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Non-Alcoholic Fatty Liver Disease, a Marker of Subclinical Atherosclerosis Applicable Only to Metabolic Syndrome?: Time to Organize the Connection between Metabolism and Atherosclerosis

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Non-alcoholic fatty liver disease (NAFLD) is being increasingly detected on routine health screening, especially in Korea and it has been reported to affect up to approximately 20% of the general population in Korea[1] and 30% in Western countries.[2][3] Although generally perceived as benign, it has been shown that the histological and clinical manifestation of NAFLD and alcoholic liver disease share some similar characteristics.[4]

Since the initial reports of the association between NAFLD and various surrogate markers, prevalence and incidence of cardiovascular disease,[5] NAFLD has been generally indicated that it may be a marker of cardiovascular disease. Indeed, abdominal obesity, impaired glucose tolerance and/or insulin resistance, hypertension and dyslipidemia, which are the key diagnostic criteria for metabolic syndrome,[6] are also much prevalent in NAFLD.[7][8] Also, the prevalence of NAFLD sores up to 80% in patients with obesity or diabetes,[9] which suggests that NAFLD may serve as a perfect marker of cardiovascular outcome.

Measurement of carotid intima-media thickness (cIMT) is safe, noninvasive and also, cost-effective, making it a good screening tool and also, a surrogate marker for cardiovascular disease.[10] Furthermore, it can be measured easily and also, when equipped under adequate setting, ready to be used widely in clinical practice. It is a good marker of future cardiovascular events as well.[11] It has been proved in previous reports that increased cIMT may be related to NAFLD, albeit in small population.[12][13]

Therefore, the report by Kang et al.[14] in this issue of the Journal of Cardiovascular Ultrasound is timely and also, expands and somewhat generalizes the above concept that cIMT may serve as a good marker of subclinical atherosclerosis burden not only in patients with metabolic disorders but more importantly, in patients without. The authors recruited 633 non-diabetic, asymptomatic, healthy patients consecutively, a relatively large cohort of patients to definitely prove the suggestions in the previous reports. What the authors mainly found was that cIMT was increased in patients with NAFLD, which is in line with previous reports. Also, patients with NAFLD were more likely to have more risk factors for atherosclerosis, i.e. tended to be older, more obese, have hypertension and/or dyslipidemia.

However, one of the novel and interesting findings of this study is that the association of increased cIMT with NAFLD was relatively independent of the presence/absence of metabolic syndrome. Two previous reports have previously provided a glimpse of an independent relationship between NAFLD and increased cIMT.[12][13] However, the number of patients was too small and more importantly, they have failed to show whether this NAFLD is a mere surrogate marker of metabolic dysregulation leading to carotid atherosclerosis or whether it is an independent predictor.

Although NAFLD is closely associated with metabolic syndrome, its independent relationship with atherosclerosis aggravation has been suggested in various experimental studies both in humans and in animal models.[9] In light of this, there have been reports demonstrating that NAFLD itself may superimpose excessive oxidative stress from increased hepatic free fatty acid oxidation.[15] More importantly, NAFLD have

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been shown to be an independent predictor of most of these inflammatory markers, irrespective of the components of metabolic syndrome.[16-18] The report of Kang et al.[14] confirms these previous findings nicely in a fairly large population, the numbers of which is sufficient for generalization of the previous findings. In addition to this possibility, NAFLD has also been shown to further aggravate lipoprotein dysmetabolism and have depressed protective lipokine secretion, such as adiponectin,[9] all of which are connected to insulin resistance and metabolic derangement.

In spite of the several possible mechanisms directly linking NAFLD with subclinical atherosclerosis, we may now be well aware and be sure of the fact that NAFLD is closely associated and a good marker of subclinical atherosclerosis. Therefore, it seems that the current diagnostic criteria of 'metabolic syndrome' needs a more generalized definition, so as to provide a warning to the medical society and the patients that even those not in a category of 'metabolic syndrome' may, in fact, have metabolic derangement as shown by the high incidence of NAFLD by this report.[14] In this context, it is noteworthy to recognize that the patients without metabolic syndrome in this report tended to be more obese and have higher levels of low-density lipoprotein-cholesterol and triglycerides.[14] Furthermore, a previous report has commented that the prevalence of metabolic syndrome and its relationship with the presence/absence of NAFLD may vary from criterion-to-criterion.[19] Indeed, the current diagnosis of metabolic syndrome is still not unified[20-22] and the basic concepts do differ from each models of definition.

Collectively, this report adds to building up the evidence that NAFLD may be associated with increased cardiovascular morbidity and mortality, independent of classical risk factors and the current diagnosis of metabolic syndrome. Based on the current body of evidence, it suggests that NAFLD patients should be treated on many aspects, not only for aggressive treatment of the liver itself, but aggressive control of underlying cardiovascular risk factors. Furthermore, it is time to think about and organize a more generalized consensus of a more clear definition of 'metabolic syndrome'.

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