

Review

## Helicobacter pylori and type 2 diabetes mellitus: searching for the links

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**Abstract:** The incidence and prevalence of type 2 diabetes mellitus is considered to be one of the most critical problems in the healthcare system. The pathophysiology of the disease has proven to be complicated and multiple factors are involved in its development. Recently *Helicobacter pylori* was proposed as a new risk factor for developing type 2 diabetes mellitus as well as other disease. This study is a review of the current data involving *Helicobacter pylori* association with type 2 diabetes mellitus and its complications.

**Keywords:** type 2 diabetes mellitus, *Helicobacter pylori*

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### Introduction

Studies show that the world prevalence of diabetes among adults will be 6.4% (285 million adults), in 2010, and will increase to 7.7% (439 million adults) by 2030. So in other worlds between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries [1].

The total number of excess deaths attributable to diabetes worldwide was estimated to be 3.96 million in the age group 20-79 years, 6.8% of global mortality. Diabetes accounted for 6.0–15.7% deaths depending on the country. Thus, diabetes is a considerable cause of premature mortality, a situation that is likely to worsen, particularly in low and middle income countries as diabetes prevalence increases [2].

The prevalence of *Helicobacter pylori* (Hp) infection is estimated to be in the range of 22% to 95% in the developing countries and 1% to 58% in the developed. The prevalence of Hp infection varies by geographic location, ethnicity, socioeconomic status, and age [3].

The latest data link the presence of Hp with the development of several diseases among which are type 2 diabetes mellitus (T2DM), chronic obstructive bronchitis, acute coronary disease, end stage renal disease (ESRD), and others [4-6].

### Pathogenesis of metabolic changes and pro-inflammatory state

Hp, previously named *Campylobacter pylori*, is a Gram-negative, microaerophilic bacterium found in the stomach and sometimes can be present in other parts of the body. It was identified and linked to peptic ulcers in 1982 by Australian scientists Barry Marshall and Robin Warren for which in 2005 they were awarded the Nobel Prize in Physiology or Medicine.

There are several mechanism how Hp can affect a host organism. Firstly, the presence of Hp in the body affects the organism by its molecular factors. The most widely studied are proteins cytotoxin associated gene A (CagA) and vacuolating cytotoxin A (VacA), which have been implicated in perturbing host immunological responses [7, 8].

VacA causes a wide variety of disturbances in host cell biology including cell vacuolation, autophagy, inhibition of T-cell proliferation, and induction of programmed necrosis. Secondly, the bacteria itself provokes the host organism to synthesize multiple immune factor such as interleukin (IL)-1 $\beta$ , IL-6, tumor necrosis factor (TNF)- $\alpha$ , transforming grow factor (TGF)- $\beta$ 1, IL-17, IL-18, IL-21 and IL-22 which are involved in gastric mucosal inflammation and general systemic pro-inflammatory state. The systemic pro-inflammatory state is a concept that is present in multiple inflammatory diseases and its presence affects all the systems in the organism [9]. After Hp eradication some of the inflammatory markers tend to lower to their normal levels [10].

Hp also affects iron, foliate, cobalamin (vitamin B-12) metabolism and antioxidant status another path that is linked to multiple target organs and systems [11].

The activation of the immune system also elevated levels of leptin (also known as "hunger hormone"), insulin and peptide YY [12].

Metabolic and inflammatory markers were evaluated in db/db mice and mice with diet-induced obesity experimentally infected with isogenic forms of Hp. Hp infected mice showed a decreased fasting blood glucose level, increased levels of leptin, improved glucose tolerance, and suppressed weight gain. This was associated with the upregulation of gene expression of gastric peroxisome proliferator-activated receptors (PPAR)  $\gamma$ -responsive genes in Hp-infected mice. On the other hand the loss of PPAR  $\gamma$  in immune and epithelial cells in mice impaired the ability of Hp to

favorably modulate glucose homeostasis provoking opposite results [13].

Current data demonstrate that Glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP) were significantly lower in mice with Hp when measured at 8- and 16-weeks post-colonization. However, the increase of GIP in germ free mice was not statistically significant. Thus Hp down-regulated the expression of host GLP-1 or accelerates the degradation of incretins (a class of neuropeptides that represent insulin secretion stimulators) [12]. Both of the peptides are implicated in adequate glucose metabolism by the cells.

Another possible explanation how Hp infection results in affects glucose metabolism, insulin tolerance and hyperinsulinemia is that Hp infection impairs insulin signaling in hepatocytes. HP infection could upregulate suppressor of cytokine signaling 3 (SOCS3) which is an insulin signaling inhibitor [14].

Thus the exact mechanism how Hp causes T2DM is not clear but multiple mechanisms are implicated in this process and probably each of them separately contributes to the development of T2DM (Figure 1).

#### Metabolic changes in Hp with T2DM

Multiple animal and human studies were performed over the years in order to understand the links between Hp and T2DM [15-17].

In one of the studies the data of 782 individuals aged >60 years and diabetes-free in 1998-1999, whose blood was tested for antibodies to multiple infection agents among which was Hp were followed until 2008 showed that those who were seropositive for Hp at enrollment were 2.7 times more likely at any given time to develop diabetes than seronegative individuals [18].

Recent data show that the presence of Hp infection significantly correlated with the level of glycalated haemoglobin (HbA1C) and the level of HbA1C after Hp eradication tends to improve [19]. Other studies show that six weeks after the end of eradication therapy, the mean fasting insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR), triglycerides (TG), light density lipoprotein C (LDL-C), and C-reactive peptide (CRP) levels in patients with successful eradication were significantly decreased from the pretreatment levels and high density lipoprotein C (HDL-C) level was significantly increased from the pretreatment levels. The mean fasting insulin, HOMA-IR, total cholesterol (TC), TG, LDL-C, CRP levels and HDL-C levels in patients with unsuccessful eradication were not significantly changed from pretreatment levels [20]. Other studies also showed positive lipid profile changes and inflammatory marker decrease [21].

Body mass index (BMI) was also higher in patients with Hp, but and a high BMI is also associated with an increased risk of the infection [22]. Besides that higher BMI potentiates impaired glucose tolerance in adults [23]. It is early to say if BMI can be affected by Hp seopositivity but the latest data show that this is possible [24].

In a study that involved 2070 participants HP infection was significantly associated with high levels of HbA1c and T2DM in participants above 65 years old and decreased insulin secretion and sensitivity in those under 45 years. Proper screening for Hp infection combined with regular monitoring of blood glucose and HbA1c levels might be effective for the early detection of glucose dysregulation and prevention of T2DM [25].

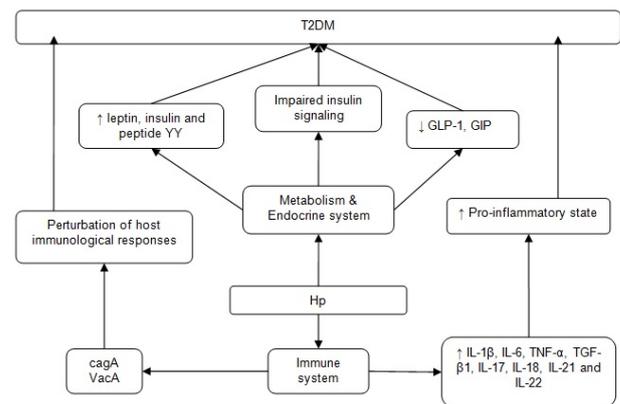


Figure 1. Possible mechanisms that are involved in T2DM development

An analysis performed on 5889 subjects showed that metabolic syndrome was more strongly associated with histologic positivity for Hp than serologic positivity, after adjusting for age, sex, smoking status, alcohol consumption, and economic status. This suggests that the effects of Hp infection on the pathogenesis of cardiometabolic outcomes may be reversible [26].

Thus current data shows that Hp eradication may improve insulin resistance, atherogenic lipid abnormalities and low-grade inflammation thus preventing coronary artery disease and metabolic syndrome which not always can be accomplished effectively [27]. In a study that involved 211 diabetic patients admitted to the endocrinology clinic data showed that T2DM patients with Hp require higher levels of serum insulin to reach the same degree of glycemic control compared to the patients with T2DM and no Hp [28].

The treatment with metformin in T2DM patients with Hp infection demonstrated more gastrointestinal side effects such as abdominal pain, nausea, bloating, and anorexia than those without Hp infection after taking metformin, 44.6% versus 21.8% [29].

Another problem that should be addressed carefully is that the eradication rate of Hp in T2DM patients is lower [30, 31].

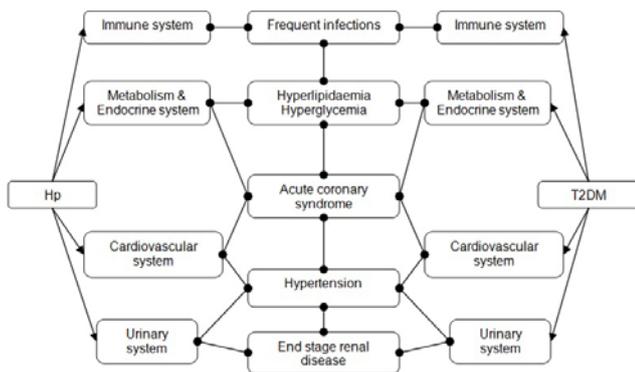
Still the links between T2DM and Hp are not always found and there are also opposite results. A meta-analytic approach showed insufficient evidence that Hp infection worsens glycemic control in patients with diabetes [32]. Other studies describe different results that Hp infection was not a risk factor for abnormal glucose tolerance, nor plays a major role in insulin resistance or beta cell dysfunction [33]. A 72 subjects study which involved 55 males, 17 females; aged 63.7 years with T2DM who received eradication therapy for Hp didn't show any improvement of HbA1C 3 months after treatment [34]. Some authors suggest that the current trend is toward more frequent Hp infections in T2DM but more randomized controlled trials should be done in the future to determine the exact results [35].

Several cross sectional studies on Hp and T2DM showed different results depending on the population, age group and method (Table 1).

**Table 1. Several cross-sectional studies on Hp and T2DM**

Number of patients	Results	References
30,810 subjects middle-age and old-age	Hp infection was associated with higher risk of T2DM after adjustment for other confounders. The association was significant among women, those who were above 65 years old, not overweight or obese, and those who did not smoke, did not consume alcohol and without family history of diabetes. However, there was no interaction between Hp infection and other traditional risk factors on T2DM risk. Subjects with Hp infection had a lower level of HDL, cholesterol and higher levels of blood pressure, total cholesterol, HbA1c and fasting blood glucose than those who did not.	[36]
3,578 subjects (18-64 years old)	Hp participants had significantly higher BMI, fasting glucose, low-density lipoprotein, and triglycerides, and lower high-density lipoprotein than uninfected ones. The prevalence of metabolic syndrome was higher in Hp positive patients than Hp negative. The association between metabolic syndrome and Hp positivity was significant in females, but only borderline significant in males.	[37]
1,300 subjects older than 60 years	Hp infection was not associated with BMI, serum glucose and lipid profile as well as blood pressure.	[38]
211 T2DM patients and 218 patients without T2DM	The prevalence of Hp infection was 55.8% in T2DM and 44.2% in nonT2DM. Insulin resistance was significantly higher in T2DM Hp positive patients.	[39]
80 T2DM patients and 60 nonT2DM	The prevalence of Hp infection was 77.5% among T2DM patients and 58.3% from control patients without T2DM. Presence of Hp infection significantly correlated with the level of HbA1C in Hp positive and in Hp negative patients.	[40]

BMI, body mass index; HbA1c, glycalated haemoglobin; HDL, high density lipoprotein; Hp, Helicobacter pylori; T2DM, type 2 diabetes mellitus.



**Figure 2. An overlap in Hp infection and T2DM**

### HP and T2DM complications

T2DM is a disease that is often accompanied with different complications. Still it is presumed that patients who at the same time are Hp positive have a higher risk for developing several of them. Among the complications that can be present in T2DM more often seen in T2DM patients with Hp were muscular (47.2%), gastrointestinal (29.8%), chronic bronchitis (22.4%), nausea (19.9%), anemia (18%), abdominal pain (12.4%), diarrhea (10.6%) and vomiting (7.5%) (41). Many of the pathologies associated with T2DM overlap with Hp probably increasing the risk for associated pathologies (Figure 2).

The results of a meta-analysis suggest a possible relationship between Hp and the risk of nephropathy and neuropathy [42]. Hp seropositivity is independently associated with microalbuminuria, and the prevalence of Hp seropositivity is associated with the severity of urinary albumin to creatinine ratio in diabetic subjects [43]. The frequency of microalbuminuria and fasting glucose levels among patients with T2DM were significantly reduced in the Hp negative group after eradication treatment [44].

A retrospective cohort study in which the Hp-infected cohort comprised 20,068 patients and each participant was frequency-matched by age and sex with 4 individuals from the general

population without Hp-infection demonstrated that the incidence of end stage renal disease (ESRD) was 3.72 times greater in the Hp-infected cohort than in the non-infected cohort. The risk of ESRD markedly increased in patients with Hp infection combined with at least one of the following comorbidities: hypertension, diabetes, hyperlipidaemia and coronary artery disease [45].

Another study where 17,075 Hp positive patients were matched randomly with 68,300 participants for the comparison group of Hp negative controls matched by age, sex, and index year from the general population. The Hp positive patients exhibited a 1.93-fold high crude hazard ratio for acute coronary syndrome, and a 1.48-fold adjusted hazard ratio after age, sex, and comorbidities were adjusted. However, the overall adjusted hazard ratio of acute coronary syndrome increased with increasing age with a 3.11 to 8.24 adjusted hazard ratio among the various age groups. Several comorbidities, such as diabetes, hyperlipidemia, and chronic obstructive pulmonary disease exhibited synergistic effects for acute coronary syndrome risk [46].

There is data that presence of Hp in the organism also elevates the risk for other comorbidities such as obstructive pulmonary disease, idiopathic pulmonary fibrosis, gestational diabetes, etc. [4-6].

### Conclusion

Hp is an infectious disease that is associated with gastric pathologies such as gastric ulcers and gastric cancer. Still the current evidence also links its presence with T2DM. Several possible conclusions can be made based on the current data:

1. The presence of Hp infection significantly correlated with the level of HbA1C and the level of HbA1C after Hp eradication tends to improve along with the decrease of inflammatory markers.
2. Changes in the immune system it can be a risk factor for T2DM. It is hard to say for now rather Hp provokes T2DM or do patients who have T2DM are more susceptible to infections among which is Hp.
3. Eradication of HP in patients with T2DM may have a beneficial effect on their health thus it should be considered

by practicing healthcare providers to better compensate their patients and prevent several complications that may be associated with Hp positivity.

Further studies in this area may prove or disprove the this theory but until then patients who have Hp should be evaluated and closely monitored for prevention of metanolic changes.

**Conflict of interest:** none declared.

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