OBSERVATIONS

Plasma PAI-1 Levels Are Increased in Patients With Nonalcoholic Steatohepatitis

Recent data suggest that nonalcoholic fatty liver disease (NAFLD) is linked to increased cardiovascular disease (CVD) risk independently of the metabolic syndrome (MetS) (1–7), although the possible molecular mediators linking NAFLD and CVD are poorly known (8).

Increased plasma plasminogen activator inhibitor-1 (PAI-1) concentrations, responsible for reduced fibrinolytic activity, play a key role in atherothrombosis (9). Since limited information is available about the relations among NAFLD, MetS, and PAI-1, we assessed whether PAI-1 correlates with liver histopathology among NAFLD patients independent of MetS features.

Plasma PAI-1 activity concentrations (Spectrolyse/PL; Biopool) were measured in 85 consecutive NAFLD outpatients (50/35 male/female, mean ± SD age 45 ± 2 years, and BMI 26.1 ± 2 kg/m^2) and 160 age-, sex-, and BMI-matched healthy control subjects. An experienced hepatopathologist blinded to subjects' details scored liver biopsy specimens (10). More details of study design and patients' characteristics have been published elsewhere (7).

Liver histopathology in NAFLD patients showed steatosis alone in 16 subjects, nonalcoholic steatohepatitis (NASH) with fibrosis stage 0 in 23 subjects, NASH/fibrosis stage 1 in 25 subjects, NASH/fibrosis stage 2 in 13 subjects, and NASH/fibrosis stage 3 in 8 subjects. No subjects had cirrhosis.

MetS, as defined by the Adult Treatment Panel III, and its individual components occurred more frequently in NAFLD patients than in control subjects. These patients also had higher values of homeostasis model assessment of insulin resistance and liver enzymes. Age, sex, BMI, smoking, and LDL cholesterol levels did not differ between the groups. PAI-1 was markedly different among the groups; the lowest levels were in control subjects, the intermediate levels in patients with simple steatosis ($n = 16$), and the highest levels in those with NASH ($n = 69$) (11.3 ± 5 vs. 16.5 ± 10 vs. 25 ± 16 AU/ml, respectively; $P < 0.001$). Almost identical results were found after excluding patients with the MetS or diabetes ($n = 43$). Notably, there was a positive, graded relationship between NASH/fibrosis stages and PAI-1 independent of age, sex, BMI, smoking, LDL cholesterol levels, homeostasis model assessment of insulin resistance, and MetS components. Concordantly, in multivariate regression analysis, increasing NASH/fibrosis stage significantly predicted PAI-1 after controlling for potential confounders.

Our findings suggest that NAFLD is associated with increased PAI-1, that NASH patients have higher PAI-1 than those with simple steatosis, and that the severity of NAFLD histology predicts PAI-1 independently of a broad spectrum of potential confounders.

Although the increased PAI-1 levels found in NAFLD might simply reflect the coexistence of underlying MetS abnormalities, we believe that our observation—that the relationship of PAI-1 with the severity of NAFLD histology is independent of insulin resistance and MetS components—provides strong evidence for a direct role of the fatty liver in the increase in circulating PAI-1 concentrations. Also highly accordant with this hypothesis are recent findings in mice suggesting that PAI-1 levels are more closely related to fat accumulation and PAI-1 expression in the liver than in adipose tissue (11).

Overall, these findings extend the results of our two small studies, in which NAFLD diagnosis was based on ultrasound imaging (12,13), giving further support to the hypothesis that NAFLD is associated with a reduced fibrinolytic activity. Moreover, although it is not possible to draw conclusions about causality in our cross-sectional study, these findings suggest a possible biological mechanism by which NAFLD might contribute to CVD pathogenesis.

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