COMMENTS AND RESPONSES

Should Nonalcoholic Fatty Liver Disease Be Included in the Definition of Metabolic Syndrome? A Cross-Sectional Comparison With Adult Treatment Panel III Criteria in Nonobese Nondiabetic Subjects

Response to Musso et al.

The importance of nonalcoholic fatty liver disease (NAFLD) and its relation to metabolic syndrome is now increasingly recognized, as recent data suggest that NAFLD predicts insulin resistance more accurately than Adult Treatment Panel III criteria (1). NAFLD is linked to increased cardiovascular risk and endothelial dysfunction, as fatty liver is an independent predictor of increased intima-media thickness. Plasma soluble intracellular adhesion molecule (sICAM-1) levels are elevated in atherosclerotic syndromes, and elevated sICAM-1 levels have been associated with endothelial dysfunction.

sICAM-1 (Diaclone, France) was measured in 118 NAFLD patients with different stages of disease severity (32 male and 86 female) and a group of 55 healthy individuals (22 male and 33 female); mean ± SD age for both groups was 52.5 ± 12.1 years. A liver biopsy was performed in 79 subjects who showed persistently abnormal liver function tests (LFTs). Fatty liver with persistently normal LFTs was observed in 39 subjects, fatty liver with persistently abnormal LFTs in 26 subjects, and nonalcoholic steatohepatitis (NASH) with evidence of fibrosis and liver cell injury in 53 subjects. Subjects had most of the features of metabolic syndrome, including high values of homeostasis model assessment (HOMA) index.

sICAM-1 levels (nanograms per milliliter) were significantly higher in NAFLD patients (584.4 ± 182.1 $P < 1 \times 10^{-6}$) than in control subjects. In addition, there was a markedly significant difference among NAFLD groups, with the lowest levels in normal subjects (356.5 ± 309.5), the highest levels in subjects with NASH (650.2 ± 44.9), and intermediate levels in subjects with less severe fatty liver disease (496.1 ± 46.1 and 553.7 ± 50.5, respectively, $P = 0.0002$, ANCOVA with HOMA as a covariate; 12.5% of the total sICAM-1 variance was explained by fatty liver disease gradation). Additionally, for each 100 units of sICAM-1, the odds ratio for NAFLD was 1.36 (95% CI 1.11–1.61, $P = 0.0043$) independent of HOMA. A graded positive relationship between NAFLD stages and sICAM-1 levels independent of sex, BMI, aspartate aminotransferase, and HOMA was observed.

In conclusion, our findings suggest that NAFLD severity is associated with sICAM-1 level; NASH patients had the higher sICAM-1 concentrations. Additionally, sICAM-1 level predicts NAFLD stages independently of potential confounders.

To date, there are not recommended noninvasive tests for evaluation of NAFLD histologic spectrum, and a complete diagnosis of the disease should include the stage and grade of its severity. Traditionally, disease severity is evaluated by liver biopsy, which is mostly indicated when patients show abnormal aminotransferases. Paradoxically, it was previously shown that LFTs are not useful enough to distinguish NAFLD stages and the sensitivity for NASH diagnosis was poor, at about 40% (2). Our findings show that sICAM-1 levels could potentially be used as a noninvasive diagnostic test to predict the severity of NAFLD, with the advantage of being a proven marker of preclinical atherosclerosis.

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References

1. Musso G, Gambino R, Bo S, Uberti B, Broli G, Pagano G, Cassader M: Should nonalcoholic fatty liver disease be included in the definition of metabolic syndrome? A cross-sectional comparison with Adult Treatment Panel III criteria in nonobese nondiabetic subjects. *Diabetes Care*: 562–568, 2008
2. Wieckowska A, McCullough AJ, Feldstein AE: Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. *Hepatology* 46:582–589, 2007