Insulin resistance and metabolic syndrome: is Helicobacter pylori criminal?

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Insulin resistance and metabolic syndrome are contributors to atherosclerosis and coronary heart disease. Insulin resistance is also responsible in pathogenesis of type II diabetes. Several studies previously evaluated the role of H. pylori infection in coronary heart disease and type II diabetes. Recently published data have described the association between H. pylori infection with insulin resistance and metabolic syndrome. However, this is still a controversial subject. Here in, we reviewed current status and present data toward this topic.

Key words: Insulin resistance - Metabolic syndrome X - Atherosclerosis - Helicobacter pylori.

The famous Helicobacter pylori (H. pylori), which is the most prevalent chronic infection worldwide, is a gram-negative, non-invasive, non-spore-forming and spiral-shaped bacteria that has been established to be responsible for several human illnesses such as peptic ulcer, gastric adenocarcinoma, and type B low-grade mucosa-associated lymphoma. Besides all, H. pylori infection has been reported to be associated with non-gastric diseases like coronary artery disease, autoimmune disorders and metabolic syndrome. In the recent years, several studies were conducted to investigate the association between H. pylori infection, insulin resistance and metabolic syndrome.

The main theory behind this topic is low grade systemic inflammatory process that may initiate by chronic H. pylori infection. However, other pathophysiological mechanisms such as alterations in counter regulatory hormones may be a link between H. pylori infection and insulin resistance.

Insulin resistance that precedes type II diabetes mellitus, along with metabolic syndrome, are risk factors for coronary artery disease that is the leading cause of death worldwide. Therefore, confirming such an association may lead to providing protocols that suggest H. pylori eradication as a way to prevent coronary artery diseases, metabolic syndrome and type II diabetes mellitus. Although current guidelines suggest testing H. pylori infection in patients with unexplained iron deficiency anemia and chronic idiopathic thrombocytopenic purpura, there is no agreement to test or eradicate it in patients with insulin resist-
ance. We sought for evidence to support testing *H. pylori* in insulin resistance.

We searched current English literature including epidemiological, cross sectional and interventional studies to overview the present situation toward association between *H. pylori* infection and insulin resistance. We searched Medline for articles published ever using *H. pylori*, insulin resistance, and diabetes type II as key words. We limited the search to human studies and viewed the articles to select those reporting association of *H. pylori*, with insulin resistance. We also searched the Ovid database Evidence-Based Medicine Reviews and Scopus but did not find any more paper.

**Cross sectional studies**

Chronic infections and inflammation have been always supposed to be involved in pathophysiology of type II diabetes; insulin resistance and metabolic syndrome. Several studies were conducted to evaluate seropositivity for some pathogens in type II diabetic patients or those with metabolic syndrome. Among hundreds of pathogens, most of attentions were focused on *Chlamydia pneumoniae*, *Herpes simplex virus type 1*, *H. pylori* and *cytomegalovirus*. Nabipour et al. were found a strong association between infections with these pathogens and metabolic syndrome. Conversely Lutsey et al. could not find any significant association between seropositivity for the above pathogens and type II diabetes. From these pathogens *H. pylori* has a notable role due to its high prevalence worldwide. In the last years of 20th century several studies were especially conducted to determine whether *H. pylori* infection is associated with type II diabetes, metabolic syndrome and insulin resistance. A case control study showed that *H. pylori* seroprevalence is higher among patients with type II diabetes compared to controls. Authors stated that this higher prevalence could not be justified only by socioeconomic status or antibiotic therapy. Afterwards several studies were conducted to evaluate the association between type II diabetes and *H. pylori* infection. While some of these studies confirmed higher prevalence of *H. pylori* infection in diabetic patients, others failed to demonstrate such an association.

These studies, although have discordant results, triggered the notion that *H. pylori* infection may correlate with the underlying cause of type II diabetes, i.e. insulin resistance.

The first study that investigated and reported the association between insulin resistance and *H. pylori* infection is a cross sectional case control study by Ademir et al. They used homeostasis model assessment of insulin resistance (HOMA-IR) to assess insulin resistance and *H. pylori* infection was confirmed histologically form tissue biopsies by upper endoscopy. Finally HOMA-IR levels were higher significantly in *H. pylori* positive patients compared to *H. pylori* negative patients. Aslan et al. reported that *H. pylori* positive patients have higher HOMA-IR levels. They considered patients to be positive for *H. pylori* if both the rapid urease test (RUT) and histological examination were positive. They have also determined serum total antioxidant capacity (TAC), total oxidant status (TOS) and oxidative stress index (OSI) and concluded that insulin resistance is associated with increased oxidative stress in *H. pylori* infection. Another study in pediatric patients confirmed the correlation between *H. pylori* infection and insulin resistance in children.

There are two other cross sectional case-control studies in the literature that both used *H. pylori*-specific immunoglobulin G antibody titers to confirm *H. pylori* infection. In a case control study at our center, we reported the higher prevalence of insulin resistance in patients with *H. pylori* infection compared to *H. pylori* negative patients. This report was important since the study population was composed of healthy subjects. A Japanese study by Gunji et al. and with larger sample size confirmed the association between *H. pylori* seropositivity and insulin resistance. Although different in their methods of *H. pylori* detection, all
of these explained studies confirmed association of insulin resistance and H. pylori infection. However there are published data against such an association. Gillum reported that there was no consistent association between H. pylori infection and prevalence of diabetes or variables of insulin resistance syndrome.25 HOMA-IR has not been also associated with H. pylori infection as reported by Gao et al. and SO et al.26, 27

Interventional studies

As previously reviewed increasing data form cross sectional case-control studies are now available toward association of H. pylori infection, insulin resistance and metabolic syndrome. To further elucidate and support of this association interventional studies seems to be more useful. In this area of research published data are not consistent again. In a retrospective study Park et al. compared pre- and post eradication (one year after) the metabolic and inflammatory parameters, such as blood sugar, lipid profiles, insulin resistance (HOMA-IR), white blood cell count and C-reactive protein. They concluded that H. pylori eradication has no significant effect on insulin resistance, metabolic and inflammatory parameters.28 Longo-Mbenza et al. reported a significant decrease in blood glucose and improvement of other metabolic parameters with H. pylori eradication.29 However, they did not check HOMA-IR or other parameters of insulin resistance. A very interesting case report has been recently published regarding improvement of type B insulin resistance following eradication of H. pylori infection.30 Type B insulin resistance is caused by polyclonal immunoglobulin G antibodies directed against the insulin receptor blocking insulin binding to the receptors and inducing severe hyperglycemia. It has been associated with other autoimmune disease.31 On the other hand, H. pylori eradication ameliorates some autoimmune disorders like immune thrombocytopenic purpura (ITP),32 antiphospholipids antibody syndrome and rheumatoid arthritis.33 Authors concluded that improvement of type B insulin resistance after eradication of H. pylori is due to the role of this pathogen in regulation of host immunity. A recent study also confirmed higher HOMA-IR in H. pylori positive patients. This study suggests fetuin A level as a possible link between insulin resistance and H. pylori infection as serum fetuin A level was higher in H. pylori infected patients.34

The first prospective interventional study about the influence of H. pylori eradication on insulin resistance, lipid profiles and inflammation parameters has been published by Gen et al. They reported that the mean fasting insulin, HOMA-IR, total cholesterol (TC), triglyceride (TG), LDL cholesterol (LDL-C) and C reactive protein (CRP) were significantly decreased from the pretreatment levels after successful eradication of H. pylori. Although this study is not a placebo controlled trial it is a good motivation for researchers to conduct randomized placebo trials to investigate whether H. pylori eradication will minimize insulin resistance.

Possible mechanisms

Insulin resistance has a central role in the pathogenesis of several diseases such as diabetes, atherosclerosis and metabolic syndrome.35 It has been established that insulin is the responsible hormone for muscle glucose uptake, adipose tissue lipolysis and suppression of glucose production. However, the underlying basis for development of insulin resistance has not been clarified yet. HOMA-IR has been used in all of reviewed studies for assessment of insulin resistance. This test with the normal range between 2 and 3 is now considered the gold standard quantitative method for measurement of insulin resistance.

Previously the role of H. pylori infection had been investigated in diabetes mellitus and atherosclerosis. Therefore, the notion that H. pylori infection might involve in insulin resistance and metabolic syndrome was intensified. Chronic inflammatory state and alteration of adipokines and gut hor-
mones by \textit{H. pylori} infection are the main described pathophysiological basis for this possible association. \textit{H. pylori} is capable of producing several antigens that can stimulate immune response and cause a chronic inflammatory state. Heat shock protein, urease, and lipopolysaccharide are from its antigens; all of them can activate macrophages and T-lymphocytes.\textsuperscript{38} These events increase production and secretion of inflammatory cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-\textalpha), and IL-8 causing chronic inflammation in the human body.\textsuperscript{39} Chronic inflammation is a factor that predisposes patients to insulin resistance and metabolic syndrome.\textsuperscript{40} Furthermore, TNF-\alpha and IL-6 are involved in insulin resistance process independent of chronic inflammation.\textsuperscript{41} It is not still clear that insulin resistance is a direct consequence of \textit{H. pylori} infection, or it is secondary to the chronic inflammatory state in the body.\textsuperscript{42} \textit{H. pylori} eradication also decreases soluble CD40 ligand, body fat mass and serum TOS as a marker of oxidative stress. CD40 ligand pathway is involved in insulin resistance and type II diabetes and thus is another target for minimizing insulin resistance via \textit{H. pylori} eradication.\textsuperscript{43, 44}

Gut hormones has been known to affect insulin resistance and \textit{H. pylori} alter these hormones.\textsuperscript{45, 46} Several studies showed the effect of \textit{H. pylori} infection on serum leptin level.\textsuperscript{47, 48} Enhanced production of leptin in gastric fundic mucosa was observed in patients with \textit{H. pylori} infection.\textsuperscript{49} Leptin is a peptide that has a pivotal role in energy expenditure and body weight and is involved in pathogenesis of insulin resistance.\textsuperscript{50}

Ghrelin is another gut hormone involved in human energy metabolism. It also acts as a modulator of insulin secretion and glucose metabolism. Ghrelin has been shown to prevent apoptosis and stimulates B cell proliferation in human islets of Langerhans. Furthermore, both acylated and unacylated ghrelin stimulate insulin secretion and improve insulin sensitivity.\textsuperscript{51} Ghrelin therapy is also associated with down regulation of IL-12 and TNF-\textalpha which are involved cytokines in insulin resistance mechanism.\textsuperscript{52} It has been shown that \textit{H. pylori} infection is associated with reduced serum ghrelin level.\textsuperscript{53} As a result; anti-apoptotic, anti-inflammatory and proliferative effects of ghrelin as well as its stimulatory action on insulin are decreased in patients with \textit{H. pylori} infection.

Fetuin A (\textalpha2-Heremans-Schmid glycoprotein [Ahsg]) is produced in hepatocytes and binds to insulin receptor tyrosine kinase in muscle and fat tissues and causes insulin resistance.\textsuperscript{54} Cross-sectional human studies confirm higher serum levels of fetuin A in patients with insulin resistance.\textsuperscript{55} Higher serum titer of fetuin A was also associated with incident diabetes mellitus in elderly patients.\textsuperscript{56} It has been recently shown that \textit{H. pylori} positive patients have

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\begin{tabular}{|l|l|l|l|l|l|l|}
\hline
\textbf{Paper} & \textbf{Number of patients} & \textbf{Year} & \textbf{Study design} & \textbf{H. pylori detection method} & \textbf{IR assessment method} & \textbf{Find an association} \\
\hline
Ademir \textit{et al.}\textsuperscript{20} & 63 & 2005 & Case-control & Endoscopy & HOMA-IR & Yes \\
Aslan \textit{et al.}\textsuperscript{21} & 103 & 2006 & Case-control & Endoscopy & HOMA-IR & Yes \\
Ozdem \textit{et al.}\textsuperscript{22} & 60 & 2007 & Case-control & Serology & HOMA-IR & Yes \\
Eshraghian \textit{et al.}\textsuperscript{23} & 71 & 2009 & Case-control & Serology & HOMA-IR & Yes \\
Gunji \textit{et al.}\textsuperscript{24} & 1107 & 2009 & Case-control & Serology & HOMA-IR & Yes \\
Gao \textit{et al.}\textsuperscript{25} & 100 & 2009 & Cross-sectional & Endoscopy & HOMA-IR & No \\
So \textit{et al.}\textsuperscript{26} & 288 & 2009 & Cross-sectional & Serology & HOMA-IR & No \\
Park \textit{et al.}\textsuperscript{27} & 169 & 2005 & Retrospective & Endoscopy & HOMA-IR & No \\
Imai \textit{et al.}\textsuperscript{28} & 1 & 2009 & Case report & UBT & - & Yes \\
Manolakis \textit{et al.}\textsuperscript{29} & 105 & 2011 & Case-control & Endoscopy & HOMA-IR & Yes \\
Gen \textit{et al.}\textsuperscript{30} & 88 & 2010 & Interventional & Serology & HOMA-IR & Yes \\
\hline
\end{tabular}
\caption{Summary of main features of studies that evaluate association of \textit{H. pylori} infection and insulin resistance.}
\end{table}
higher level of fetuin A. This protein can be the missed ring between insulin resistance and *H. pylori* infection.\(^5\)

Monocyte chemoattractant protein–1 (MCP-1) is a potent chemotactic chemokine which is mainly produced by macrophages and endothelial cells. MCP-1 has been identified to be involved in insulin resistance, metabolic syndrome and atherogenesis. Kanda and co-workers showed that increased MCP-1 expression in adipose tissue causes macrophage infiltration into this tissue, insulin resistance and hepatic steatosis in genetically obese mice.\(^6\) Another study in transgenic mice with over expression of MCP-1 in adipose tissue causes macrophages recruitment and insulin resistance.\(^7\) Pioglitazone treatment reduced expression of MCP-1 and decreased macrophages infiltration in adipose tissue and improved insulin sensitivity.\(^8\) These studies together confirm a pivotal role for MCP-1 in pathogenesis of insulin resistance. On the other hand *H. pylori* stimulates MCP-1 expression in gastric epithelial cells \(via\) COX-2 expression.\(^9\) *H. pylori* induced MCP-1 gene transcription in gastric epithelial cells is mediated by activation of nuclear factor kappa B (NF-κB).\(^10\) NF-κB is a novel intracellular signaling molecule for hormones, chemokines, cytokines and growth factors. Activation of NF-κB signaling pathway has been participate in insulin resistance, metabolic syndrome and cardiovascular events.\(^11\) It has been recently found that cell translocating kinase A (CtkA) is a virulent *H. pylori* factor that is capable of up regulation of NF-κB signaling \(via\) phosphorylation of NF-κB p65 subunit.\(^12\) These mechanisms can be tested in other animal and human studies for better clarification of the subject.

**Conclusions**

Although it is still a controversial topic; many studies have shown association of *H. pylori* infection with insulin resistance and metabolic syndrome. These studies are mostly cross sectional and there is only one prospective interventional study in this area of research. Considering the increasing incidence and prevalence of diabetes and atherosclerosis worldwide, investigation to find a causal relationship between *H. pylori* infection with insulin resistance and metabolic syndrome will be an interesting topic for prospective cohorts and placebo randomized trials in the future.

**Riassunto**

*Insulinoresistenza e sindrome metabolica: l’Helicobacter pylori è colpevole?*

L’insulinoresistenza e la sindrome metabolica favoriscono l’aterosclerosi e la coronaropatia. L’insulinoresistenza è anche responsabile della patogenesi del diabete di tipo II. Molti studi precedenti hanno già valutato il ruolo dell’infezione da *H. pylori* nella coronaropatia e nel diabete di tipo II. Dati pubblicati di recente hanno evidenziato l’associazione dell’infezione da *H. pylori* con l’insulinoresistenza e la sindrome metabolica. Tuttavia, la questione è ancora controversa. Nel nostro articolo, prendiamo in esame la situazione attuale e i dati oggi disponibili sull’argomento.


**References**

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