Inflammation Warms Up the Metabolic Syndrome

To the Editor:

We read with interest the article by Hung et al claiming that activation of interleukin 18 (IL-18) is involved in the pathogenesis of the metabolic syndrome. These data add to the mounting evidence describing association between circulating markers of vascular inflammation and features of metabolic syndrome, either alone or in combination. The potential clinical implications of the study must be tempered by some limitations. As correctly acknowledged by the authors, an observational study cannot prove that the association between IL-18 levels and the metabolic syndrome is causal. Although they made efforts to adjust for several relevant potential confounders, they had no information about factors such as drugs or mental stress, and unmeasured or unmeasurable lifestyle factors cannot be adjusted for. For instance, body mass index (BMI) showed a progressive increase in parallel with the increment in the number of the components of the metabolic syndrome; this could be a marker for a generally unhealthy lifestyle, including preference for fatty and sweet foods and sedentary lifestyle. There is evidence that IL-18 concentrations are modulated by body weight and macronutrients present in familiar food stuffs. Despite these limitations, most would accept that the link between inflammation and the metabolic syndrome is causal because there are several mechanisms whereby inflammation could impair insulin sensitivity. Insulin resistance has been considered the basis of most if not all of the features of the syndrome that could be accounted for by the resistance to the actions of insulin on carbohydrate and lipid metabolism.

We evaluated circulating levels of IL-18, flow-dependent vasodilation, and insulin sensitivity in patients with the metabolic syndrome, following the criteria of the Adult Treatment Panel III, and in subjects without the metabolic syndrome matched for age, sex, and BMI. Serum IL-18 concentrations were measured with a high-sensitive, quantitative sandwich enzyme assay (Quantikine HS). Endothelium-dependent flow-mediated vasodilation was evaluated in the right brachial artery with a high-resolution ultrasound machine (Aloka 5500) and calculated as the percent change in diameter compared with baseline. Estimation of insulin sensitivity in the fasting state was assessed with HOMA (homeostasis model assessment) and calculated with the formula: fasting plasma glucose (mmol/L) x fasting serum insulin (µU/mL)/22.5 as originally described by Matthews et al. Patients with the metabolic syndrome (n=60) were matched for age (48±4.2 years, mean±SD), sex (32 male/28 female), and BMI (29.1±3.9 kg/m²) with control subjects (46.5±4.1 years, 30 male/30 female, and 28.2±4.1, respectively). The results are given in the Figure. Compared with control subjects, patients with the metabolic syndrome showed higher concentrations of serum IL-18, higher HOMA values, indicating insulin resistance, and lower flow-mediated vasodilation. Spearman rank correlation coefficients revealed significant associations between IL-18 levels and HOMA score (r=0.35, P=0.01) and flow-mediated vasodilation (r=-0.30, P=0.01).

Our results indicate that inflammation, insulin resistance, and endothelial dysfunction are strictly associated in patients with the metabolic syndrome and may influence each other, amplifying the cascade of metabolic and vascular derangements. The proinflammatory state that accompanies the metabolic syndrome associates with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes which is highly deleterious for vascular functions. Obviously, this has implications for novel therapeutic strategies because drugs that reduce inflammation would be predicted to improve both metabolic and endothelial function. Indeed, recent clinical studies have demonstrated additive beneficial endothelial and metabolic effects of combining statins with angiotensin II type 1 receptor blockers in patients with type 2 diabetes. Appropriate intervention studies are urgently needed to address this important topic.

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Circulating levels of IL-18, flow-mediated dilation (FMD), and HOMA values in 60 patients with the metabolic syndrome and 50 control subjects. Data are presented as median (interquartile range) for IL-18 and FMD, and mean±SD for HOMA.
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