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EDITORIAL

Adipose compartmentalization and insulin resistance among obese HIV-infected women: the role of intermuscular adipose tissue^{1,2}

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Changes in adipose tissue volume and distribution have been linked to the development of insulin resistance and the metabolic syndrome in non-HIV-infected individuals. These changes may occur in conjunction with obesity or disorders of altered body fat distribution, often termed lipodystrophy. Indeed, the distribution of adipose tissue is an important determinant of metabolic risk, including insulin resistance. In this regard, both increases in visceral adipose tissue (VAT) and decreases in subcutaneous adipose tissue (SAT) are independently associated with metabolic abnormalities and increased insulin resistance in non-HIV-infected adults (1).

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Among HIV-infected patients, metabolic abnormalities and changes in fat distribution are common. Approximately 20—50% of HIV-infected individuals will develop a change in adipose tissue distribution, dyslipidemia, or insulin resistance within 2 y of beginning antiretroviral therapy (2). Changes in adipose tissue in HIV-infected patients are typically manifested as peripheral fat loss, often in the lower extremities, with or without associated central fat gain. Both peripheral fat loss and visceral fat gain are independently associated with increased insulin resistance in this population ($\frac{3}{4}$). Moreover, HIV-related adipose tissue changes are often associated with hypertriglyceridemia, low HDL concentrations, elevated free fatty acid (FFA) concentrations, and an elevated intramyocellular lipid (IMCL) content ($\frac{2}{4}$, $\frac{4}{5}$).

Early studies determining muscle attenuation from computed tomography (CT) in the HIV-infected population suggest that muscle adiposity (relative fat content of muscle in a specified area) is higher in HIV-infected individuals with increased truncal and reduced extremity fat than in HIV-infected patients without changes in fat distribution or in non HIV-infected subjects. Moreover, it was shown that muscle attenuation, or degree of adiposity, was a strong independent predictor of hyperinsulinemia in the HIV-infected population with metabolic abnormalities (4). Subsequently, it was shown that muscle adiposity improved with exercise in association with improvements in insulin sensitivity in HIV-infected individuals (6). However, CT does not specifically quantitate the IML content of muscle adipose tissue, whereas magnetic resonance spectroscopy does.

Among HIV-infected patients, Gan et al (7) found that increased visceral fat was strongly associated with IMCL concentrations, as assessed by magnetic resonance spectroscopy. Increased IMCL content was a strong predictor of insulin-stimulated glucose disposal during a hyperinsulinemic euglycemic clamp. A model for the pathogenesis of insulin resistance in HIV-infected individuals was proposed by Balasubramanyam et al (8). In this model, dysregulation of fatty acid metabolism in peripheral fat depots is hypothesized to contribute to increased lipolysis and increased circulating FFA concentrations. The increased FFA transport into skeletal muscle is thought to result

in increased intramyocellular concentrations of fatty acyl coenzyme A, increased IMCL deposition, and suppression of insulin-mediated glucose transport into skeletal muscle, which thereby induces insulin resistance (8). Data in support of this hypothesis, recently published by Hadigan et al (9), indicate that treatment with acipimox (a nicotinic acid analog not currently approved by the Food and Drug Administration in the United States) to inhibit lipolysis improved insulin sensitivity while decreasing the IMCL content.

Recently, the accumulation of intermuscular adipose tissue (IMAT) was recognized as an important determinant of insulin resistance. IMAT refers to the adipose tissue between muscle fibers, whereas IMCL refers to the adipose tissue within muscle. Measurement of IMAT was initially based on the CT measurement of decreased attenuation. Subsequently, IMAT was assessed more directly with magnetic resonance imaging (MRI). Goodpaster et al (10) found that intermuscular and intramuscular fat are independently and positively associated with insulin resistance in obese nondiabetic and diabetic non-HIV-infected individuals. Recently, Albu et al (11) showed that whole-body IMAT, assessed by using MRI, was a predictor of insulin resistance in non-HIV-infected women, independent of race, weight, height, and total skeletal muscle volume. These data highlight the importance of intermuscular adipose tissue accumulation as a critical factor regulating glucose trafficking

What is the influence of IMAT on insulin sensitivity among HIV-infected patients? In this issue of the Journal, Albu et al (12) present the results of a cross-sectional study that compared the relation of adipose distribution with insulin resistance in 17 obese HIV-infected women with that in 32 obese but otherwise healthy HIV-negative controls. Whole-body MRI was used to determine SAT, VAT, and whole-body IMAT. Insulin sensitivity was assessed by intravenous glucose tolerance testing. HIV-infected women had relatively less SAT but more VAT and IMAT than did HIV-negative women. Increased whole-body IMAT and reduced leg SAT were independent correlates of insulin resistance in HIV-infected women in this cross-sectional study.

This study by Albu et al provides important new information regarding the assessment of IMAT in obese HIV-infected women and the relation of IMAT to insulin resistance in this population. Taken together with prior data in non-HIV-infected women, the studies of Albu et al suggest that IMAT appears to have a strong independent effect on insulin resistance in women in general and greater effects in HIV-infected patients, in whom IMAT accumulation is excessive. In addition, the inverse relation between leg SAT and insulin resistance shown in HIV-infected women supports the model of insulin resistance proposed by Balasubramanyam et al (8) Specifically, decreased storage capacity of fat in leg SAT could lead to the "spillover" of fatty acids into plasma and ultimately into skeletal muscle, which would contribute to insulin resistance. Whether this "spillover" is responsible for the increase in IMAT and for the significant association between IMAT and insulin resistance remains to be elucidated.

The current study by Albu et al has some important limitations. It was conducted in obese HIV-infected women who had been recruited for a study on weight loss, which limited the generalizability of the findings to this specific subpopulation of HIV-infected patients. Furthermore, the study provided little information on the effect of IMAT on other metabolic variables, including lipid concentrations, and no information on physical activity and dietary intake. Specifically, it is not clear whether physical activity or dietary intake differed between the 2 groups and, if so, whether such differences account for the variations in adipose deposition and insulin resistance. Further studies are needed to investigate the relation between reduced SAT, increased IMAT, and dyslipidemia. Similarly, longitudinal studies of the effect of specific antiretroviral medications on IMAT are needed. Nonetheless, the current study provides new information regarding the importance of intermuscular adipose tissue accumulation in the HIV population receiving antiretroviral therapy.

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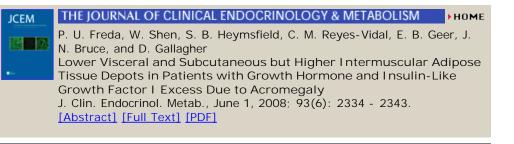
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