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Trunk Fat as a Determinant of Liver Disease

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Metabolic diseases such as atherosclerosis and diabetes have been long known to correlate with obesity. Careful investigation, however, has shown that these conditions are more closely related to body fat distribution than to excess weight per se.¹ Research in this area began with a simple distinction between persons having primarily “upper body” fat or “lower body” fat, which revealed that individuals with upper body fat were at risk for metabolic complications.² Methodologic advancements subsequently permitted the subdivision of body compartments into smaller regions of interest; the end result was the identification of abdominal and specifically visceral (omental plus mesenteric) fat as a mediator of the metabolic syndrome and its attendant complications of diabetes and cardiovascular disease.³ Visceral fat is considered a logical trigger of metabolic dysfunction because of its enhanced lipolytic activity and more abundant cytokine expression than other fat depots.^{4,5} In addition, because of its direct portal venous drainage, visceral fat is believed to have a direct influence on the metabolic state of the liver. Indeed, in a recent population-based study, visceral fat was identified as an important determinant of hepatic steatosis.⁶

Given the connection between visceral fat and the presence of fat within the liver, a logical next question is whether visceral fat is linked also to the more serious and progressive entity nonalcoholic steatohepatitis (NASH). Efforts have been made to address this issue on a large scale, but the task has been challenging because investigators have relied on surrogate measures to assess visceral fat and liver disease. Ruhl and Everhart⁷ pursued the question in 2003 by studying 5,724 individuals from the National Health and Nutrition Examination Survey (NHANES) III cohort. Using the information gathered from the cohort, they determined that the waist–hip ratio, an indicator of total (visceral plus subcutaneous) abdominal fat, was indeed a predictor of abnormal alanine aminotransferase (ALT; >43 IU/L) independent of body mass index (BMI). This finding was corroborated by Stranges et al⁸ in a separate, population-based study utilizing abdominal height as a measure of visceral obesity. The acquisition of dual x-ray absorptiometry (DXA) data on NHANES participants from 1999 through 2004, however, presented an opportunity for Ruhl and Everhart to revisit the relationship between visceral fat and ALT in more depth and with more precision than had been possible in their original study. In this issue of *GASTROENTEROLOGY*,⁹ they used the 1999–2004 NHANES cohort to evaluate ALT as a function of 4 body composition

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Conflicts of interest

Dr. Maher discloses no conflicts.

measurements by DXA. Importantly, in the new study, they adopted gender-specific cutoff levels for ALT (44 IU/L for men and 31 IU/L for women) that were based on the 95th percentile of ALT from the cohort.

The current study is more than twice the size of the one conducted in 2003, with clinical data being obtained from 11,821 patients (5,903 men and 5,918 women). Complete body composition measurements were collected from 78% of the cohort and imputed from the remainder so that all 11,821 were included in the final analysis. DXA data were separated into 4 categories: trunk fat mass, trunk lean mass, extremity fat mass, and extremity lean mass. All body composition measures were divided into quintiles and the risk of an ALT elevation reported as an odds ratio compared with the lowest quintile. Although in the initial evaluation all 4 body composition measurements correlated positively with a risk of ALT elevation, multivariate adjustment revealed that trunk fat was associated independently with ALT. This relationship was true for both men and women, although it was more striking in men. Importantly, when trunk fat was evaluated together with BMI and waist circumference in a multivariate-adjusted model, trunk fat persisted as a predictor of an abnormal ALT level, whereas BMI and waist circumference did not. This speaks to a specific connection between abdominal (presumably, visceral) fat and a marker of actual liver disease. Intriguingly, when the cohort was subdivided into ethnic groups, the fact that non-Hispanic black men had lower trunk fat emerged as the explanation why they also had lower ALT levels than non-Hispanic white men. Differences in trunk fat, however, could not account for ethnic differences in ALT between white and Hispanic men or any ethnic group in women. This deserves further attention, because differences among whites, blacks, and Hispanics in the prevalence of hepatic steatosis have been attributed to ethnicity-based differences in visceral fat.⁶ That the relationship between visceral fat and liver disease (measured by ALT) could be independent of the relationship between visceral fat and hepatic steatosis is intriguing. Such a theory has been proposed recently by van der Poorten et al.¹⁰

When the data comparing ALT with trunk fat in the NHANES cohort were adjusted for serum markers of diabetes or the metabolic syndrome, the magnitude of the correlation diminished but remained significant in both men and women. The fact that some of the relationship between trunk fat and ALT was unrelated to the metabolic syndrome is in accord with evidence that other hepatic abnormalities, such as hepatic steatosis, also align with visceral fat independently of insulin resistance.⁶ Taken together, these observations raise the possibility that hepatic steatosis and NASH, 2 entities we have tried hard to argue belong in the metabolic syndrome, may arise in part from factors unrelated to insulin resistance. This is not a disavowal that insulin resistance is related to the pathogenesis of nonalcoholic fatty liver disease,¹¹ but rather an opportunity to think broadly that visceral fat may have effects on the liver that transcend insulin resistance. Yet another point that should be considered is that visceral fat may not be the primary adipose tissue compartment triggering the metabolic syndrome in all individuals.^{6,12–14} This is true despite the undisputed metabolic activity of visceral fat.¹⁵

One important limitation of the NHANES study was that DXA, despite its greater sophistication than waist–hip ratio for measuring abdominal fat, still could not distinguish

visceral from subcutaneous fat in the study subjects. This shortcoming could explain why the authors observed a higher prevalence of ALT levels in men than women at the same quintiles of trunk fat. Women have more subcutaneous abdominal fat than men¹⁶; consequently, a woman with an identical trunk fat measurement to a man by DXA will have less visceral fat, and presumably therefore lower ALT. Despite the imperfections of DXA, it was remarkable that the multivariate-adjusted correlation between trunk fat and ALT was nearly linear across trunk fat quintiles for men and women. This is quite different than the relationship between waist–hip ratio and ALT in the NHANES cohort from 2003, which did not increase until the waist–hip ratio reached the upper half of the measured range. Stated alternatively, trunk fat seems to be a more sensitive indicator of liver injury than the waist–hip ratio. It predicts that even a small amount of fat within the abdomen poses an important risk of liver disease. Ruhl and Everhart lamented that cross-sectional nature of the NHANES study prevented them from determining whether reducing trunk fat would improve liver injury. Although this is true, other studies are emerging that prove aerobic exercise can reduce visceral fat¹⁷ and improve serum ALT¹⁸ in patients with nonalcoholic fatty liver disease without causing changes in body weight or insulin sensitivity. Indeed, the ability of exercise to preferentially mobilize abdominal/visceral fat has been recognized for many years.¹⁹

Based on the work of Ruhl and Everhart,⁹ as well as another large-scale population study published in 2009,⁶ it is evident that abdominal/visceral fat coincides with hepatic steatosis and also with ALT. Does this information help us to discern who among the viscerally obese is at risk for both hepatic steatosis and increased ALT in the form of NASH? Unfortunately, not necessarily. Although hepatic steatosis and ALT have at times been shown to vary together in relation to visceral obesity,^{20,21} at other times visceral obesity predicts liver injury independent of hepatic steatosis.^{10,22} This argues against a linear model in which visceral fat promotes steatosis and thereafter steatohepatitis, but instead supports a complex relationship in which visceral fat influences steatosis and liver injury independently (Figure 1). The findings from the NHANES cohort will no doubt spark further investigation into the nature of this intricate relationship.

In summary, Ruhl and Everhart provide definitive evidence in a large, US population that trunk fat is a harbinger of liver disease. Importantly, the connection between trunk fat and liver injury cannot be fully explained by the ability of trunk fat to promote the metabolic syndrome. The findings suggest that visceral adipose tissue interacts with the liver in complex ways to influence hepatic steatosis and steatohepatitis—they pave the way for future exploration of the axis between visceral adipose tissue and the liver.

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Figure 1.

(*Top panel*) Linear model, in which visceral fat promotes fatty liver disease by stimulating hepatic steatosis, which then progresses to liver disease (elevated ALT; NASH). (*Bottom panel*) An alternative model, in which visceral fat can influence hepatic steatosis and liver disease independently, while retaining the potential for steatosis to progress to steatohepatitis without additional specific input from visceral fat. Scheme based on concepts proposed previously by van der Poorten et al.¹⁰