, while successful eradication restored ghrelin levels and increased net weight gain[27].

Adults

Data in adults are scarce and controversial. In a 4742 cohort of subjects from North Ireland, *H. pylori* infection was not associated with height in males, but mean height in infected women was lower even after adjusting for age and socioeconomic status. Body mass index (BMI) was not different in sero-positive and negative males and females[28]. In a Danish adult population with 2913 participants, people with upper quartile of BMI (> 26.8 kg/m^2) were more likely to be seropositive to anti-*H. pylori* IgG (OR = 1.6, 95%CI: 1.1-2.4) than persons with a lower BMI[29]. In 598 Swedish subjects, combined positive serology for *H. pylori* and *Chlamydia pneumoniae* was associated with higher BMI (27.3% *vs* 25.8%), therefore the authors considered that obesity might be a marker for greater susceptibility to infections[30]. In Leeds, height was measured in 2932 persons and *H. pylori* status determined by ^{13}C-UBT. *H. pylori* infected women were 1.4 cm and men 0.7 cm shorter than the infected cases but this was considered to be due to residual confounding[31]. In 2436 Czeh subjects, *H. pylori* status was assessed by ^{13}C-UBT a *H. pylori* positivity was associated with lower BMI il children under 15 years and a higher prevalence was found in older, overweight or obese subjects[13].

In the United States, the Third National Health and Nutrition Survey evaluated 7003 subjects between 1998 and 2004, the unadjusted odds of being overweight were significantly higher in CagA$^+$-*H. pylori* infected persons, but after adjustment for confounding variables, they were not significant[32]. There was no association between *H. pylori* CagA$^+$ or CagA$^-$, *H. pylori* status and serum leptin levels.

Successful eradication of the infection, however, induced an increase in body weight and BMI in Japanase workers, probably by cessation of dyspepsia, increased acid secretion, improved apetite and nutrition[33,34]. In a British randomised trial including 1558 patients, it was shown that eradication increased significantly BMI from 27.5% to 27.8% at 6 mo as compared to placebo[35]. In adults, in a systematic review of 592 cases, no change of circulating ghrelin levels was reported after eradication, although the treatment increased mucosal ghrelin mRNA[36].

It is difficult to interpret these data. In children, most of studies were performed in low-income populations with high prevalence of *H. pylori*; in adults, studies are coming from industrialized western countries, with low prevalence of infection. This implies the intervention of unmeasured factors such as eating habits, nutritional intake in the period of *H. pylori* acquisition and adulthood. Hormonal influences could have a role in females, where it was suggested that cytokines released by *H. pylori* disturb ovarian functions[16]. The mechanisms leading to *H. pylori*-associated growth delay/retardation in children and overweight/obesity in adults are probably different and undefined as yet. Determination of gastric mucosal and circulating cytokine profile in infected/uninfected children and adults will probably be of some help. The decrease of *H. pylori* and increase of overweight/obesity prevalence in western countries will generate further controversies in interpreting the correlation between growth, stature and *H. pylori* infection.

LIPID METABOLISM AND *H. PYLORI*

CLGIs may modify serum lipid profile. The association of *H. pylori* infection with lipid profile changes was observed in 1996 in Finnish subjects, where serum cholesterol (C) and triglicerid levels were significantly higher in *H. pylori* infected male persons, after adjustment for age, BMI and smoking status[37]. Since then, some studies have been performed in different populations: the results are given in Table 2. The results, although equivocal, suggest that *H. pylori* infection in different populations is associated either with elevated total C or low density lipoprotein (LDL)-L and lower high density liporotein (HDL)-C and apo A and B. Serum triglycerides were found also elevated in some, but not all, studies. The elevated C and LDL-C along with decreased HDL-C creates an atherogenic lipid profile which promotes atherosclerosis in different sites (carotid, cerebral, coronary and peripheral vessels)[38-45]. Two studies demonstrated a positive correlation between the degree of mucosal inflammation and lipid levels[42,43]. While the CLGI is a lifelong condition, the alterations of lipid profile induced are also long-lasting.

The mechanism by which *H. pylori* infection increases

Table 2 Lipid metabolism alterations in *Helicobacter pylori* infection

Year	Ref.	Population	No. of cases (*H. pylori* positive)	No.of controls (*H. pylori* negative)	Results	Comments
1996	[37]	Finnish	72	62	T level was higher, HDL-C was lower in controls and *H. pylori* positive patients with confirmed CHD	*H. pylori* could modify lipid concentrations in a way that could increase the risk of CHD
1999	[38]	Finnish	467	423	Serum T and total C was higher in males infected with *H. pylori*	Adjustment for age, BMI and social class had no influence on the association
2003	[39]	Italian	144	65	Total and LDL-C and lipoprotein A increased in infected subjects	The differences persisted after adjustment for covariates, especially in $cagA^+$ cases
2003	[40]	French	82	56	Trend to lower total C in infected cases; duodenal ulcer cases has lower C than *H. pylori* positive or negative dyspeptic patients	HDL-C, LDL-C , apoA and B all were lower in duodenal ulcer patients
2008	[41]	Greek			DU patients have lower C as compared with dyspepsia cases, regardless of *H. pylori* status	None
2009	[42]	Chinese	668	383	HDL-C were lower in *H. pylori* positive cases	No association of *H. pylori* with the severity of coronary atherosclerosis
2009	[43]	Turkish	163	81	Total C and LDL-C were significantly higher in *H. pylori* positive cases	A positive correlation was found between LDL-C and updated Sydney System score
2010	[44]	Japanese	2375	2702	LDL-C levels were higher, HDL-C lower in *H. pylori* positive cases in males but not in females	In Japanese males, high LDL and low HDL-C is significantly associated with *H. pylori* infection
2011	[45]	South Korea	193	261	Total C, LDL-C levels were higher in *H. pylori* positive cases; no association with HDL and T was found	The OR of *H. pylori* infection for high LDL-C level was 3.1

H. pylori: *Helicobacter pylori*; LDL: Low density lipoprotein; HDL: High density liporotein; BMI: Body mass index; DU: Duodenal ulcer.

lipid synthesis remains to be elucidated. An early study from 1992 showed that *H. pylori in vitro* adsorb C from serum and egg yolk, suggesting that it even decrease the absorbtion of alimentary C[46]. An experimental study has shown that IL-8-which is overexpressed in *H. pylori* infected mucosa[10]-production is stimulated by oxidized LDL by monocytes and thus, these potent chemoattractant cytokine increase the recruitment of T lymphocytes and smooth muscle cells, contributing to plaque fomation[47]. IL-10 production by mononuclear cells is also is also influenced by the inflammation and conversely, HDL-C itself could also modulate cytokine production[48]. However, there are no human studies.

An argument favouring the role of CLGI in the lipid profile alterations is that successful eradication of *H. pylori* infection induced an increase of HDL-C, apo A, while total C and LDL remained unchanged[48,49]. These results were not reproduced in large Spanish and Chinese trials and the minor changes of blood lipids were attributed rather to lifestyle modifications[50-52].

In summary, at least some of the infected patients, *H. pylori* induces a long-standing atherogenic lipid profile which could promote atherosclerosis, with its manyfold clinical manifestations (coronary heart disease, stroke, peripheral vascular occlusive disease).

Identification of patients at risk for this association and eradication of the infection might reduce the prevalence of these conditions and their complications: this warrants further studies.

GLUCOSE HOMEOSTASIS AND *H. PYLORI*

Diabetes mellitus (DM), metabolic syndrome and obesity have a mild (2-3-fold) increase of circulating cytokines in common[3]. The cytokine profile of chronic gastritis and DM shows some similarities and CRP, IL-6, TNF α are increased in both conditions. The prevalence of *H. pylori* infection in type 1 and 2 DM was found to be either increased, decreased or equal with non-diabetic controls: an analysis of these studies is beyond the scope of this article. Even if the causal association of DM and *H. pylori* infection is controversial, the later could induce changes of glycaemic control in diabetics.

H. pylori infection could lower fasting blood glucose level: several studies detected in *H. pylori* infected diabetics lower fasting plasma glucose than in non-infected controls[53-55] because both basal and meal-stimulated glucose is decreased. Antral gastrin release is increased by *H. pylori* and this, in turn, inhibit glucose absorbtion in the small intestine and amplifies glucose-stimulated insulin release in females, but not in men[56]. This could at least theoretically, even protect against development of type 2 DM in cases where the infection is acquired before occurrence of diabetes: this was not substantiated by the

epidemiological data.

HgbA1c is the most valuable indicator of long-term glycaemic control. The relationship between *H. pylori* infection and HgbA1c levels is also controversial. In children with type 1 DM, *H. pylori* infection was associated either with similar[57-59]. or increased[60] HbA1c values as compared to non-infected controls. In 141 type 2 DM patients and 142 non-diabetic subjects, no differences of fasting blood glucose and HbA1c levels were encountered, although neuropathy was more frequent than in infected cases[61]. Conversely, in 2060 Chinese diabetic participants, HbA1c levels were significantly higher in those *H. pylori* infected, especially in elderly patients[62]. In a recent study on 7417 participants in the National Health and Nutrition Examination Survey, *H. pylori* and especially $CagA^+$ status was associated with increased HbA1c levels and BMI after exclusion of confounders[63].

Insulin resistance is a central pathogenetic element in type 2 DM, metabolic syndrome and obesity. It can be measured with a homeostasis model assessment model of insulin resistance (HOMA-IR). In 63 Turkish patients, the HOMA-IR level was significantly higher is *H. pylori* positive patients as compared to negative cases[64]. Another Turkish study found in dyspeptic, non-diabetic patients the insulin resistance higher, the total antioxidant capacity lower in *H. pylori* infected patients[65] Conversely, in asymptomatic Japanese subjects, *H. pylori* seropositivity was significantly higher in insulin resistant cases as compared to those without resistance (39.4% *vs* 28.7%) after adjustment for gender, age, alcohol consumption, dietary habits, thus suggesting that the infection independently promotes insulin resistance in asymptomatic population[66]. In Iranians, there was no difference of mean fasting glucose, BMI, age and gender, but the HOMA-IR score was significantly higher and associated with seropositivity[67]. In a cohort of 5889 South Korean subjects, metabolic syndrome was more strongly associated with histologic (OR = 1.16, 95%CI: 1.08-1.48) than serologic *H. pylori* positivity (OR = 1.12, CI: 0.95-1.32): however, no data on glucose homeostasis were reported[68].

In a systematic review of 7 cross-sectional and 2 non-randomised open label trials, a potential association between *H. pylori* infection and insulin resistance was found in all but one study[69]. This could be of pivotal importance in obesity and metabolic syndrome, where circulating adiponectin levels are decreased and correlated with insulin sensitivity. Adiponectin levels have not been determined in relation to *H. pylori* infection, but epidemiologic data suggest that the prevalence of infection is increased in obese as compared to slim people[70].

An association of metabolic syndrome and CRP, E-selectin and vascular cell adhesion molecule 1,but not with IL-1β, IL-2, IL-4, IL-8, IL-10, TNF α and INF was found in a Swedish study[71], while in Brazilian patients, the metabolic Z score correlated with BMI, waist circumference, INFγ and TNF α levels as well as HOMA-IR values[72]. In 180 type 2 DM Romanian patients, increased levels of IL-1β and high C were associated with increased risk of thrombotic complications, but the *H. pylori* status was not included in this study[73].

Based on these data, some experts suggested to perform large interventional trials aimed at evaluating the benefit of *H. pylori* eradication on the prevention of metabolic syndrome and type 2 DM[74]. In the most recent study of 308 Lebanese subjects, no association of *H. pylori* with insulin resistance and metabolic syndrome was found and the authors concluded, that eradication of the infection to prevent these conditions is not warranted. The study had, however, methodological drawbacks[75].

Metabolic syndrome, however, is a multifactorial condition in which *H. pylori* infection seems to play only a minor, if any role. The prevalence of the infection is decreasing spontaneously in the developed countries, while that of metabolic syndrome is constantly increasing: parallel epidemiologic studies of these 2 conditons have not been performed and it would be intriguing to see whether spontaneous and/or eradication-induced decrease of *H. pylori* burden of the general population will result any change in the development and natural course of metabolic syndrome.

Although the association of *H.pylori* with glucose metabolism abnormalities is varied and differs between populations, the most consistent findings confirming the relationship of *H. pylori* and diabetes came from therapeutic trials, where both in type 1 and type 2 DM the rates of eradication of infection were significantly lower in diabetics than in nondiabetic patients. In a meta-analysis of 16 papers published until 2011, including 371 diabetic and 281 non-diabetic cases, we have shown a pooled eradication rate of 60.5% (95%CI: 52.8-69.3) in diabetics and 79.3% (95%CI: 68.1-91.3, $P = 0.03$) in non-diabetics. The number of cases included was rather low and the studies were heterogenous. Being diabetic increase the OR of unsuccessful treatment to 1.7 (95%CI: 1.5-2.0)[76]. Clarithromycin resistance is also more frequent in type 2 diabetics and influences negatively the eradication results[77]. A decrease in gastric mucosal blood flow was assumed to contribute to the poor eradication rates in diabetics. None of the international guidelines includes special recommendations of eradication in diabetics.

It was also shown that fasting insulin, HOMA-IR, C, CRP and C-LDL levels decreased in *H. pylori* positive patients 6 wk after successful eradication with a sequential regimen, suggesting a beneficial effect on atherogenic metabolic abnormalities and CLGI[78]. Other authors confirmed the improvement of lipid and haemostasis parameters (plasminogen activator inhibitor, CRP, fibrinogen, thrombin/antithrombin complex and von Willebrand antigen) contributing to improvement of cardiovascular risk factors[79].

In the most recent survey, successful eradication of *H. pylori* infection with triple and quadruple regimen in type 2 DM did not led to significant decrease of plasma glucose and HbA1c levels as compared to pre-treatment

levels and values found in non-diabetic controls[80].

CONCLUSION

In conclusion, *H. pylori* infection could induce metabolic disturbances mediated by the cytokines produced in the inflammed gastric mucosa. The epidemiologic link between the infection, growth disturbances, alterations of lipid and glucose metabolism are multi-faceted, and controversial. Delayed growth was described mainly in the low-income regions with high prevalence of *H. pylori* and eradication of infection will lead to a healthier development of the young population, along with preventing peptic ulcer/gastric cancer. Increase of C and LDL-C and decrease of HDL-C levels in a part of infected people creates an atherogenic lipid profile which could promote atherosclerosis with its complications. It must be proven, however, by future controlled long-term trials, whether eradicating the infection will result prevention of these conditions. In case of glucose metabolism, the most consistent association was found between *H. pylori* and insulin resistance: again, proof that eradication prevents this common metabolic abnormality by eradication is expected. Optimal regimens for eradication of the infection in diabetics must be found in the future.

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