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ASSOCIATION BETWEEN HELICOBACTER PYLORI INFECTION AND INSULIN RESISTANCE: A SYSTEMATIC REVIEW

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Abstract

Most studies in the past decades show that screening of Helicobacter Pylori (HP) together with monitoring the inflammatory markers, plasma glucose and HbA1c levels can help prevent or delay type 2 diabetes mellitus. ***There is a double interrelation*** *between HP infection and diabetes; thus diabetic patients are more susceptible to infection with HP via multiple mechanisms (decreased cellular and humoral immunity induced by diabetes, reducing gastrointestinal motility and secretion of hydrochloric acid, impaired glucose metabolism with the advent of chemical modifications of the gastric mucosa, the last two mechanisms favoring the intestinal colonization with HP). At the same time, those infected with HP can develop diabetes.*

The purpose of this paper is reviewing the data from the medical literature on the role of the chronic infection with HP on the induction of type 2 diabetes. The studies presented below lead us to the conclusion that the chronic infection with HP, in addition to local specific effects (simple gastritis, peptic ulcer and malignant diseases), also has extra-digestive effects. The one approached in our work is that HP is being able to induce type 2 diabetes by complex mechanisms related to insulin resistance, chronic low-grade inflammation, decreased insulin secretion, and influences on glucose and lipid absorption.

key words: *Helicobacter Pylori, Type 2 Diabetes, chronic low-grade inflammation, insulin resistance.*

Introduction

Helicobacter Pylori (HP) is a gram-negative, spiral, multiflagellate, unipolar, microaerophilic bacteria, secreting extremely active urease, characters that allow it to move freely in the gastric epithelium that they colonize in a specific manner, inducing the classic diseases: chronic gastritis, gastric ulcer and / or malignant gastric tumors, but also contributing to different extra-gastric events: hematological (anemia, iron deficiency, vitamin B12 deficiency, immune thrombocytopenia), autoimmune diseases (autoimmune thrombocytopenic purpura, Sjogren's syndrome, Henoch-Schonlein, autoimmune thyroid disease, Parkinson's disease, chronic idiopathic hives, rosacea, alopecia areata), cardiovascular disorders

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(ischemic heart disease, stroke, migraine, Raynaud's primary syndrome), respiratory disorders (chronic obstructive pulmonary disease, bronchiectasis, lung cancer, asthma, pulmonary tuberculosis) and other diseases (growth retardation, liver cirrhosis, Alzheimer's dementia) and, finally, metabolic manifestations (metabolic syndrome, type 2 diabetes) [1,2].

Epidemiology

The infection with HP is of interest for more than 50% of the world population, representing the 2nd infection in frequency after tooth decay and it is considered a primary etiologic agent for the gastric cancer, being classified in class I of carcinogenic agents by the International Agency for Cancer Research, a branch of the WHO. The analysis of the genetic sequence shows HP is an infection dating more than 58,000 years ago, about the time of the first migrations from Africa [1]. Diabetes is a pandemic responsible for over 3.8 million deaths worldwide [3]. A possible association between the two entities would have an impact over the future diabetes and diabetic complications. HP infection occurs mainly in childhood and persists throughout life if not properly treated. The major risk factor for the infection is the socioeconomic status of the family during childhood. In the United States, the prevalence in the white population decreased in the middle and upper class younger than 50 years, remaining high among the elderly (infected at youth), those socially disadvantaged and in immigrant populations.

HP was discovered in the water, stool, saliva and dental plaque. Transmission through water has been first proven in Peru and Colombia. The main mode of transmission is from person to person by fecal-oral and oral-oral routes.

Physiopathology

The colonization of gastric mucosa induces an acute infiltration of polymorphonuclears which is gradually replaced by an immunologically mediated infiltration with mononuclear cells, triggering a major local inflammatory response, which can cause chronic gastritis, gastric ulcer and / or malignant tumors and a low grade systemic inflammatory response, the net result being an increased production of pro-inflammatory cytokines (IL-1, IL-6, IL-8, tumor necrosis factor alpha (TNF alfa) and C-reactive protein (CRP). To this we should add strong growth in the flow of leukocytes, the appearance of platelets and leucocyte-platelet aggregates, as well as the production of oxygen reactive species, all mediating the potential occurrence of the cardiovascular diseases and metabolic syndrome [3,4]. The increased levels of inflammatory cytokines can phosphorylate the serine residues on the insulin receptor substrate, preventing the proper interaction with insulin, with the final effect of decreased insulin action [5].

The low degree systemic inflammatory response is associated with type 2 diabetes, where the chronic infections with various pathogens can contribute, including HP which triggers an important inflammatory and immune response, even if it is a non-invasive micro-organism [2,3].

As a result, we witness the disruption of the insulin secretion and induction/aggravation of insulin resistance under the influence of HP infection. The mechanism might involve, besides chronic low-grade chronic inflammation, the impaired secretion of gastrointestinal hormones that are involved in insulin action [3].

Among the gastrointestinal hormones involved in the pathogenesis of diabetes are leptin, ghrelin, somatostatin and gastrin.Ghrelin is a peptide hormone produced particularly by P / D1 cells located in the stomach (fornix) and by the epsilon cells in the pancreas. It has a role in stimulating the appetite and it lowers the energy

consumption, favoring the weight gain, in particularly the organism's fat mass. Leptin is a peptide hormone, mainly produced by adipocytes. It inhibits the appetite and increases the energy consumption. HP infection alters ghrelin and leptin production, a disorder which could favor fasting hyperinsulinemia, obesity, finally insulin resistance and the appearance of type 2 diabetes. Gastrin is a peptide hormone secreted by the G cells in the pyloric antrum, under the influence of food, especially proteins that contribute to the glucose stimulated release of insulin. Somatostatin is a pancreatic hormone secreted by the delta cells of the islets of Langerhans, stomach and intestine, as well as the periventricular nucleus of the hypothalamus. It inhibits the secretion of insulin. During the HP infection, the basal and stimulated gastrin secretion is increased and somatostatin secretion decreases leading to disturbances in insulin homeostasis [3].

Arguments regarding the relationship between HP infection and type 2 diabetes

The first study concerning the association between diabetes and HP infection was conducted in 1989. Simon et al. found a prevalence of HP infection in subjects with diabetes of 62% compared to 21% in the control group, irrespective of the patient's age [6]. A meta-analysis of 41 studies involving 14080 patients revealed a high prevalence of HP infection in patients with type 2 diabetes [7]. A recent prospective study on 768 patients who were observed over a period of 10 years found that HP seropositivity was accompanied by a higher incidence of diabetes [7]. The conclusion of these studies is that subjects with type 2 diabetes have a high prevalence of infection with HP.

The study conducted by Jeon et al. in 2012 on a group of 782 people aged over 60, during a 10 year period, undiagnosed with diabetes at baseline and whose serology was tested twice a year in order to detect antibodies to HP, Gondi Toxoplasma as well as for various viruses, showed that the infection with HP causes the increase of the incidence of diabetes, even corrected with other reference factors (age, sex, health education, smoking, body mass index - BMI, blood pressure and lipid profile); HP seropositive patients had a risk two times greater to trigger diabetes compared to those not infected with HP and with those who had the other infections which have not led to the increase of the incidence of diabetes, which is why PPI and antibiotics therapy proved very important in stopping the occurrence of diabetes [5]. The conclusion of this study is that the HP infection determines the increase of the incidence of the noninsulin diabetes, the HP seropositive ones proving to have double the risk of developing diabetes than those who were seronegative, which is why the treatment of triple association involves a potential role in preventing diabetes.

HbA1c role in diagnosing prediabetes and diabetes is well-known. Using data from two large studies, National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2000, Chen and Blaser provided new information regarding the association between HP infection sero-positivity and average HbA1c levels demonstrating that the presence of HP and especially of CagA (cytotoxin-associated gene A) of HP correlates with a higher average glycated hemoglobin level, especially in adults over 18 years old. At the same time these studies have shown an association between HP and BMI on the one hand and increased levels of HbA1c on the other hand, confirming the role of the infection with HP in the alteration of glucose tolerance, which could be boosted by an increased BMI [8].

A confirmation of the NHANES study came from a recent long-term study in Taiwan by Hsieh et al. which showed that the infection with HP is accompanied by an increase in HbA1c, insulin secretion decrease and a higher prevalence of type 2 diabetes [9].

HP infection was also connected to the moderately elevated albuminuria (microalbuminuria) represented by values between 30-300mg/24h of the urinary albumin or a urinary albumin-to-creatinine ratio between 30-300mg/g, an indicator of early diabetic renal disease. In a cross-sectional study on 2716 patients, Chung et al. found a percentage increase of the seropositive patients proportional to that of the albumin-to-creatinine ratio; the proportion of those with HP being the highest in case of those with moderately elevated albuminuria (microalbuminuria) and diabetes [10]. The conclusion of this study was that in diabetics, HP infection may be associated with moderately elevated albuminuria that reflects the early manifestations of diabetic nephropathy.

Given the conclusions of multiple studies showing that presence of type 2 diabetes correlates with increased levels of markers of low-grade systemic inflammation (such as CRP, the plasminogen activator inhibitor 1 (PAI-1), IL-6, the number of white cells and (TNF-α)) it can be easily inferred that any entity that increases the level of inflammation markers including the infection with HP, leads to an increase of the prevalence of type 2 diabetes. Also, the presence of the gram-negative bacteria in the intestinal flora, such as HP, triggers increased production of lipopolysaccharides that activate the Toll-like receptors and thus the inflammatory processes with subsequent development of insulin resistance [5].

It is a fact that gastrointestinal mucosal injury caused by the infection with HP alters the absorption of glucose and lipids, already unbalanced in type 2 diabetes. In addition, the production of oxygen reactive species associated with the low-grade systemic inflammation during the infection with HP leads to changes in ghrelin and leptin. The alteration of the levels of ghrelin and/or leptin leads to uncontrolled food intake, and ultimately obesity, strongly correlated with the risk of type 2 diabetes [11,12]. There is the tempting hypothesis that treating the HP infection might help preventing obesity, coronary heart disease and other metabolic syndrome elements associated with it.

Hamed et al performed a study on 80 diabetic patients where the prevalence of infection with HP, the connection between diabetic arteriopathy and the infection with HP and the influence of this infection on inflammation, atherosclerosis and cardiovascular events were monitored [13]. The study showed that 85% of the patients were infected and the intima-media thickness ratio of the carotid artery significantly increased in those infected. Il-6 and TNF-α were mainly related to the infection by HP and in those infected with cerebral ischemia due to atherothrombotic causes, specific changes in glucose, triglycerides, ESR (Erythrocyte Sedimentation Rate), Il-6 and TNF-α were found. According to this study it may be remarked that HP infection is common among diabetics and appears to be associated with the presence of atherosclerosis and cerebro-vascular events (stroke) [13].

Another transversal medical study conducted in Japan from April 2006 to March 2007 on a total of 7394 patients out of which 74.22% men and 25.78% women, investigated the relationship between HP infection and metabolic syndrome, ascertaining a significantly higher percentage of HP seropositivity as well as a correlation between the HP seropositive status and systolic blood pressure, low serum levels of

HDL-cholesterol and elevated LDL-cholesterol levels [14].

Knowing that insulin resistance increases the cardiovascular risk, the effect of the HP infection on insulin resistance was searched. Thus, Aydemir et al. performed a study on 63 patients divided according to seropositivity status in a group of 36 HP seropositive individuals (57.14%) and 27 seronegative individuals (42.86%). Using the HOMA-IR (Homeostasis Model for the Assessment of Insulin Resistance) model they found a higher HOMA-IR level in the infected group (2.56±1.54) compared to the uninfected group (1.73±1.1) [15].

In another study performed in Japan between May 2007 and July 2008, Gunji et al. analyzed 1107 patients from which 988 men (89.25%) and 119 women (10.75%) and found a significantly higher percentage of HP seropositivity among subjects with insulin resistance. The conclusion of this study was that HP infection contributes independently and significantly to insulin resistance occurrence in an asymptomatic population [16].

Eshraghian et al. performed a similar study (between January and April 2007) on a group of 71 individuals and sought a connection between HP infection and insulin resistance. Among the subjects, 43 (60.6%) were infected and 28 (39.4%) were uninfected. The HOMA-IR was significantly higher in those infected (3.54±2.2) compared with those uninfected (2 46±1.9), the "fasting" serum insulin levels being higher in those infected (19.41±3.08 μU/ml) than in those uninfected (16.57±2.02 μU/ml), suggesting again a role of HP infection as a risk factor for insulin resistance [17].

The studies described so far have revealed the connection between HP infection and the presence of insulin resistance. It was logical then to examine the effects of HP eradication on insulin resistance, serum lipids and low-grade inflammation markers. In this regard, the study of Ramazan et al. is relevant [18]. Thus, 159 patients, out of which 88 with the HP infection and 71 without HP infection, were treated sequentially for 14 days. The authors also used HOMA-IR for the assessment of insulin resistance as well as other benchmark factors such as total cholesterol, LDL-cholesterol, triglycerides and CRP, whose levels were significantly elevated in those infected, and HDL cholesterol whose level was significantly decreased in those infected [18]. After the HP sequential treatment, the eradication rate was 53.4% in the treated patients. Six weeks after completion of the eradication therapy, the HOMA-IR levels, the total cholesterol, LDL-cholesterol, triglycerides and CRP in these patients were significantly lower compared to the levels before the treatment and the HDL cholesterol levels increased. In patients in whom HP eradication was not successful, the levels of the studied parameters remained unchanged [18]. Thus, the result of this study showed the benefit of the eradication of the HP infection on insulin resistance, on atherogenic lipids and CRP as an indicator of the low-grade inflammation.

Finally, a meta-analysis of data on 2120 patients published in 2011, suggested insulin resistance changes after eradication of HP infection [19].

Conclusions

All patients infected with HP, should be monitored for glucose, HbA1c, inflammatory markers, lipid profile, BMI, blood pressure, all of which can contribute to an early discovery of the changes in blood glucose and thus help prevent or delay the emergence of type 2 diabetes, as well as of the potential complications of this disease.

At the same time, according to the studies discussed above, the HP treatment could have an

important role in improving insulin resistance, metabolic syndrome components, NASH and some inflammation markers.

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