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EDITORIAL

# Is *Helicobacter pylori* a new kid on the block?

## ¿Es el *Helicobacter pylori* un recién llegado?

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It is well known that traditional risk factors for atherosclerosis, such as age, smoking, diabetes mellitus, dyslipidemia, hypertension, and chronic inflammation, only account for approximately 50% of the incidence of atherosclerosis.[1] Therefore, identifying new risks factors that contribute to atherosclerosis development may help to better recognize people with a high cardiovascular risk in the early stages of the disease. *Helicobacter pylori* infection has been recently identified as a potential atherosclerotic risk factor.[2] *H. pylori* is a gram-negative bacterium that colonizes the stomach of approximately half of the world's population. This infection is a major cause of several gastric diseases and it also increases the risk of gastric cancer.[3] However, since this bacterial infection produces not only local inflammation, but also systemic inflammation, *H. pylori* infection has also been linked to many extra-gastrointestinal manifestations, including atherosclerosis.[2] In fact, recent evidence indicate that *H. pylori* infection is involved in the initiation, progression and complication of the atherosclerotic plaque through several mechanisms. Thus, it has been reported that a positive correlation exists between *H. pylori* infection and the increase in carotid intima-media thickness (CIMT).[2] This parameter is obtained by measuring the thickness of the inner and middle layers of the carotid artery and is used as a marker of subclinical and asymptomatic atherosclerotic. In addition, the systemic inflammation caused by chronic *H. pylori* infection may accelerate atherosclerotic plaque formation. Likewise, this bacterial infection can destroy gastric parietal cells, which secrete intrinsic factor, a key factor involved in vitamin $B_{12}$ absorption, ultimately leading to deficiency of this vitamin. As a result of this deficiency, the enzyme methionine synthase is inhibited, causing an increase in homocysteine that promotes atherosclerosis. Finally, *H. pylori* infection may precipitate dyslipidemia and the release of cytoxin-associated gene A (CagA) by *H. pylori*-infected cells promotes foam cell formation.

Although many studies have reported a positive correlation between *H. pylori* infection and atherosclerosis, this correlation remains controversial since some studies do not support it.[4,5] In this issue of Clínica e Investigación en Arteriosclerosis, Baspinar O. et al. address this subject by examining the presence of subclinical atherosclerosis by measuring CIMT in patients without comorbid disease and positive or negative for *H. pylori* infection. In agreement with previous studies,[2,6] the authors observed that CIMT was increased in patients infected with *H. pylori* compared with those not infected, indicating the presence of subclinical atherosclerosis in these patients. Moreover, CIMT increased with the bacterial density in

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endoscopic biopsy material, reinforcing the presence of a positive relationship between *H. pylori* infection and CIMT. The patients infected with *H. pylori* studied did not show dyslipidemia or vitamin $B_{12}$ deficiency, thereby demonstrating that these alterations did not contribute to subclinical atherosclerosis associated with *H. pylori* infection.

Interestingly, the authors of this study also found that patients infected with *H. pylori* exhibited increased levels of growth differentiation factor 15 (GDF-15) and that a significant correlation was found between GDF-15 and CIMT, while no significant correlation was observed between these parameters and other studied atherosclerosis markers. GDF-15 is a stress-induced cytokine with circulating serum GDF-15 levels in healthy subjects ranging from 200 to 1000 pg/mL, but these levels are remarkably elevated under conditions of cellular stress such as in several diseases (especially in cancer, cardiovascular disease, obesity, mitochondrial diseases, and aging).[7] In fact, the presence of increased levels of this cytokine in subjects suffering many of these diseases has led GDF-15 to be considered as a biomarker of these pathologies, being associated with overall mortality. In this line, GDF-15 is a reliable biomarker in patients with stable and acute coronary artery disease.[8] However, GDF-15 has been reported to protect against aging-mediated systemic inflammatory responses[9] and to mediate anti-inflammatory effects in mice with acute myocardial infarction.[10] The finding that serum GDF-15 concentration is positively associated with atherosclerosis, as reported by Baspinar O. et al., agrees with a previous recent study conducted in Japanese individuals aged 60–69 years.[11] The mechanism responsible for this association remains unknown. However, since GDF-15 deficiency attenuates macrophage activity,[12] individuals with higher levels of GDF-15 might have increased macrophage activity. As macrophages play an important role in atherosclerosis development,[13] this could indicate that patients with increased circulating levels of GDF-15 are at higher risk of developing atherosclerosis. In addition, since inflammatory cytokines induce the expression of GDF-15, cytokine release caused by endothelial dysfunction or by *H. pylori* infection could be the mechanism underlying the increase in GDF-15. Further studies are needed to evaluate whether serum GDF-15 concentrations are an earlier marker for subclinical atherosclerosis that could help us to estimate the risk of atherosclerosis.

In conclusion, the study by Baspinar O. et al. provides new evidence supporting that *H. pylori* infection may exacerbate atherosclerosis. However, further studies are needed before establishing its place among classical risk factors of atherosclerosis. If finally confirmed, strategies to eradicate *H. pylori* might contribute to reduce the incidence of atherosclerosis. Moreover, this study also highlights the potential role of GDF-15 as a biomarker for subclinical atherosclerosis that might allow preventive strategies to be instituted early in the disease process. However, the use of GDF-15 as a biomarker might be challenging since GDF-15 is regulated by many factors, including body weight, age, thyroid hormone activity, and drug treatment, among others. Therefore, although promising, additional studies should confirm the potential of GDF-15 as a biomarker for atherosclerosis.

## Conflict of interest

The authors declare that they have no conflict of interest.

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