Review Article

The Interaction of *Helicobacter pylori* Infection and Type 2 Diabetes Mellitus

Abstract

Helicobacter pylori is one of the most common human pathogens that can cause gastrointestinal (GI) disorders, including simple gastritis, gastric ulcer, and malignant gastritis. In some cases, such as immunodeficiency and underlying diseases, it can be problematic as opportunistic infections. Diabetes mellitus (type 2) (T2DM) is one of the *H. pylori* underlying diseases. Since GI problems are observed in diabetic patients, it is necessary to treat *H. pylori* infection. In this review, we aimed to evaluate the possible relationship between *H. pylori* and T2DM according to epidemiological surveys of 70 studies retrieved from databases, including Scopus, PubMed, and Google Scholar about the relationship between *H. pylori* and T2DM, and discuss the reported background mechanisms of this correlation. According to the results of our study, the different studies have shown that *H. pylori* is more prevalent in Type 2 diabetic patients than healthy individuals or nondiabetic patients. The reason is development of *H. pylori* infection-induced inflammation and production of inflammatory cytokines as well as different hormonal imbalance by this bacterium, which are associated with diabetes mellitus. On the other hand, by tracing anti-*H. pylori* antibodies in patients with diabetes mellitus and occurrence of symptoms such as digestive problems in >75% of these patients, it can be concluded that there is a relationship between this bacterium and T2DM. Considering the evidence, it is crucially important that the probability of infection with *H. pylori* is evaluated in patients with T2DM so that medical process of the patient is followed with higher cautious.

Keywords: *Diabetes, diabetes mellitus, Helicobacter pylori, Type 2 diabetes*

Seyed Abolfazl Hosseininasab Nodoushan, Amin Nabavi[1]

From the Departments of Microbiology and [1]Biochemistry, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Introduction

In 1983, Warren (a biologist) and Marshall (a clinician) described *Helicobacter pylori*.[1] First, they named the bacterium *Campylobacter pyloridis*, and then, it was named *Campylobacter pylori*. Diagnosis and treatment of the upper gastroduodenal disease have been changed dramatically since 20 years ago that *H. pylori* was cultured for the first time.[2-4] Peptic ulcer disease is now approached as an infectious disease.[5] The role of *H. pylori* infection is increasingly recognized in gastric cancers as well as evaluating its role in other gastrointestinal (GI) diseases.[6]

Elevated antibodies level against *H. pylori* also attracted the attention to some extra-gastric diseases, including diabetes mellitus.[7,8]

Among the patients referring to diabetes clinics, as many as 75% of them will report significant GI symptoms.[9,10] The entire GI tract can be affected by diabetes from the oral cavity and esophagus to the large bowel and anorectal region. Thus, the experienced symptom complex may be vary widely.[11] The common complaints can include dysphagia, early satiety, reflux, constipation, abdominal pain, nausea, vomiting, and diarrhea. Many patients remain undiagnosed and undertreated because the GI tract has not been conventionally associated with diabetes and its complications.[12]

Type 2 diabetes mellitus (T2DM) is turning to be pandemic so that it is responsible for death of 3.8 million of the adult population in the world and regarded as a serious risk for public health.[13,14] Increasing blood sugar, which is chronically observed in the patients with diabetes, may cause long-term damage to different organs, especially eyes, kidney, nervous system, heart, and blood vessels. At least 80% of the patients with diabetes will die due to consequences of cardiac complications.[14-16]

Address for correspondence:
Mr. Seyed Abolfazl Hosseininasab Nodoushan, Department of Microbiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: majidhoseini1001@yahoo.com

Pathogenic mechanisms of diabetes mellitus include insulin resistance (IR), chronic inflammation, insufficiency of insulin secretion (due to impaired pancreatic beta-cells), glucose toxicity, and lipotoxicity.[14]

Relationship between *Helicobacter pylori* and Type 2 Diabetes Mellitus

Evidence indicates that diabetes may accompany by *H. pylori* infection, which chronic and insulin-resistant inflammation may increase the risk for T2DM. In addition, gastritis resulting from *H. pylori* may potentially affect gut-related hormones and inflammatory cytokines.[14,17]

Although there is no strong evidence for this relationship, some reasons can be considered to discuss it, which are summarized in the following:

First, diabetes causes impairment in the function of the cellular and humoral immunity, which also increases the individual's sensitivity to *H. pylori* infection.[18] Second, it reduces GI movements and secretion of gastric acid, which in turn increases colonization and bacterial infections.[19] Third, changes in glucose metabolism may alter chemical production in the gastric mucosa, which results in colonization of more bacteria.[20] Ultimately, diabetic patients are more likely to be exposed to pathogens than healthy people, due to their more presence in the hospital environment.[21]

There is controversy about the link between *H. pylori* infection and diabetes as some studies indicate a higher prevalence of infection in diabetic patients,[22-24] whereas in the others, no difference has been reported.[25-27] Jeon *et al*. have been reported for the first time that *H. pylori* infection leads to increase the incidence of T2DM using a prospective cohort of 782 Latino individuals older than 60 years.[19] This study showed that people with *H. pylori* infection would more suffer from diabetes in comparison to healthy individuals.

It is found that 84.6% of diabetic patients with *H. pylori* infection had diabetics for >10 years. Besides the glycemic control, diabetes duration is the main risk factor of increasing the risk of chronic diabetes-related complications, which its importance in our study is the autonomic neuropathy and gastropathy that are critical predictors for *H. pylori* infection in diabetics.[12,28]

Bayati *et al*. in a study concluded that 61.5% of those with *H pylori*-positive status had one or more of the chronic diabetic complications. This finding is in agreement with the findings of a study indicating that diabetic patients with a history of retinopathy, nephropathy, or neuropathy should be presupposed to have GI abnormalities until proven otherwise.[29]

Role of Inflammatory Cytokines

At the initial phases of infection, polymorphonuclear cells penetrate into GI mucus. After a while, these cells are replaced by mononuclear cells at chronic phase of infection. Mononuclear cells are specified by the production of inflammatory cytokines, which in addition to local effect can be effective also as released on other tissues and organs. It causes increase in the extraintestinal diseases in people with *H. pylori* infection, such as cardiovascular, neurological, autoimmune, thyroid, liver, and biliary diseases.[30] Therefore, the bacteria cause to develop inflammation and production of different cytokines and impairment in absorption of nutrients and medicines and can lead to the induction and development of various diseases.[31-35] In a study by Zojaji *et al*. on 85 patients referring to a endocrinology clinic of Shahid Beheshti University of Medical Sciences in Tehran, Iran, it concluded that the most important produced inflammatory cytokines include C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), which contribute to IR and diabetes incidence.[36-41] High levels of CRP (high-sensitive CRP [hsCRP]) are important determinants in diabetes-related research so that the most papers reported strong relationship between CRP level and diabetes risk. Various studies introduced this factor as the connection between *H. pylori* and Type 2 diabetes; as of 11 prospective studies, seven reported a significant positive association between hsCRP levels and diabetes risk[30,42-48] while it found no association in the others.[49-52] Various studies have identified this factor as a bridge between *H. pylori* and Type 2 diabetes as El Hadidy *et al*. reported a significant increase in CRP level and *H. pylori* infection among Type 2 diabetic patients as well as Oshima *et al*. found a significant increase in CRP level in nonsmoker healthy individuals seropositive for *H. pylori* infection. Markus *et al*. found significant association between CRP and *H. pylori* seropositivity.[30,37,53]

A study by Aydemir *et al*. showed higher homeostatic model assessment-estimated IR scores in *H. pylori*-positive individuals.[54] Furthermore, a Japanese study in 2009 conducted on a large population of 1107 asymptomatic individuals showed that *H. pylori* was significantly and independently related to IR.[55] However, Gillum supported that there are no consistent associations between *H. pylori* infection and prevalence of diabetes or syndrome-related variables of the IR in American men of 40–74 years.[56] Furthermore, Park *et al*. reported that metabolic and inflammatory parameters, including blood sugar, lipid profiles, IR, white blood cell count, and CRP levels, were not changed after *H. pylori* eradication. It is worth noting that *H. pylori* infection was not determined in all studies by organisms' histologic detection of mucosal biopsy specimens, which is considered the diagnostic gold standard.[14,57]

Role of Hormones

Helicobacter by induction of gastritis is potentially able to influence the secretion of hormones, such as leptin, ghrelin,

gastrin, and somatostatin, and subsequently increases the diabetes risk. Gastrin increases insulin secretion and somatostatin leads to reduction. *Helicobacter* causes to increase gastrin concentration and lower serum somatostatin concentration through influencing these hormones and thus affects insulin secretion.[58-60]

Reduced insulin secretion is one of the major factors in the incidence of Type 2 diabetes. In the studies by So *et al.*, it indicated that *H. pylori* interdependently can predict dysfunction of pancreatic beta-cells in Chinese males.[61]

In addition, Rahman *et al.* found a positive relationship between *H. pylori* infection and defective insulin secretion so that insulin molecules are highly susceptible to damage from oxidative stress and inflammation. Hence, *Helicobacter* inflammation probably causes defection in insulin production.[62]

In addition, in the study by Hsieh *et al.*, it reported that patients infected *by H. pylori*, especially at young ages are defective in insulin secretion, which is considered as a risk factor for Type 2 diabetes.[63] In addition, Gen *et al.* proved that elimination of pylori infection considerably reduces insulin level.[64]

Ghrelin causes reduction of energy consumption and increasing the weight, whereas leptin reduces food absorption, on the one hand, and increases energy consumption, on the other hand.[60,65]

It has been shown that *H. pylori* infection impairs ghrelin production and enhances leptin production.[66-68] Low ghrelin levels are associated with elevated fasting insulin concentrations, IR, and T2DM.[69] Leptin has also been implicated in IR development, and elevated levels correlate with IR in lean men and patients with T2DM[70-72] [Figure 1].

Insulin resistance and abnormal insulin secretion are central to the development of Type 2 diabetes mellitus. On the one hand, *Helicobacter pylori* infection brings about chronic low-grade inflammation with upregulation of several cytokines such as C-reactive protein, tumor necrosis factor, and interleukin-1β, which may impact insulin action and pancreatic β-cell secretion. On the other hand, Helicobacter pylori-induced gastritis can potentially affect gastric hormones secretion, including leptin, ghrelin, gastrin, and somatostatin, which could affect insulin sensitivity and glucose homeostasis. In addition, other mechanisms and mediators may be involved in the possible causative relationship between *Helicobacter pylori* infection and Type 2 diabetes mellitus.[73,74]

Helicobacteria Can also Be Associated with Other Diseases due to Type 2 Diabetes

Diabetic patients are at risk of cardiovascular and thrombo-occlusive cerebral diseases. There is a possible correlation between *H. pylori* infection and cardiovascular or cerebrovascular diseases. Chronic *H. pylori* colonization may be in association with an increased risk of atherosclerosis. It is hypothesized that *H. pylori* infection has atherogenic capacities by activating chronic low grade of homeostasis cascade.[73-75] The association between *H. pylori* and acute cerebrovascular disease may be due to a higher prevalence of virulent *H. pylori* strains in atherosclerotic stroke patients.[76]

El Hadidy *et al.* also found a significant increase in fibrinogen level as one of the risk factors of atherosclerosis in *H. pylori*-positive diabetic patients in comparison to negative patients.[30] The same results were found by Schumacher *et al.* in patients with coronary heart disease.[77] Zito *et al.* reported the increased level of plasma fibrinogen in *H. pylori*-infected patients even after controlling of possible related confounding factors either infection or fibrinogen.[78]

Conclusions

In this regard by studying various studies, we can conclude that:
1. *H. pylori* infection is more common in diabetic patients
2. There is higher frequency of *H. pylori* infection among elderly diabetics
3. *H. pylori* infection enhances the presence of chronic diabetic complications in its different categories
4. There is no significant difference in male-to-female ratio distribution of *H. pylori* infection.

However, as already mentioned, there are opposite results in this regard, though diabetes mellitus is a multifaceted and multistep disease that is improbably resulted from a single cause, as the risk factors that deserve attention include GI infections and the intestinal microbiota composition. Evidence supporting an etiological role of *H. pylori* in T2DM developing would indicate that preventive measures, such as improving hygiene and treatments using
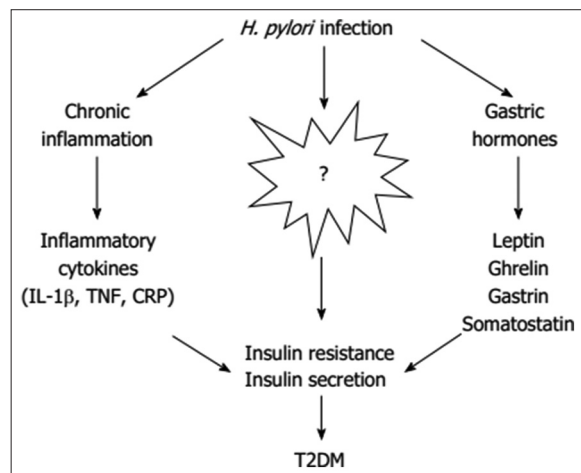

Figure 1: Potential mechanisms for *Helicobacter pylori* contribution to Type 2 diabetes mellitus

antibiotics and proton-pump inhibitor combinations, should be explored as the target of interventions in high-risk communities.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311-5.
2. Papamichael KX, Papaioannou G, Karga H, Roussos A, Mantzaris GJ. *Helicobacter pylori* infection and endocrine disorders: Is there a link? World J Gastroenterol 2009;15:2701-7.
3. Suerbaum S, Michetti P. *Helicobacter pylori* infection. N Engl J Med 2002;347:1175-86.
4. Khademi F, Faghri J, Poursina F, Esfahani BN, Moghim S, Fazeli H, *et al.* Resistance pattern of *Helicobacter pylori* strains to clarithromycin, metronidazole, and amoxicillin in Isfahan, Iran. J Res Med Sci 2013;18:1056-60.
5. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet 2009;374:1449-61.
6. Hosseini E, Poursina F, de Wiele TV, Safaei HG, Adibi P. *Helicobacter pylori* in Iran: A systematic review on the association of genotypes and gastroduodenal diseases. J Res Med Sci 2012;17:280-92.
7. Feldman R. Epidemiologic observations and open questions about disease and infection caused by *Helicobacter pylori*. In: Achtman M, Serbaum S, editors. *Helicobacter pylori*: Molecular and Cellular Biology. Uk: Horizon Scientific, 2001:29-51.
8. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of *Helicobacter pylori* infection. Gut 1994;35:742-5.
9. Frenck RW Jr., Clemens J. Helicobacter in the developing world. Microbes Infect 2003;5:705-13.
10. Granquist A, Bredberg A, Sveger T, Axelsson I. A longitudinal cohort study on the prevalence of *Helicobacter pylori* antibodies in Swedish children and adolescents. Acta Paediatr 2002;91:636-40.
11. Rajashekhar V, Bhasin DK, Ray P, Vaiphei K, Sharma BC, Singh K, *et al. Helicobacter pylori* infection in chronic smokers with non ulcer dyspepsia. Trop Gastroenterol 2000;21:71-2.
12. Bakka AS, Salih BA. Prevalence of *Helicobacter pylori* infection in asymptomatic subjects in Libya. Diagn Microbiol Infect Dis 2002;43:265-8.
13. van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: An emerging pandemic. Eur J Cardiovasc Prev Rehabil 2010;17 Suppl 1:S3-8.
14. He C, Yang Z, Lu NH. *Helicobacter pylori* infection and diabetes: Is it a myth or fact? World J Gastroenterol 2014;20:4607-17.
15. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: A systematic review and meta-analysis. Int J Epidemiol 2011;40:804-18.
16. Qi L, Hu FB, Hu G. Genes, environment, and interactions in prevention of Type 2 diabetes: A focus on physical activity and lifestyle changes. Curr Mol Med 2008;8:519-32.
17. Chen Y, Blaser MJ. Association between gastric *Helicobacter pylori* colonization and glycated hemoglobin levels. J Infect Dis 2012;205:1195-202.
18. Borody T, Ren Z, Pang G, Clancy R. Impaired host immunity contributes to *Helicobacter pylori* eradication failure. Am J Gastroenterol 2002;97:3032-7.
19. Jeon CY, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, *et al. Helicobacter pylori* infection is associated with an increased rate of diabetes. Diabetes Care 2012;35:520-5.
20. de Luis DA, de la Calle H, Roy G, de Argila CM, Valdezate S, Canton R, *et al. Helicobacter pylori* infection and insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 1998;39:143-6.
21. Gentile S, Turco S, Oliviero B, Torella R. The role of autonomic neuropathy as a risk factor of *Helicobacter pylori* infection in dyspeptic patients with Type 2 diabetes mellitus. Diabetes Res Clin Pract 1998;42:41-8.
22. 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;30:22-6.
23. Bener A, Micallef R, Afifi M, Derbala M, Al-Mulla HM, Usmani MA, *et al.* Association between Type 2 diabetes mellitus and *Helicobacter pylori* infection. Turk J Gastroenterol 2007;18:225-9.
24. Gulcelik NE, Kaya E, Demirbas B, Culha C, Koc G, Ozkaya M, *et al. Helicobacter pylori* prevalence in diabetic patients and its relationship with dyspepsia and autonomic neuropathy. J Endocrinol Invest 2005;28:214-7.
25. Anastasios R, Goritsas C, Papamihail C, Trigidou R, Garzonis P, Ferti A, *et al. Helicobacter pylori* infection in diabetic patients: Prevalence and endoscopic findings. Eur J Intern Med 2002;13:376.
26. Ko GT, Chan FK, Chan WB, Sung JJ, Tsoi CL, To KF, *et al. Helicobacter pylori* infection in Chinese subjects with Type 2 diabetes. Endocr Res 2001;27:171-7.
27. Stanciu OG, Trifan A, Sfarti C, Cojocariu C, Stanciu C. *Helicobacter pylori* infection in patients with diabetes mellitus. Rev Med Chir Soc Med Nat Iasi 2003;107:59-65.
28. Parsonnet J, Shmuely H, Haggerty T. Fecal and oral shedding of *Helicobacter pylori* from healthy infected adults. JAMA 1999;282:2240-5.
29. Kozák R, Juhász E, Horvát G, Harcsa E, Lövei L, Sike R, *et al. Helicobacter pylori* infection in diabetic patients. Orv Hetil 1999;140:993-5.
30. El Hadidy M, Abdul-Aziz MY, Mokhtar AR, El Ata MM, El Gwad SS. *Helicobacter pylori* infection and vascular complications in patients with Type 2 diabetes mellitus. J Taibah Univ Med Sci 2009;4:62-72.
31. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.
32. Fernández-Real JM, López-Bermejo A, Vendrell J, Ferri MJ, Recasens M, Ricart W, *et al.* Burden of infection and insulin resistance in healthy middle-aged men. Diabetes Care 2006;29:1058-64.
33. Howard BV, Best L, Comuzzie A, Ebbesson SO, Epstein SE, Fabsitz RR, *et al.* C-reactive protein, insulin resistance, and metabolic syndrome in a population with a high burden of subclinical infection: Insights from the genetics of coronary artery disease in Alaska natives (GOCADAN) study. Diabetes Care 2008;31:2312-4.
34. Misiewicz JJ. Current insights in the pathogenesis of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1995;7:701-3.

35. Mishra RR, Tewari M, Shukla HS. Association of *Helicobacter pylori* infection with inflammatory cytokine expression in patients with gallbladder cancer. Indian J Gastroenterol 2013;32:232-5.

36. Diomedi M, Stanzione P, Sallustio F, Leone G, Renna A, Misaggi G, *et al.* Cytotoxin-associated gene-A-positive *Helicobacter pylori* strains infection increases the risk of recurrent atherosclerotic stroke. Helicobacter 2008;13:525-31.

37. Oshima T, Ozono R, Yano Y, Oishi Y, Teragawa H, Higashi Y, *et al.* Association of *Helicobacter pylori* infection with systemic inflammation and endothelial dysfunction in healthy male subjects. J Am Coll Cardiol 2005;45:1219-22.

38. Jackson L, Britton J, Lewis SA, McKeever TM, Atherton J, Fullerton D, *et al.* A population-based epidemiologic study of *Helicobacter pylori* infection and its association with systemic inflammation. Helicobacter 2009;14:108-13.

39. Hamed SA, Amine NF, Galal GM, Helal SR, Tag El-Din LM, Shawky OA, *et al.* Vascular risks and complications in diabetes mellitus: The role of *Helicobacter pylori* infection. J Stroke Cerebrovasc Dis 2008;17:86-94.

40. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005;115:1111-9.

41. Zojaji H, Ataei E, Sherafat SJ, Ghobakhlou M, Fatemi SR. The effect of the treatment of *Helicobacter pylori* infection on the glycemic control in Type 2 diabetes mellitus. Gastroenterol Hepatol Bed Bench 2013;6:36-40.

42. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing Type 2 diabetes mellitus. JAMA 2001;286:327-34.

43. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, *et al.* The relation of markers of inflammation to the development of glucose disorders in the elderly: The cardiovascular health study. Diabetes 2001;50:2384-9.

44. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, *et al.* Low-grade systemic inflammation and the development of Type 2 diabetes: The atherosclerosis risk in communities study. Diabetes 2003;52:1799-805.

45. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, *et al.* C-reactive protein is an independent predictor of risk for the development of diabetes in the west of Scotland coronary prevention study. Diabetes 2002;51:1596-600.

46. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing Type 2 diabetes in women. Diabetes 2004;53:693-700.

47. Thorand B, Löwel H, Schneider A, Kolb H, Meisinger C, Fröhlich M, *et al.* C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: Results from the MONICA Augsburg Cohort Study, 1984-1998. Arch Intern Med 2003;163:93-9.

48. Laaksonen DE, Niskanen L, Nyyssönen K, Punnonen K, Tuomainen TP, Valkonen VP, *et al.* C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. Diabetologia 2004;47:1403-10.

49. Festa A, D'Agostino R Jr., Tracy RP, Haffner SM; Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of Type 2 diabetes: The insulin resistance atherosclerosis study. Diabetes 2002;51:1131-7.

50. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM, *et al.* Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City diabetes study. Diabetes Care 2002;25:2016-21.

51. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y, *et al.* Inflammatory markers, adiponectin, and risk of Type 2 diabetes in the Pima Indian. Diabetes Care 2003;26:1745-51.

52. Snijder MB, Dekker JM, Visser M, Stehouwer CD, Yudkin JS, Bouter LM, *et al.* Prospective relation of C-reactive protein with Type 2 diabetes: Response to Han *et al.* Diabetes Care 2003;26:1656-7.

53. Markus HS, Risley P, Mendall MA, Steinmetz H, Sitzer M. *Helicobacter pylori* infection, the cytotoxin gene A strain, and carotid artery intima-media thickness. J Cardiovasc Risk 2002;9:1-6.

54. Aydemir S, Bayraktaroglu T, Sert M, Sokmen C, Atmaca H, Mungan G, *et al.* The effect of *Helicobacter pylori* on insulin resistance. Dig Dis Sci 2005;50:2090-3.

55. Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, *et al. Helicobacter pylori* infection significantly increases insulin resistance in the asymptomatic Japanese population. Helicobacter 2009;14:144-50.

56. Gillum RF. Infection with *Helicobacter pylori*, coronary heart disease, cardiovascular risk factors, and systemic inflammation: The third national health and nutrition examination survey. J Natl Med Assoc 2004;96:1470-6.

57. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, *et al. Helicobacter pylori* eradication has no effect on metabolic and inflammatory parameters. J Natl Med Assoc 2005;97:508-13.

58. Jeffery PL, McGuckin MA, Linden SK. Endocrine impact of *Helicobacter pylori*: Focus on ghrelin and ghrelin o-acyltransferase. World J Gastroenterol 2011;17:1249-60.

59. Roper J, Francois F, Shue PL, Mourad MS, Pei Z, Olivares de Perez AZ, *et al.* Leptin and ghrelin in relation to *Helicobacter pylori* status in adult males. J Clin Endocrinol Metab 2008;93:2350-7.

60. Kaneko H, Konagaya T, Kusugami K. *Helicobacter pylori* and gut hormones. J Gastroenterol 2002;37:77-86.

61. So WY, Tong PC, Ko GT, Ma RC, Ozaki R, Kong AP, *et al.* Low plasma adiponectin level, white blood cell count and *Helicobacter pylori* titre independently predict abnormal pancreatic beta-cell function. Diabetes Res Clin Pract 2009;86:89-95.

62. Rahman MA, Cope MB, Sarker SA, Garvey WT, Chaudhury HS, Khaled MA, *et al. Helicobacter pylori* infection and inflammation: Implication for the pathophysiology of diabetes and coronary heart disease in Asian Indians. J Life Sci 2009;1:45-50.

63. Hsieh MC, Wang SS, Hsieh YT, Kuo FC, Soon MS, Wu DC, *et al. Helicobacter pylori* infection associated with high HbA1c and Type 2 diabetes. Eur J Clin Invest 2013;43:949-56.

64. Gen R, Demir M, Ataseven H. Effect of *Helicobacter pylori* eradication on insulin resistance, serum lipids and low-grade inflammation. South Med J 2010;103:190-6.

65. Calam J. *Helicobacter pylori* modulation of gastric acid. Yale J Biol Med 1999;72:195-202.

66. Osawa H, Nakazato M, Date Y, Kita H, Ohnishi H, Ueno H, *et al.* Impaired production of gastric ghrelin in chronic gastritis associated with *Helicobacter pylori*. J Clin Endocrinol Metab 2005;90:10-6.

67. Osawa H. Ghrelin and *Helicobacter pylori* infection. World J Gastroenterol 2008;14:6327-33.

68. Nishi Y, Isomoto H, Uotani S, Wen CY, Shikuwa S, Ohnita K, *et al.* Enhanced production of leptin in gastric fundic mucosa with *Helicobacter pylori* infection. World J Gastroenterol 2005;11:695-9.

69. Pöykkö SM, Kellokoski E, Hörkkö S, Kauma H, Kesäniemi YA, Ukkola O, *et al.* Low plasma ghrelin is associated with insulin

resistance, hypertension, and the prevalence of Type 2 diabetes. Diabetes 2003;52:2546-53.

70. Cohen B, Novick D, Rubinstein M. Modulation of insulin activities by leptin. Science 1996;274:1185-8.

71. Segal KR, Landt M, Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. Diabetes 1996;45:988-91.

72. Fischer S, Hanefeld M, Haffner SM, Fusch C, Schwanebeck U, Köhler C, *et al.* Insulin-resistant patients with Type 2 diabetes mellitus have higher serum leptin levels independently of body fat mass. Acta Diabetol 2002;39:105-10.

73. de Luis DA, Garcia Avello A, Lasuncion MA, Aller R, Martin de Argila C, Boixeda de Miquel D, *et al.* Improvement in lipid and haemostasis patterns after *Helicobacter pylori* infection eradication in Type 1 diabetic patients. Clin Nutr 1999;18:227-31.

74. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, *et al.* Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses.

BMJ 2000;321:199-204.

75. Sawayama Y, Ariyama I, Hamada M, Otaguro S, Machi T, Taira Y, *et al.* Association between chronic *Helicobacter pylori* infection and acute ischemic stroke: Fukuoka harasanshin atherosclerosis trial (FHAT). Atherosclerosis 2005;178:303-9.

76. Pietroiusti A, Diomedi M, Silvestrini M, Cupini LM, Luzzi I, Gomez-Miguel MJ, *et al.* Cytotoxin-associated gene-A – Positive *Helicobacter pylori* strains are associated with atherosclerotic stroke. Circulation 2002;106:580-4.

77. Schumacher A, Seljeflot I, Lerkerød AB, Sommervoll L, Otterstad JE, Arnesen H, *et al.* Positive chlamydia pneumoniae serology is associated with elevated levels of tumor necrosis factor alpha in patients with coronary heart disease. Atherosclerosis 2002;164:153-60.

78. Zito F, Di Castelnuovo A, D'Orazio A, Negrini R, De Lucia D, Donati MB, *et al. Helicobacter pylori* infection and the risk of myocardial infarction: Role of fibrinogen and its genetic control. Thromb Haemost 1999;82:14-8.

To,
The Editor

Submission of Manuscript for publication

Dear Sir,

We intend to publish an article entitled

_____

in your journal.
On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward.

Prior presentation of the data reported in this manuscript:

Organisation
Place
Date

We have done sufficient work in the field to justify authorship for this manuscript.

We hereby transfer, assign, or otherwise convey all copyright ownership, including any and all rights incidental thereto, exclusively to the journal, in the event that such work is published by the journal.

Thank you,
Yours' sincerely,

Name of corresponding contributor

Signature

Title of the manuscript:

Type of manuscript:
Running title:
Contributors:

	First name	Middle name initial	Last name	Highest academic degree	Names of departments and institutions (including city and state)	Email addresses
1						
2						
3						
4						
5						
6						

Corresponding Author:
Name:
Address:
Phone numbers:
Facsimile numbers:
E-mail address:

Total number of pages:
Total number of tables:
Total number of figures:
Total number of supplementary files:
Word counts: For abstract: For the text:

Contribution details (to be ticked marked as applicable):   Contributors' form

	Contributor 1	Contributor 2	Contributor 3	Contributor 4	Contributor 5	Contributor 6
Concepts						
Design						
Definition of intellectual content						
Literature search						
Clinical studies						
Experimental studies						
Data acquisition						
Data analysis						
Statistical analysis						
Manuscript preparation						
Manuscript editing						
Manuscript review						
Guarantor						