LETTER TO THE EDITOR

The potentially dual-faceted nature of fetuin-A in *Helicobacter pylori* infection and insulin resistance

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We read with interest the study by Kebapcilar et al.[1] on the effect of *Helicobacter pylori* (*HP*) eradication on serum fetuin-A concentrations. Specifically, baseline serum fetuin-A was lower in *HP*-positive participants than in *HP*-negative matched participants. Furthermore, fetuin-A levels significantly increased after successful *HP* eradication treatment.[1] To our knowledge, this is the first report on the effect of *HP* eradication on serum fetuin-A.

Recently, Manolakis et al. proposed serum fetuin-A as a mediator linking *HP* infection and insulin resistance (IR).[2] This is also an interesting concept with therapeutic potential because it suggests that *HP* eradication might decrease IR and IR-related morbidity, including type II diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD),[3] although the effect on CVD is highly debatable.[4] We have recently performed a systematic review on the association between *HP* infection and IR.[5] Existing data indicate a potential association between *HP* infection and IR, as assessed by homeostatic model assessment IR (HOMA-IR). However, although histology is considered the gold standard diagnostic test for *HP*, some studies used other methods to determine *HP* status. The serum anti-*HP*-specific IgG antibody level may be of diagnostic value, but it does not discriminate between past and current infections. Furthermore, given that serum remains positive for anti-*HP*-specific IgG even after eradication of *HP*, it is unclear whether *HP* infection is the inducer or the promoter of IR.[5]

However, in the study by Manolakis et al., baseline fetuin-A was higher in *HP*-positive participants than in *HP*-negative participants.[2] The reason for this discrepancy between the two studies[1,2] is largely unknown. Both studies recruited non-diabetic patients with dyspeptic symptoms, and their exclusion criteria were similar. However, the mean age and BMI of the *HP*-positive group were higher in the Manolakis et al. study[2] than in the Kebapcilar et al. study[1] (57.3 ± 16.1 versus 29.1 ± 7.5 years and 25.8 ± 12.7 versus 22.9 ± 4.5 kg/m^2, respectively, after converting SEM to SD in the first study), and these two differences could have affected IR. There were also ethnic differences, which might have affected IR and possibly serum fetuin-A. Finally, in the two studies, serum fetuin-A was measured by different commercial ELISA kits.

Fetuin-A is an acute-phase glycoprotein synthesized and secreted almost exclusively by the liver that plays a role in bone mineralization and insulin-signaling regulation.[6] Fetuin-A binds a form of insoluble calcium phosphate, inhibiting pathological extraosseous calcification and thereby playing a protective role in the evolution of arterial calcification. However, when dysregulated, fetuin-A can lead to ectopic calcification of soft tissues in the vasculature, thereby contributing to atherosclerosis. Likewise, by binding the extracellular portion of the β-subunit of the insulin receptor, fetuin-A inhibits insulin-receptor tyrosine kinase, thereby attenuating, under normal conditions, excessive insulin signaling. However, when dysregulated, fetuin-A results in excessive inhibition of insulin signaling in the liver and in skeletal muscle, thereby triggering IR. Subsequently, increased serum fetuin-A has been associated with IR-related morbidity, including T2DM, visceral obesity, NAFLD, CVD and ischemic stroke.[6,7] Fetuin-A also seems to play a role in inflammation by downregulating the pro-inflammatory cytokines produced by macrophages.[1] Fetuin-A is regarded as an anti-inflammatory mediator that contributes to macrophage deactivation, and moreover, it possesses anti-fibrotic activity and inhibits apoptosis in vascular smooth muscle cells. Nonetheless, fetuin-A downregulates adiponectin, an anti-inflammatory and insulin-sensitizing adipokine. Finally, although fetuin-A induces lipid accumulation in the liver, it may attenuate hepatic fibrosis by modifying the effects of transforming growth factor-β signaling in hepatocytes.[7] Summarizing all the above-mentioned data, fetuin-A may possess a dual-faceted nature in the metabolic and inflammatory milieu. It may be protective by inhibiting extraosseous calcification or excessive insulin signaling in lean, metabolically healthy individuals, but, in other situations, it may also be harmful, especially if its action is persistently elevated and prolonged. This dual-faceted nature may also apply to most cytokines and adipocytokines.[8]

In the Kebapcilar et al. study,[1] serum fetuin-A was low in young, *HP*-positive individuals with a negative history of diabetes, obesity and known cardiovascular risk factors. Furthermore, successful *HP* eradication was associated with a fetuin-A increase and a simultaneous decrease in both C-reactive protein and macrophage migration inhibitory factor. This result seems rational for this specific population, in whom the counteracting mechanisms, including fetuin-A, are beneficial. In the Manolakis et al. study,[2] serum fetuin-A was increased in non-diabetic, *HP*-positive individuals with established IR, who generally were older and had a higher BMI than the *HP*-positive individuals of the Kebapcilar et al. study.[1] This finding also

seems rational for this specific population, in whom the counteracting mechanisms may no longer be beneficial, and thus fetuin-A may contribute, at least in part, to IR. In conclusion, serum fetuin-A may represent a promising index for assessing the *HP*-related contributions to inflammation, IR and IR-related conditions, including T2DM, NAFLD and CVD; however, further clinical trials are necessary to confirm its diagnostic efficacy.

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