Nonalcoholic Fatty Liver Disease and Atherosclerosis

To the Editor:

I read with interest the article by Brea et al indicating the strong relationship between nonalcoholic fatty liver disease (NAFLD) and carotid atherosclerosis (as measured by intima-media thickness [IMT] and plaque prevalence) in a sample of predominantly obese and hypertensive subjects.

Notably, they reported substantially similar results to those recently published by our group in a sample of nonobese healthy men, thus further supporting the notion that people with NAFLD are at increased risk of CVD.

However, I partly disagree with the authors’ conclusions suggesting that NAFLD is a strong risk factor for carotid atherosclerosis beyond its association with the metabolic syndrome (MetS).

In both studies, patients with NAFLD had, other than several features resembling MetS, a marked increase in carotid IMT values compared with those without NAFLD. However, in the study by Brea et al the increase in carotid IMT (but not that in the prevalence of carotid plaques) remained statistically significant after adjustment for the presence of MetS (as defined by ATP-III or WHO criteria). On the contrary, in our study the increase in carotid IMT was largely mediated by the extent of visceral fat accumulation, as measured by computed tomography (CT). It is known that WHO and ATP-III definitions of MetS include waist circumference (or waist/hip ratio) among their diagnostic criteria. However, it is also known that waist circumference provides only an indirect and crude estimation of visceral fat, so we cannot be certain that the results of the study by Brea et al completely exclude an effect of visceral adipose tissue.

This could be done by controlling for a more accurate measure of visceral fat obtained by CT or MRI. We have substantiated this showing that carotid IMT remained significantly different between those with and without NAFLD when CT-measured visceral fat was replaced as a covariate by waist circumference.

Overall, therefore, I think there is now greater published evidence to support the possibility that the relationship between NAFLD and carotid atherosclerosis reflects the overall adverse impact of MetS (particularly insulin resistance and increased visceral fat, possibly through its multiple secreted factors, ie, free fatty acids, tumor necrosis factor-alpha, and other adipocytokines) more rather than a direct impact of NAFLD on carotid atherosclerosis. Accordingly, several studies showed a strong association of carotid IMT with abdominal fat distribution and insulin resistance. Moreover, interventional studies reported a beneficial impact of weight loss, known to primarily reduce intra-abdominal fat deposits, on the progression rate of early carotid atherosclerosis in obese individuals. Similarly, a gradual weight loss significantly improved liver-biopsy features and liver-test results in most NAFLD patients, and the results of small pilot trials evaluating metformin and thiazolidinediones, drugs that are effective for insulin resistance, have recently suggested that these medications may be of potential benefit for NAFLD patients.

All of these findings, therefore, strongly support a pivotal role of visceral fat and insulin resistance in the development of atherosclerosis and NAFLD; this further emphasizes the use of aggressive nonpharmacological and pharmacological interventions capable of avoiding abdominal obesity and reducing insulin resistance (ie, lifestyle changes and drugs specifically targeting the MetS phenotype), with the aim of preventing atherosclerotic diseases and improving NAFLD and its potential complications.

Prospective studies are clearly needed to corroborate these cross-sectional findings and better estimate the individual CVD risks associated with the presence of MetS and NAFLD.

Giovanni Targher
Division of Internal Medicine and Diabetes Unit
Ospedale “Sacro Cuore – don G. Calabria”,
Negrar (VR), Italy

respectively; \( P=0.009 \), while showing similar WC measures (86.8±10.6 versus 88.8±11.8 cm, respectively; \( P=0.3 \)) (data not shown in the original article). Recent data from large populations show an association of elevated liver enzymes with C-reactive protein independent of body mass index.\(^8,9\) Given that elevated C-reactive protein levels worsen the cardiovascular prognosis of individuals with the MetS,\(^10\) these findings support our conclusion that the hepatic inflammation characteristic of NAFLD is an important contributor to systemic inflammation and accelerated atherogenesis.

Angel Brea
Lipid Clinic, Internal Medicine Service
Hospital San Millán-San Pedro
Logroño, Spain

Emilio Ros
Lipid Clinic, Endocrinology and Nutrition Service
Institut d’Investigacions Biomediques August Pi Sunyer
Hospital Clínic
Barcelona, Spain


