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LETTER

Endothelial dysfunction and carotid atherosclerosis in non-alcoholic fatty liver disease

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Dear Editor

With great interest we have read the article by Arinc et al. (1). In this study, the relationship of liver enzymes with endothelial dysfunction and carotid atherosclerosis was evaluated in subjects with biopsy-proven non-alcoholic steatohepatitis (NASH). Patients with NASH had impaired flow-mediated dilatation (FMD) and higher carotid intima-media thickness (CIMT) when compared with healthy controls. In addition, serum concentrations of gamma glutamyl transferase (GGT) and alanine amino transferase (ALT) were found to be associated with FMD and CIMT. Consequently, they suggested that serum GGT and ALT concentrations might have a predictive value to demonstrate the presence of endothelial dysfunction and carotid atherosclerosis in subjects with NASH. The major strengths of this study were the use of liver biopsy, which is the gold standard method for the diagnosis of non-alcoholic fatty liver disease (NAFLD), and the use of FMD and CIMT, which are well known and accepted methods to assess endothelial dysfunction and carotid atherosclerosis. However, we would like to share our thoughts and experiences with Arinc et al.

Obesity and NAFLD are both well-known metabolic risk factors for prediabetes and diabetes mellitus (DM) (2). Keeping in mind that both macrovascular and microvascular complications can occur in patients with prediabetes, they should be examined carefully in terms of cardiovascular disease (CVD) risk assessment (3). In the article by Arinc et al., body mass index values were in the range of overweight or obesity in most subjects with NASH. Despite being specified that there were no diabetic subjects with NASH, these data were obtained using only the results of fasting plasma glucose (FPG), and standard oral glucose tolerance tests (OGTT) were not performed. OGTT is currently the gold standard method for the diagnosis of DM. In several studies conducted in patients with NAFLD and no history of DM, it is stated that the use of the measurement of FPG alone is not sufficient to assess glucose tolerance and OGTT is recommended for routine evaluation of this clinically relevant condition (4,5). Moreover, it has been reported that 120-min OGTT results were independent risk factors for advanced stages of liver fibrosis in patients with NAFLD (5).Therefore, we think that the presence of prediabetes should be investigated both in terms of cardiovascular risk management and prognosis of liver disease in patients with NAFLD.

Increased CIMT is associated with cardiovascular risk factors, and also CVD. In addition, CIMT is an important marker in the evaluation of subclinical atherosclerosis and a well-known predictor in the development of cardiovascular events (independent of other cardiovascular risk factors) (6). CIMT levels were reported to be higher in patients with NAFLD compared with healthy controls in many studies, as well as in the study of Arinc et al. In addition, in patients with NASH, CIMT levels were higher than in patients with simple steatosis (SS) and healthy controls. Moreover, there was a relationship between CIMT and the degree of liver damage (independent of the presence of insulin resistance, traditional risk

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factors, and MetS) in some of these studies (7). On the other hand, contrary to these findings, Petit et al. were unable to find any relationship between hepatic steatosis and CIMT in patients with DM (8). This finding also accords with our previous observations, which showed no association between CIMT and histological severity in NAFLD (9).

We consider a number of possible explanations regarding the different reports on the relationship between carotid atherosclerosis and NAFLD. Firstly, most studies that investigate the association of CIMT with NAFLD were performed in subjects with ultrasonographically diagnosed fatty liver. Although there is a well-known correlation with the histological findings of fatty infiltration, liver ultrasonography is not sufficiently sensitive to detect liver inflammation and fibrosis. Secondly, when the above-mentioned studies were analysed separately, it can be seen that some of the patients with NAFLD had metabolic confounders like morbid obesity, DM, and hypertension. In addition, some of these subjects were using medications related to these metabolic problems. It has been reported that CIMT levels may be affected by these metabolic risk factors and also medications (6). Thirdly, it is well known that there is a strong and independent relationship between age and CIMT. Moreover, differences as small as 0.1 mm of CIMT were found in longitudinal studies after 20 years when a combination of adverse risk factors clustered together (10). In light of these data as well as our own findings (9,11), we think that age may be an important determinant for the development of carotid atherosclerosis in NAFLD, and a longer exposure time to fatty liver may be required to develop higher CIMT. Thus, a recent study reported no association between CIMT and NAFLD in children and adolescents (12). Lastly, CIMT may not reflect all components of cardiovascular risk, and other markers of endothelial function such as asymmetric dimethylarginine and flow-mediated dilatation may be more useful indexes of early vascular changes (13). In light of these data, we suggest that NAFLD may have no direct impact on carotid atherosclerosis and it may contribute to CVD by acting in concert with metabolic abnormalities. In agreement with this hypothesis, a recent cross-sectional study found NAFLD to be associated with CIMT only in people with MetS (14).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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