COMMENTS AND RESPONSES

Comment on: Jeon et al. *Helicobacter pylori* Infection Is Associated With an Increased Rate of Diabetes. Diabetes Care 2012;35:520–525

Jeon et al. (1) stated that infectious agents might have an impact on cardiovascular disease (CVD) and metabolic syndrome, potentially mediated by increased inflammatory markers, including C-reactive protein (CRP) and interleukin (IL)-6. However, epidemiological studies investigating the impact of pathogen burden on diabetes have been limited; cross-sectional studies examining systemic pathogens and insulin resistance (IR) or prevalent diabetes have produced equivocal findings, and *Helicobacter pylori* infection (*Hp*-I) shows no association with IR or prevalent diabetes.

We previously conducted a systematic review summarizing the epidemiological evidence regarding the association between *Hp*-I and IR quantitative-only indices (2). A positive association between *Hp*-I and homeostasis model assessment of insulin resistance (HOMA-IR), used to quantify IR in all nine selected studies, appears to exist. More specifically, when the study groups were divided according to *Hp* status (negative or positive), higher HOMA-IR was found in all but one study (2).

The authors (1) reported that individuals who developed diabetes had a higher HOMA-IR, but not IL-6 and CRP, than those who did not develop diabetes; however, the association between *Hp*-I and diabetes incidence remained significant after adjustment for HOMA-IR, IL-6, and CRP, indicating that *Hp*-I may affect diabetes independently of these factors. Nevertheless, glucose, insulin, CRP, and IL-6 were measured at baseline and not when each individual was diagnosed with diabetes. HOMA-IR, IL-6, and CRP might have been significantly higher when the diagnosis of diabetes was established than in the baseline assessment, and *Hp*-I might not have been associated with diabetes independently of these factors.

Hp-I may influence the pathophysiology of IR and IR syndrome, including diabetes, through several possible mechanisms (2,3): *1*) *Hp*-I releases large amounts of proinflammatory and vasoactive substances, such as cytokines (IL-1, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor [TNF]-α, interferon-γ), eicosanoids (leukotrienes, prostaglandins), and acute-phase proteins (CRP, fibrinogen). Fibrinogen appears to be significantly higher in diabetic patients with CVD, and our and others' series (2) demonstrate that increased fibrinogen levels are associated with *Hp*-I and can be significantly reduced by *Hp* eradication. *2*) *Hp*-I promotes platelet activation and aggregation and increases various proatherogenic factors including homocysteine, a risk factor for type 2 diabetes, obesity, and CVD. *3*) *Hp*-I produces reactive oxygen species and increases circulating concentrations of lipid peroxides, also associated with diabetes and CVD. *4*) Finally, *Hp*-I influences the apoptotic process. *Hp* could indirectly affect the pancreas and other target organs, e.g., the heart, through the release of numerous cytokines, such as TNF-α, acting at a distance (TNF-α–mediated β-cell dysfunction and apoptotic destruction in human islets) (4,5). Besides, *Hp* vacuolating cytotoxin stimulates apoptosis via a mitochondria-dependent pathway (5) and downregulation of antiapoptotic Bcl-2, upregulation of proapoptotic Bax, and increased activation of caspase-9 and -3 also indicate that apoptosis in patients with diabetes occurs via an intrinsic mitochondrial pathway.

However, further studies are needed to elucidate in depth the role of the aforementioned parameters in the pathophysiology of IR/diabetes-related disorders and the potential treatments of diabetes inferred from the *Hp*-related pathophysiology.

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