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## Abdominal fat: does it predict the development of type 2 diabetes?<sup>1,2</sup>

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The incidence of type 2 diabetes (T2DM) is rapidly increasing worldwide. There is a great deal of evidence that both genetic and environmental factors are of importance in the pathogenesis of T2DM. Whereas the genetic factors are still poorly understood, numerous studies have shown that obesity (in particular, central obesity), physical inactivity, a high-fat diet, and a diet rich in saturated fatty acids increase the risk of diabetes (1). T2DM is increasingly common among young people and even children; it constitutes a major health problem in both developed and developing countries; and, with obesity, it is becoming one of the largest challenges to health care systems. Therefore, any measures that could prevent or delay the development of diabetes are urgently needed. In this issue of the Journal, the report by Bray et al (2) tries to answer the question of whether preferential abdominal fat accumulation could predict the development of T2DM in US adults with elevated fasting and postprandial glycemia.

The role of abdominal obesity in the development of T2DM is controversial (3). Several studies have shown the association among abdominal adiposity, insulin resistance, and hyperglycemia (3). Visceral fat (VF) is increased in proportion to body mass index (BMI) (4), and obesity is one of the main risk factors for the development of T2DM (1). Moreover, visceral adipocytes release an excess amount of free fatty acids (FFAs) and are very resistant to the antilipolytic effect of insulin (3).

Several lines of evidence support the concept that FFAs are important regulators of glucose metabolism and that elevated FFAs are associated with insulin resistance at the level of liver and muscle (5). Thus, to explain the association between VF and hepatic insulin resistance, it has been postulated that a preferential influx of FFAs (and, possibly, other molecules produced by visceral abdominal adipocytes) via the portal circulation to the liver can induce or augment hepatic insulin resistance, in particular by enhancing gluconeogenesis (3). This hypothesis was in part confirmed by a recent study showing that obese persons have a greater release of FFAs and glycerol into the portal circulation than do nonobese persons (6). Moreover, in both nondiabetic persons and persons with T2DM, gluconeogenesis is increased in proportion to VF (4), although overall hepatic glucose production may not increase because glycogenolysis is reduced by chronic hyperinsulinemia. This adaptation is called “hepatic autoregulation.”

Excess FFAs also are linked to muscle insulin resistance. However, the total amount of VF rarely exceeds 10–15% of total body fat, even in obese subjects (7). Therefore, it is difficult to

imagine that FFAs released from visceral depots can directly affect muscle glucose metabolism. Rather, VF releases adipokines such as leptin, adiponectin, or tumor necrosis factor- $\alpha$ , which seem to be implicated in skeletal muscle insulin resistance. Thus, the observed relation between greater fat mass and insulin resistance (4) may be due to other endocrine and metabolic functions of VF.

The study by Bray et al tests the hypothesis that measures of abdominal fat taken at baseline predict the development of diabetes after 3.2 y (2). The subjects ( $n = 1106$ ) were part of a large study group ( $n = 3234$ ) enrolled in the Diabetes Prevention Program (DPP) (8). They were on average obese subjects [mean BMI (in kg/m<sup>2</sup>): 32 in males and 33 in females] with central obesity (ie, large waist circumference). The DPP study compared the effect of metformin treatment or intensive lifestyle intervention with that of placebo on the development of diabetes in subjects at high risk of T2DM. The results showed that both the metformin and lifestyle interventions reduced the incidence of diabetes, but the latter was more effective (8).

In this analysis by Bray et al (2), preferential abdominal fat accumulation was found to be associated with a greater risk of developing T2DM in the placebo group, a finding that is in agreement with previous studies (9). The analysis of Bray et al was conducted separately in men and women because men tend to accumulate more VF (3). Among the measures of abdominal fat taken at baseline—VF and subcutaneous fat (ScF) fat measured by CT scan, the ratio of ScF to VF, waist circumference, or waist/hip ratio—VF measured at baseline was the strongest predictor of T2DM in men, whereas the ratio of VF to ScF was the best predictor in women.

In the metformin group, none of the measures of abdominal fat taken at baseline predicted T2DM. This is not surprising, because subjects lost weight and metformin has multiple metabolic effects, many of which appear to be largely independent of weight loss (10).

Also in the lifestyle intervention group, the results differed significantly between men and women. In male subjects, only waist/hip ratio at baseline was significantly associated with the risk of diabetes, whereas, in female subjects, a greater risk was

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associated with initial high VF and BMI. The subjects enrolled in this group lost a significant amount of weight (8), and a recent analysis of the DPP study showed that the weight lost proportionately came from VF more than from ScF, especially in men (24% compared with 18% in women) (11). In women, changes in VF were less important in predicting T2DM than was total weight loss (11). Thus, it is possible that other mechanisms also are involved. In fact, all subjects in this group were following not only a hypocaloric diet but also an exercise program. Because physical activity improves maximal oxygen consumption ( $\dot{V}O_{2\max}$ ) and insulin sensitivity, thus decreasing the risk of diabetes, one limitation of this study is the use of baseline measurements to predict the development of T2DM rather than taking into account the changes due to the intervention.

In conclusion, this study supports the current view that abdominal fat accumulation carries a greater risk for T2DM and highlights the importance of lifestyle intervention in the prevention of T2DM.

The author had no personal or financial conflict of interest.

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