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Nonalcoholic fatty liver disease: The hepatic trigger of the metabolic syndrome

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COMMENTARY ON:

Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Fabbrini E, Magkos F, Mohammed BS, Pietka T, Abumrad NA, Patterson BW, Okunade A, Klein S. Proc Natl Acad Sci USA 2009;106:15430–15435. Copyright (2009) by the National Academy of Sciences; USA. Abstract reprinted with permission from the National Academy of Sciences.

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Abstract: *Visceral adipose tissue (VAT) is an important risk factor for obesity-related metabolic disorders. Therefore, a reduction in VAT has become a key goal in obesity management. However, VAT is correlated with intrahepatic triglyceride (IHTG) content, so it is possible that IHTG, not VAT, is a better marker of metabolic diseases. We determined the independent association of IHTG and VAT to metabolic functions, by evaluating groups of obese subjects, who differed in IHTG content (high or normal) but matched on VAT volume or differed in VAT volume (high or low) but matched on IHTG content. Stable isotope tracer techniques and the euglycemic–hyperinsulinemic clamp procedure were used to assess insulin sensitivity and very-low-density lipoprotein-triglyceride (VLDL-TG) secretion rate. Tissue biopsies were obtained to evaluate cellular factors involved in ectopic triglyceride accumulation. Hepatic, adipose tissue, and muscle insulin sensitivities were 41%, 13%, and 36% lower ($p < 0.01$), respectively, whereas VLDL-triglyceride secretion rate was almost double ($p < 0.001$), in subjects with higher than normal IHTG content, matched on VAT. No differences in insulin sensitivity or VLDL-TG secretion were observed between subjects with different VAT volumes, matched on IHTG content. Adipose tissue CD36 expression was lower ($p < 0.05$), whereas skeletal muscle CD36 expression was higher ($p < 0.05$), in subjects with higher than normal IHTG. These data demonstrate that IHTG, not VAT, is a better marker of the metabolic derangements associated with obesity. Furthermore, alterations in tissue fatty acid transport could be involved in the pathogenesis of ectopic triglyceride accumulation by redirecting plasma fatty acid uptake from adipose tissue toward other tissues.*

Keywords: NAFLD; Metabolic syndrome; Liver fat; Visceral fat; Insulin resistance.
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Nonalcoholic fatty liver disease (NAFLD) is a chronic metabolic disorder with significant impact on overall mortality [1]. Although the gastroenterologist's focus is mainly on its hepatic complications, patients with NAFLD have a risk of cardiovascular diseases highly exceeding the risk of liver-related deaths [2]. NAFLD has been proposed as the hepatic manifestation of the metabolic syndrome (MetS), with insulin resistance (IR) as the common pathophysiological mechanism [3]. The relationship between NAFLD and MetS is bidirectional. Liver fat content is significantly increased in subjects with MetS as compared with those without, independent of age, gender, and body mass index (BMI); in turn, the presence of NAFLD is a strong predictor of MetS, and markers of NAFLD are associated with the future risk of Type 2 diabetes and cardiovascular mortality, i.e. the worrisome outcomes of MetS [2,4].

The most recent definition of MetS by the International Diabetes Federation [3] focuses on abdominal obesity as a necessary feature, because it is thought to be 'an early step in the aetiological cascade leading to the full metabolic syndrome', as demonstrated by several epidemiological and clinical studies. Nevertheless, each component of MetS is also associated with increased liver fat content [5], and the relative role of abdominal versus hepatic fat in the onset of MetS is a recent matter of debate.

The article by Fabbrini et al. [6] significantly adds to this intriguing puzzle. The authors evaluated two groups of obese patients. Subjects in each group were matched on age, sex, BMI, and percentage of body fat, but differed in either intrahepatic triglyceride (IHTG) content or visceral adipose tissue (VAT) volume. The authors used state-of-the-art techniques (2-step hyperinsulinemic–euglycemic clamp combined with stable isotope tracers) to assess hepatic, skeletal muscle, and adipose tissue insulin sensitivities and to evaluate VLDL-TG secretion rate. Compared with subjects with low IHGT matched on VAT, subjects with high IHTG content had a significantly lower hepatic, adipose tissue, and muscle insulin sensitivities (respectively reduced by 41, 13, and 36%; $p < 0.01$) and a twofold increased VLDL-triglyceride secretion rate ($p < 0.001$). On the contrary, no differences in insulin sensitivity or VLDL-TG secretion were observed between subjects with different VAT volumes, matched on IHTG content. The author's conclusion was that IHTG content, rather than VAT, is the main determinant of insulin resistance at the whole-body level.

Some drawbacks in the presentation of data should be pointed out. At first glance, the impression is that only patients with increased IHTG content display metabolic abnormalities, and the lack of a control group considerably contributes to it. In a

previous study [7] using the same two-step clamp methodology, total glucose disposal was stimulated 3-fold by insulin in non-diabetic subjects with NAFLD, compared with 6-fold in matched lean healthy controls. The insulin sensitivity index (reciprocal of insulin resistance index) in the NAFLD group was, on average, 0.5. With the proviso that a direct comparison is inappropriate, both patients matched for liver fat with high or low VAT, or matched for intra-abdominal fat with high or low IHTG content, had a degree of insulin-stimulated glucose disposal, and indices of hepatic insulin sensitivity comparable to the NAFLD group mentioned above, i.e. all of them were anyway significantly insulin resistant both in the liver and in the muscle. Nevertheless, subjects with increased IHTG had further impairment in insulin sensitivity at the whole-body level and, most significantly, secreted a significantly higher amount of VLDL derived from intrahepatic sources, i.e., lipolysis of intrahepatic triglyceride, hepatic lipolysis of circulating triglyceride, and *de novo* hepatic fatty acid synthesis.

Whether a fatty liver is the consequence or an active player in the progression of insulin resistance is the "chicken or the egg" tale, and cannot be discriminated by cross-sectional studies; however, the liver is the major source of endogenously produced glucose, and determines the plasma glucose concentration. Liver fat has been shown to be closely associated with impaired insulin inhibition of hepatic glucose production both in non-diabetic subjects and in type 2 diabetic patients [5]. Analogous to fat in the liver, increased intramyocellular triglyceride content closely correlates with muscle IR and is a better predictor of impaired insulin action than visceral adiposity [8].

Organ-specific deposition of fat is a strong predictor of insulin resistance, as highlighted by inherited or highly active antiretroviral therapy (HAART)-related forms of lipodystrophy, where the selective loss of subcutaneous and visceral fat is associated with steatosis, hypertriglyceridemia, and severe IR [9]. On the other hand, in patients with familial hypobetalipoproteinemia (FHBL), which have high levels of IHTG because of a genetic defect in hepatic export of triglycerides, insulin sensitivity in the liver and in the muscle is comparable to healthy controls, suggesting that fatty liver per se does not necessarily mean hepatic IR [10]. Similarly, gene variants of adiponutrin are associated with increased IHTG but not with IR in the general population [11]. Of note, hepatic steatosis induced by reduced triglycerides clearance, such as in genotype 3 chronic hepatitis C, appears less able to induce IR, pointing out the importance of lipotoxicity from increased free fatty acid (FFA) delivery rather than from triglycerides, which might represent an inert form of fat accumulation [12]. In this light, visceral fat can thus be considered the first buffer of lipotoxic FFA fluxes, being a site less metabolically active than the liver, even though mesenteric adipocytes are a crucial source of FFAs entering portal circulation and providing the substrates to increase gluconeogenesis and hepatic glucose production [13].

Once ectopic fat accumulates in the liver, clinical consequences will become more relevant in terms of impaired glucose production, leading to increased probability of diabetes, and altered lipid profile, leading to atherosclerosis. Alternatively, subjects who display a better ability to clear fat from the liver would probably be those at lower risk of developing the complications of MetS.

Finally, the comparison of relatively small groups of subjects cannot provide meaningful quantitative estimates of the relative contribution to MetS of the two fat depots, but the quantity of liver fat has been shown to predict the presence of the typical glucose and lipid metabolic disturbances of MetS independently of VAT also in the large population of the Framingham Heart Study [4]. In an another large study, both VAT and liver fat explained variation in serum triglyceride, HDL cholesterol, and insulin concentrations independently of each other, but liver fat was the only predictor of fasting glucose levels [14].

In conclusion, because of its master function in the regulation of glucose and lipid disposal, the liver should be considered as the hepatic trigger of the MetS, rather than its target. In the future, the presence of fatty liver as a strong predictor of cardiovascular and metabolic complications should not be ignored in the international guidelines for MetS. Prospective clinical studies are warranted to evaluate whether the treatment of fatty liver could be effective in the prevention of cardiovascular events.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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