

information in mind, the standard 12-week stopping rule can be used, and this will reduce the exposure to antiviral therapy in patients for whom no response would occur.

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Both Insulin Resistance and Alanine Aminotransferase Level Increase the Risks of Cardiovascular Disease in Fatty Liver Disease

To the Editor:

We read with great interest the article by Gastaldelli et al.¹ Their analyses were based on the RISC (relationship between insulin sensitivity and cardiovascular disease risk) Study, an ongoing prospective project aiming to evaluate the possible relation between insulin resistance (IR) and cardiovascular risk in a clinically healthy European Caucasian population, free of diabetes, hypertension, and cardiovascular diseases. The authors also evaluated the associations among fatty liver, IR, carotid intima media thickness (IMT), and risk of coronary heart disease. Although their results provided additional data to this area of active investigation, several issues deserve further discussion.

First, FLI (Fatty Liver Index), an algorithm on the basis of body mass index, waist circumference, triglycerides, and gamma-glutamyl transferase, was used to identify fatty liver.² However, this index was constructed to predict ultrasonographic fatty liver after excluding subjects with hepatitis B virus or hepatitis C virus infection and limited by the inherent flaws of ultrasound, such as operator dependent interpretation, reduced sensitivity in the morbidly obese, and inability to precisely quantify hepatic fat content and detect small amounts of fatty infiltration.³ The index is conceptually insulin-related; however, insulin level is not included in the index because it is not routinely measured.² Therefore, the use of FLI in their analyses cannot avoid the confounding error of insulin resistance. Taken together, their findings may only indicate a significant association between carotid IMT, risks of coronary heart disease, and insulin resistance but not fatty liver. To show an association with fatty liver, the authors should conduct a subgroup analysis with patients who are free of insulin resistance.

Second, alanine aminotransferase (ALT) elevation is an independent predictor of nonalcoholic steatohepatitis,⁴ and ALT level is also independently associated with insulin resistance.⁵ Our recent data further showed that ALT level is proportionally associated with the risk of carotid IMT in subjects with fatty liver.⁶ Although the authors already identified a difference in ALT levels among the three groups, further subgroup analyses to evaluate the effects of ALT level on these associations would be more informative.

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Reply:

Dr. Hsu and colleagues in their letter raised two issues. The first was related to the validity of the fatty liver index (FLI) and its relation-

ship with insulin resistance (IR). FLI was developed in a general population¹ in which the gold-standard technique for the diagnosis of nonalcoholic fatty liver disease (NAFLD), liver biopsy, is neither feasible nor ethically acceptable. The limitations of ultrasonography are well known, but in epidemiology, there is no alternative.¹ Although FLI includes parameters associated with IR, this index was developed as a predictor of fatty liver, not IR. We have demonstrated that FLI is strongly related to IR [measured with the insulin sensitivity index (M/I) during the euglycemic-hyperinsulinemic clamp].² From the FLI formula, this was somehow expected (although not necessarily true). Nonetheless, NAFLD and nonalcoholic steatohepatitis are strongly related to IR, and they are now considered the hepatic manifestations of metabolic syndrome. Indeed, the ability of FLI to predict clinically important outcomes was virtually unmodified after correction for IR.² In a multivariate model, independent determinants of intima media thickness (IMT) were M/I ($P = 0.01$), age, systolic blood pressure, low-density lipoprotein cholesterol, and gender (all $P < 0.0001$, adjusted $R^2 = 0.27$). When FLI was added, it replaced M/I as an independent predictor of IMT ($P = 0.0001$, adjusted $R^2 = 0.27$). Thus, FLI can be considered a good predictor of early carotid atherosclerosis.

The second issue was related to alanine aminotransferase (ALT) independent of IR. A recent American Association for the Study of Liver Diseases position statement³ cited some evidence that ALT may be a predictor of cardiovascular disease in the general population. However, the role of ALT as a predictor of nonalcoholic steatohepatitis and liver fibrosis in patients with NAFLD is more controversial. In a recent study, ALT was not a predictor of liver histology,⁴ and in the Dionysos study, most participants had normal liver aminotransferases, despite the presence of fatty liver.¹ The case is different for subjects with diabetes and/or cardiovascular diseases, who often have higher liver enzymes. In the Relationship Between Insulin Sensitivity and Cardiovascular Disease (RISC) population, although IMT was correlated with ALT, the correlation coefficient was weak ($r = 0.11$, $P < 0.0001$) and much lower than the FLI index ($r = 0.30$, $P < 0.0001$).

In conclusion, our data show a moderate association between IR or ALT and cardiovascular disease, whereas FLI is strongly associated with fatty liver and also with early atherosclerosis.

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“Defragmenting” the Noninvasive Diagnosis of Nonalcoholic Steatohepatitis: Hopes from Cytokeratin-18

To the Editor:

The multicenter study by Feldstein and colleagues¹ on the usefulness of caspase-generated cytochrome-18 (CK-18) fragments in the noninvasive diagnosis of nonalcoholic steatohepatitis (NASH) is definitely interesting. The authors convincingly demonstrated that elevated levels of CK-18 fragments, which serve as markers of hepatocyte apoptosis, are a strong and independent biochemical correlate of NASH, as well as of the presence of liver fibrosis. These results confirm and expand our original observation that CK-18 fragments might serve to noninvasively distinguish steatohepatitis in the setting of nonalcoholic fatty liver disease.² Altogether, these findings hold great promise to downgrade the role of invasive liver biopsy as the only reliable way of diagnosing NASH and monitoring disease progression.

Of note, the authors have also provided evidence that the addition of routinely available laboratory tests did not significantly improve the sensitivity and specificity of CK-18 fragments to diagnose NASH.¹ It is possible, however, that the addition of biomarkers that cover different pathophysiological facets of steatohepatitis (beside hepatocyte apoptosis) may further improve the diagnostic ability of CK-18 fragments. In this regard, it would be interesting to analyze the predictive value of CK-18 fragments in relation to

biomarkers associated with the metabolic facets of NASH, i.e., novel biochemical markers of the metabolic syndrome that have been proven to be valuable tools to identify patients with NASH, such as soluble RAGE (receptor for advanced glycation end-products)³ and pentraxin 3.⁴ The promise for the future is not only to further validate the clinical usefulness of existing biomarker panels for NASH incorporating measurements of CK-18 fragments,⁵ but also to develop novel combinations of different enzyme-linked immunosorbent assay–based assays with improved sensitivity and specificity that may definitely reduce the need for liver biopsies.

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