Potential role of *Helicobacter pylori* infection in nonalcoholic fatty liver disease

Meng Li, Zhe Shen, You-Ming Li

**Abstract**

Accumulating evidence has implicated *Helicobacter pylori* (*H. pylori*) infection in extragastrointestinal diseases, including obesity, type 2 diabetes mellitus, cardiovascular disease, and liver disease. Recently, there has been a special focus on *H. pylori* infection as a risk factor for the development of nonalcoholic fatty liver disease (NAFLD). NAFLD is currently considered to be the most common liver disorder in western countries, and is rapidly becoming a serious threat to public health. The mechanisms of pathogenesis underlying NAFLD remain unclear at present and therapeutic options are limited. The growing awareness of the role of *H. pylori* in NAFLD is thus important to aid the development of novel intervention and prevention strategies, because the eradication of *H. pylori* is easy and much less expensive than long-term treatment of the other risk factors. *H. pylori* infection is involved in the pathogenesis of insulin resistance (IR), which is closely linked with NAFLD. It provides a new insight into the pathogenesis of NAFLD. This review probes the possible relationship between *H. pylori* and NAFLD, from the perspective of the potential mechanism of how *H. pylori* infection brings about IR and other aspects concerning this correlation.

**Key words:** Helicobacter pylori; Nonalcoholic fatty liver disease; Insulin resistance; Inflammation; Cytokines

**Core tip:** A growing body of evidence suggests that *Helicobacter pylori* (*H. pylori*) infection is linked with nonalcoholic fatty liver disease (NAFLD). There are some potential pathogenic mediators and mechanisms involved in this progress, including fetuin-A, tumor necrosis factor-α and adiponectin. Long-term *H. pylori* infection may cause insulin resistance and inflammation, contributing to NAFLD. *H. pylori* toxins in the portal circulation arising from the gastroduodenal area may be another intriguing point, which might be related to the increased intestinal permeability in patients with NAFLD. It is hoped that eradication of *H. pylori* will provide a new treatment strategy for NAFLD.
including chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. This persistent infection elicits a chronic inflammatory and immune response, inducing both local and remote lesions. The interaction of the host with H. pylori can have profound systemic effects. A growing body of evidence has implicated H. pylori infection in extragastrointestinal diseases such as cardiovascular, liver and biliary diseases. The possible causative role of H. pylori infection in these diseases is intriguing. The contribution of H. pylori to the development of hepatic encephalopathy and hyperammonemia has been revealed, and the possible correlation of H. pylori with other liver diseases has attracted a lot of attention. Recent reports have emerged on the relationship between H. pylori infection and nonalcoholic fatty liver disease (NAFLD).

In recent years, there has been increased appreciation of the significance of NAFLD, which is currently considered to be the most common liver disorder in western countries, affecting up to 25%-30% of individuals. NAFLD encompasses a range of related disorders. The earliest stage is simple steatosis. It can progress to nonalcoholic steatohepatitis (NASH) with the cardinal features including hepatocyte injury, and inflammation with or without fibrosis. NASH, in turn, may progress to cirrhosis and ultimately liver cancer in some patients. Consequently, NAFLD is rapidly becoming a serious threat to public health. However, the mechanisms of the pathogenesis underlying NAFLD are complex and remain unknown at present.

NAFLD is now regarded as the liver manifestation of the metabolic syndrome (Mets). It is strongly associated with obesity, diabetes, cardiovascular disease (CVD) and dyslipidemia, because they spring from a “common soil”, namely, insulin resistance (IR). A growing body of experimental evidence suggests that NAFLD and IR are closely related.

H. pylori infection is implicated in the pathogenesis of IR, which is important in the development of NAFLD, therefore, investigating the impact of H. pylori infection as a risk factor for IR might have implications in understanding its effect on NAFLD. It is hoped that the eradication of H. pylori can provide a novel strategy for the treatment of NAFLD. This review focuses on the possible relationship between H. pylori and NAFLD; mainly from the perspective of the potential mechanism of how H. pylori infection brings about IR and other aspects concerning this correlation (Figure 1).

EXPERIMENTAL EVIDENCE LINKING H. PYLORI WITH NAFLD

A novel finding in the study of Cindoruk et al. was the presence of 16S rDNA of H. pylori in the liver sample of a 44-year-old woman with NASH. They used polymerase chain reaction-based techniques to amplify 16S rDNA sequences of H. pylori. In that study, 27 of 75 patients with suspected liver disease were diagnosed with NASH. It turned out in one sample that 16S rDNA of H. pylori was detected. This observation suggested that H. pylori play a role in NAFLD.

H. pylori is mainly identified by 16S rDNA sequencing. In bacteria, there are three types of rDNA that are readily identifiable by size: the 120-nucleotide (nt) 5S rDNA, the 1600-nt 16S rDNA, and the 3000-nt 23S rDNA. Researchers have recently tended to use genetic criteria including virulence gene and 16S rDNA sequencing for distinguishing it from other curved Gram-negative rods.

In 2009 another study added credence to this finding, in which Pirouz et al. noticed that patients with various chronic liver diseases (CLDs) had a greater probability of positive H. pylori 16S rDNA compared with the control group. In the 46 liver biopsies from patients with CLD, they detected H. pylori DNA in five of 11 samples from patients who were diagnosed with NAFLD.

CLINICAL EVIDENCE LINKING H. PYLORI WITH NAFLD

Polyzos et al. showed that NAFLD patients had significantly higher anti-H. pylori IgG, insulin, homeostatic model of assessment insulin resistance (HOMA-IR), and tumor necrosis factor (TNF)-α, but less total and high-molecular-weight adiponectin compared to the control group. However, there were no significant differences in steatosis grade, fibrosis stage, lobular or portal inflammation, or ballooning, when NAFLD patients were divided into subgroups according to H. pylori IgG seropositivity or C-urea breath test positivity. This might be a clue that H. pylori infection is strongly linked to the pathogenesis of early-stage NAFLD, which is described as simple steatosis. Yet at the same time, it indicates that H. pylori infection may not contribute to the progression of NASH.

A randomized controlled single-blind study from
Doğan et al. showed that fatty liver was significantly more frequent in *H. pylori*-positive patients. The severity of the fatty appearance assessed by ultrasonography was also higher in the *H. pylori*-positive group. A study conducted in Japan demonstrated that *H. pylori* infection was one of the independent risk factors for the development of NAFLD. These studies had some limitations and further research is warranted with larger, longer-term studies to confirm their findings. It is hard to determine if *H. pylori* is responsible for the natural course of NAFLD, or if it is merely an incidental finding. If this association is confirmed, eradication of *H. pylori* infection may have certain therapeutic perspectives in NAFLD.

**POTENTIAL PATHOGENETIC MEDIATORS AND MECHANISMS**

**IR: a possible bond linking *H. pylori* with NAFLD**

IR is a key pathogenic factor in NASH. It leads to hyperinsulinemia and favors accumulation of free fatty acids (FFAs) in the liver because of decreased mitochondrial β-oxidation, on account that insulin inhibits mitochondrial β-oxidation of fatty acids. Moreover, IR predisposes the liver to oxidative stress by stimulating microsomal lipid peroxidases.

*H. pylori* infection is involved in diverse biological processes, comprising inflammation, metabolism and oncogenic transformation. In view of its effect on metabolic variables, *H. pylori* is associated with IR.

*H. pylori* infection is implicated in the pathogenesis of obesity and type 2 diabetes mellitus (T2DM), which are closely related to MetS. IR is thought to be the underlying mechanism for MetS. However, so far, only limited clinical data directly suggest that *H. pylori* infection is involved in the development of NAFLD. Polyzos et al. showed that the contribution of *H. pylori* to NAFLD might be achieved indirectly through increasing IR, or directly, given that it can predict NAFLD independently from IR. Inspired by this hypothesis, studies investigating the relationship between *H. pylori* infection and IR would be of importance to infer the mechanism of how *H. pylori* induce NAFLD. A few studies have explored the possible link between *H. pylori* infection and IR. Besides, research on the influence of eradication therapy on IR and other metabolic parameters has been conducted. However, results are controversial, and whether *H. pylori* infection plays a role in IR remains to be determined. Assessed by HOMA-IR, existing data indicate a potential association between *H. pylori* infection and IR. HOMA-IR, which derives from fasting insulin and glucose levels, is the most common method for assessment of IR in clinical practice and epidemiological studies. Using this method, a high HOMA-IR score denotes low insulin sensitivity. In 2011, Polyzos et al. performed a systematic review, summarizing the evidence for the association between *H. pylori* infection and quantitative indexes of IR. Summary data indicate a potential association between *H. pylori* infection and IR.

Eshraghian et al. showed that HOMA-IR score was significantly higher in the *H. pylori*-positive group compared with the negative group. They suggest that *H. pylori* infection is a risk factor for IR. However, Naja et al. have suggested no association of *H. pylori* infection with IR or MetS. They take the view that eradication of *H. pylori* infection to prevent IR or MetS is not warranted.

We must take into consideration that most of the studies that investigated the association between *H. pylori* and IR or MetS were small and did not adjust for potential confounders. Many of them did not control for the bacterial strain type or the host genetic factors. Due to the limited quantity and quality of these studies, more high-quality, multicenter, large-scale randomized controlled trials are required to clarify the association between *H. pylori* infection and IR development. A positive link between *H. pylori* infection and IR could have certain therapeutic prospects.

**A peculiar intermediary: fetuin-A: *H. pylori* infection has been proposed in an attempt to elucidate the multifaceted aspects of the pathogenesis of IR. However, the pathogenetic link between *H. pylori* infection and IR is not fully understood as yet.**

Among the various factors capable of inducing IR and subsequent IR syndrome, fetuin-A is peculiar because it is a glycoprotein that is produced exclusively in the liver and then secreted into the circulation in high concentrations. Previous studies have shown that fetuin-A is closely related to IR, and it has been linked with impaired insulin sensitivity, glucose metabolism, and the onset of diabetes mellitus.

Recent studies have investigated whether the *H. pylori*-induced IR is mediated through fetuin-A. In the study of Kebapcilar et al., fetuin-A level significantly decreases in *H. pylori*-infected patients when compared to control subjects. Moreover, *H. pylori* eradication reduces the levels of proinflammatory cytokines such as migration inhibitory factor and high-sensitivity C-reactive protein (CRP), with a significant increase in fetuin-A. They regarded fetuin-A as a potential anti-inflammatory cytokine, on the basis of the theory that anti-inflammatory cytokines produced during inflammation tend to modulate the inflammatory reaction. However, the findings of Manolakis et al. were the opposite. They noted that *H. pylori*-infected individuals showed higher levels of fetuin-A, insulin and HOMA-IR than controls. In addition, there was a positive correlation between fetuin-A and HOMA-IR. This has interesting therapeutic implications because it suggests that *H. pylori* eradication might decrease IR. This observation coincides with the results of Ou et al., who showed that fetuin-A is considered to be a key proinflammatory mediator that plays a pivotal role in inflammatory and immune diseases. They suggest that elevated fetuin-A level has clinical implications in NAFLD and impaired glucose tolerance, which are features of IR.

Fetuin-A is an endogenous inhibitor of insulin receptor tyrosine kinase in the liver and skeletal muscle. Srini-
vas et al have revealed that fetuin-A specifically inhibits insulin-stimulated insulin receptor autophosphorylation in vitro and in vivo, as well as exogenous substrate tyrosine phosphorylation. Moreover, they have demonstrated that fetuin-A influences insulin signaling by inhibiting insulin-induced tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and insulin-dependent mitogenesis. The glucose-regulatory effects derived from insulin are predominantly exerted in three tissues consisting of liver, muscle and fat. Thus, when IR occurs, the liver can be the point of attack. Based on the theory that fetuin-A inhibits insulin signaling in hepatocytes, it is reasonable to assume that the elevated fetuin-A in patients with NAFLD may contribute to the deteriorated hepatic IR.

Although the mechanism underlying fetuin-A-mediated IR remains elusive, it is a novel concept that fetuin-A may represent a promising index for assessing the H. pylori-related contributions to IR and MetS. If this particular association is confirmed, fetuin-A could be a potential target for therapy of IR and IR-related disorders, including T2DM, CVD and NAFLD.

Chronic inflammation, cytokines and adipokines: Helicobacter spp. are strong inducers of proinflammatory cytokines. Long-standing H. pylori infection induces inflammation by stimulating excessive release of proinflammatory cytokines and vasoactive substances, such as interleukin (IL)-6, IL-8, IL-1β and TNF-α. H. pylori-positive individuals exhibit elevated levels of these proinflammatory cytokines.

A growing body of evidence supports that inflammation is involved in the pathogenesis of IR and IR-related disorders. Festa et al have suggested that low-grade inflammation is a risk factor for the development of T2DM. Several studies indicate that chronic subclinical inflammation is associated with CVD.

Hotamisligil et al and Feinstein et al have demonstrated that TNF-α is able to induce IR. Therefore, we reckon that TNF-α may be a key mediator of both direct and indirect effects of H. pylori infection on NAFLD.

TNF-α interferes with insulin signaling, thereby favoring steatosis, and may play a proinflammatory role in the pathogenesis of NASH. On the one hand, TNF-α promotes Ser phosphorylation of IRS-1, resulting in a net decrease in insulin-receptor-mediated signaling. On the other hand, TNF-α can inhibit the autophosphorylation of insulin receptor or tyrosyl phosphorylation of IRS-1. In addition, TNF-α downregulates the expression of key genes in adipose cells such as GLUT4, resulting in decreased glucose transport. Besides, TNF-α is capable of accelerating lipolysis, leading to an increase in FFAs, which can cause detrimental effects in hepatocytes, including oxidative stress, induction of endoplasmic reticulum stress and subsequent expression of proinflammatory cytokines. TNF-α promotes and is activated by IR via activation of IKK-β, which is a central coordinator of inflammatory responses through activation of nuclear factor (NF-κB).

kB is a proinflammatory “master switch” that regulates inflammatory mediators including CRP, plasminogen activator inhibitor, TNF-α, IL-6 and IL-1β.

Lower adiponectin level was observed in H. pylori-positive patients with NAFLD in the study of Polyzos et al. This finding gives us a new clue that adiponectin may play a part in the process of H. pylori-induced NAFLD. Adiponectin, the adipocyte-derived hormone, is implicated in the pathogenesis of IR and NASH. Low serum adiponectin levels in NAFLD patients are suggestive of advanced hepatic fibrosis. Adiponectin exerts several anti-inflammatory effects, including inhibition of NF-κB activation and suppression of macrophage function. Adiponectin and TNF-α are mutually antagonizing adipokines. In contrast to TNF-α, adiponectin has an antilipogenic effect. Thus, when adiponectin is decreased, its effects of controlling FFA entry and oxidation in the mitochondria are subsequently weakened, allowing FFAs to accumulate in the cytoplasm.

Lipid metabolism

Inflammation, IR and aberrant lipid metabolism may be interlinked components of the MetS. Abnormalities of serum lipid concentrations are common in patients with NASH. It is acknowledged that hypertriglyceridemia is involved in the pathogenesis of NASH. Each of the steps involved in hepatic lipid accumulation is altered in NAFLD, although to a different extent. Sato et al have shown that H. pylori infection is a significant and independent risk factor for a modified lipid profile, including high low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C) in Japanese men, whereas these associations are not significant in women. Kebapcilar et al demonstrated that H. pylori infection is significantly associated with lower HDL-C, but they showed that eradication of H. pylori had no effect on the lipid profile. Akbas et al reported that there was no significant difference in serum HDL-C, LDL-C, or total cholesterol between H. pylori-seropositive and H. pylori-seronegative individuals, whereas serum triglyceride level was higher in the H. pylori-positive group.

Increased intestinal permeability, H. pylori toxins and cross-reactive antibody response

H. pylori is thought to have deleterious consequences on the hepatobiliary tract because the biliary epithelium can easily be colonized by bacteria from the duodenum. The human gastrointestinal tract is an ecosystem integrated by microbiota. The mucosal epithelium of the small intestine is the barrier between the microbiota and gut lumen. It is reported that increased intestinal permeability and small intestinal bacterial overgrowth (SIBO), may reflect qualitative and quantitative changes in the microbiota, leading to disruption of the intestinal barrier, subsequent bacterial translocation, and development of portal endotoxemia. As a result, lipopolysaccharide, which is produced by Gram-negative bacteria, is increased in the portal circulation and accompanied by increased levels of...
endotoxin-mediated cytokines in the liver. Bacterial translocation occurs due to impaired barrier function[^9], and bacterial constituents enhance hepatic inflammation and fibrosis[^9]. Miele *et al.*[^10] found that in NAFLD patients, increased gut permeability and the prevalence of SIBO correlated with the severity of steatosis but not with the presence of NASH.

In light of the above considerations, we speculate that the liver may be damaged by *H. pylori* toxins and constituents circulating in the blood coming out from the gastroduodenal area. And it is probably linked with the increased intestinal permeability in patients with NAFLD. Abenavoli *et al.*[^10] reported a case of a 36-year-old woman with diagnosis of celiac disease (CD), primary biliary cirrhosis (PBC) and *H. pylori* infection. They found that strict adherence to a gluten-free diet, associated with ursodeoxycholic acid administration and eradication of *H. pylori* infection, led to a marked histological and serological improvement of PBC. *Helicobacter* spp. are implicated in the pathogenesis of PBC, because microbial DNA is found in liver tissue and bacterial antibodies in the serum of patients with PBC[^9][^10], which is characterized by the presence of antimitochondrial antibodies directed predominantly against the E2 subunit of the pyruvate dehydrogenase complex[^9]. They indicated that increased permeability to intraluminal antigens could induce an immune response against antigens sharing common epitopes to self-liver proteins and/or against cryptic antigens unmasked by the reaction with gliadin. Their study supports the pathogenetic role of increased intestinal permeability in the course of CD and *H. pylori* infection to induce PBC. However, this concept remains obscure. More studies are needed to clarify the reality of this association.

**CONCLUSION AND OUTLOOK**

NAFLD affects both adults and children who present with particular risk factors, including obesity, sedentary lifestyle and/or a predisposing genetic background[^9]. In some individuals it can progress to cirrhosis, or even hepatocellular carcinoma. Treatment strategies ranging from simple lifestyle modifications to pharmacological agents and even invasive surgical procedures[^10] have been investigated as potential treatments for NAFLD. However, at present, it is regrettable that there is no one ideal therapy suitable for all patients[^10]. Thus, new treatment strategies are important to halt the progression of NAFLD.

IR assumes importance in the pathogenesis of NAFLD progression[^10]. Recent studies, largely on the possible contribution of *H. pylori* to IR, provide new insights into the link between *H. pylori* and NAFLD. Eradication of *H. pylori* is easy and relatively inexpensive, therefore, the interest in exploring its involvement in extrahepatic diseases is of importance for public health. Thus, understanding the pathogenetic role of *H. pylori* in NAFLD is important for devising new specific management strategies.

The clinical data regarding *H. pylori* infection in NAFLD are limited, thus, it is premature to advocate intervention measures in patients with NAFLD. However, once this particular association is confirmed, it could drastically change our understanding of pathophysiology and treatment of NAFLD. Therefore, further studies are warranted to verify such associations before the strategy can be recommended in routine clinical practice.

**REFERENCES**

1. Dunn BE, Cohen H, Blaser MJ. Helicobacter pylori. *Clin Microbiol Rev* 1997; 10: 720-741 [PMID: 9336670]
2. Wu MS, Lee WJ, Wang HH, Huang SP, Lin JT. A case-control study of association of Helicobacter pylori infection with morbid obesity in Taiwan. *Arch Intern Med* 2005; 165: 1552-1555 [PMID: 16098973 DOI: 10.1001/archinte.165.13.1552]
3. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. *Clin Microbiol Rev* 2006; 19: 449-490 [PMID: 16847081]
4. Banatvala N, Mayo K, Megraud F, Jennings R, Deeks JJ, Feldman RA. The cohort effect and Helicobacter pylori. *J Infect Dis* 1993; 168: 219-221 [PMID: 8515114]
5. Amieva MR, El-Omar EM. Host-bacterial interactions in Helicobacter pylori infection. *Gastroenterology* 2008; 134: 306-323 [PMID: 18166359 DOI: 10.1053/j.gastro.2007.11.009]
6. Trinchieri G. Cancer and inflammation: an old intuition with rapidly evolving new concepts. *Ann Rev Immunol* 2012; 30: 677-706 [PMID: 22224761 DOI: 10.1146/annurev-immunol-020711-075008]
7. Takuma Y. Helicobacter pylori infection and liver diseases. *Gan To Kagaku Ryoho* 2011; 38: 362-364 [PMID: 21403438]
8. Pellicano R, Ménard A, Rizzetto M, Megraud F. Helicobacter pylori species and liver diseases: association or causation? *Lancet Infect Dis* 2008; 8: 254-260 [PMID: 18355266 DOI: 10.1016/s1473-3099(08)7006-5]
9. Pellicano R, Fagonee S, Rizzetto M, Ponzetto A. Helicobacter pylori and chronic heart disease: which directions for future studies? *Crit Rev Microbiol* 2003; 29: 351-359 [PMID: 14636044 DOI: 10.1080/713608015]
10. Abdel-Hady H, Zaki A, Badra G, Lotty M, Selmi C, Giorgini A, El-Sayed M, Badr R. Helicobacter pylori infection in hepatic encephalopathy: Relationship to plasma endotoxins and blood ammonia. *Hepatol Res* 2007; 37: 1026-1033 [PMID: 17610507 DOI: 10.1111/j.1872-034X.2007.00146.x]
11. Esmat G, El-Bendary M, Zakarya S, Ela MA, Zalata K. Role of Helicobacter pylori in patients with HCV-related chronic hepatitis and cirrhosis with or without hepatocellular carcinoma: possible association with disease progression. *J Viral Hepat* 2012; 19: 473-479 [PMID: 22676359 DOI: 10.1111/j.1365-2893.2011.01567.x]
12. de Alwis NM, Day CP. Non-alcoholic fatty liver disease: the mist gradually clears. *J Hepatol* 2008; 48 Suppl 1: S104-S112 [PMID: 18304679 DOI: 10.1016/j.jhep.2008.01.009]
13. Bhala N, Jouness RI, Bugianesi E. Epidemiology and natural history of patients with NAFLD. *Curr Pharm Des* 2013; 19: 5169-5176 [PMID: 2394091]
14. Bellantoni S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis* 2010; 28: 155-161 [PMID: 20469005 DOI: 10.1159/000282880]
15. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science* 2011; 332: 1519-1523 [PMID: 21708065]
16. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999; 94: 2467-2474 [PMID: 10484010]
17. Tiniakos DG, Vos MB, Brunt EM. Nonalcoholic fatty liver disease.
Helicobacter pylori persistence: biology and disease. J Clin Invest 2004; 113: 321-333 [PMID: 14755296 DOI: 10.1172/jci20925]

Huang FY, Chan AO, Rashid A, Wong DK, Cho CH, Yuen MF. Helicobacter pylori induces promoter methylation of E-cadherin via interleukin-1β activation of nitric oxide production in gastric cancer cells. Cancer 2012; 118: 4969-4980 [PMID: 22415887]

Arslan E, Attilan H, Yavasgozlu I. The prevalence of Helicobacter pylori infection in obese subjects. Eur J Intern Med 2009; 20: 695-697 [PMID: 19818289 DOI: 10.1016/j.ejim.2009.07.013]

Vaara O, Yki-Jarvinen H. Diabetes: Should we treat infection or inflammation to prevent T2DM? Nat Rev Endocrinol 2012; 8: 323-325 [PMID: 22430880]

Leon CY, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, Aiello AE. Helicobacter pylori infection is associated with an increased rate of diabetes. Diabetes Care 2012; 35: 520-525 [PMID: 22729028 DOI: 10.2373/dci11-1043]

Eshraghian A, Pellicano R. Comment on: Jeon et al. Helicobacter pylori infection is associated with an increased rate of diabetes. Diabetes Care 2012; 35: 520-525. Diabetes Care 2013; 36: e20 [PMID: 23264304 DOI: 10.2337/dci12-0570]

Kantartzis K, Machann J, Schick F, Fritsche A, Häring HU, Stefan N. The impact of liver fat vs visceral fat in determining categories of prediabetes. Diabetologia 2010; 53: 882-889 [PMID: 20090957 DOI: 10.1007/s00125-010-1663-6]

Bonora E, Targher G, Alberti G, Bonadonna RC, Saggiani F, Zennere MB, Monauini T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000; 23: 57-63 [PMID: 10857969]

Eshraghian A, Hashemi SA, Hamidjan Jahromi A, Eshraghian H, Masoompour SM, Davarpanah MA, Eshraghian K, Taghavi SA. Helicobacter pylori infection as a risk factor for insulin resistance. Dis Gez Sozial Med 2009; 54: 1966-1970 [PMID: 19099348 DOI: 10.1007/s00125-008-0557-7]

Naja F, Nasreddine L, Hwaalla N, Moghames P, Shoaih B, Fatfat M, Sibaï A, Gali-Muhtasib H. Association of H. pylori infection with insulin resistance and metabolic syndrome among Lebanese adults. Helicobacter 2012; 17: 444-451 [PMID: 22068475 DOI: 10.1111/j.1120-799X.2012.00970.x]

Denecke B, Gräber S, Schäfer C, Heiss A, Wölfe M, Jahn-Duchent W. Tissue distribution and activity testing suggest a similar but not identical function of fetuin-B and fetuin-A. Biochim Biophys Acta 2003; 1651: 135-145 [PMID: 12943536 DOI: 10.1016/j.bbcan.20030676]

Pal D, Dasgupta S, Kundu R, Maitra S, Das G, Mukhopadhyay S, Ray S, Majumdar SS, Bhattacharya S. Fetuin-A acts as an endogenous ligand of TLIR4 to promote lipid-induced insulin resistance. Nat Med 2012; 18: 1279-1285 [PMID: 22824477]

Srinivas PR, Wagner AS, Reddy LV, Deutsch DD, Leon MA, Gousten AS, Grunberger G. Serum alpha 2-HS-glycoprotein is an inhibitor of the human insulin receptor at the tyrosine kinase level. Mutat Res 1993; 35: 145-145 [PMID: 7906861]

Ishibashi A, Ikeda Y, Ogihara T, Kuma Y, Yamanaka S, Takata H, Inoue M, Suehiro T, Terada Y. Serum fetuin-A is an independent marker of insulin resistance in Japanese
