Metabolic Complications of Antiretroviral Therapy

Characteristics of metabolic complications observed in patients receiving potent antiretroviral therapy were discussed at the Cleveland course by Steven K. Grinspoon, MD.

The body fat abnormalities and metabolic derangements that constitute the so-called "HIV lipodystrophy syndrome" were initially reported in patients receiving protease inhibitor-containing antiretroviral regimens. However, the metabolic abnormalities associated with HIV-1 disease have also been reported in protease inhibitor-naive patients, suggesting a complex pathophysiologic mechanism related only in part to protease inhibitor therapy. The syndrome is characterized by (1) changes in body composition ("fat redistribution"), including dorsocervical fat deposits (buffalo hump) and truncal obesity, facial and peripheral fat atrophy, and breast enlargement in women; (2) insulin resistance and hyperglycemia; and (3) lipid abnormalities ("dyslipidemia") including hypertriglyceridemia and reduced high-density lipoprotein (HDL) levels. However, there is significant heterogeneity in the presentation of HIV lipodystrophy syndrome, with variable prevalence estimates depending on the definition of the syndrome. One group has reported a prevalence of 83% among patients receiving protease inhibitors based on self-reporting and clinical examination, whereas others have reported prevalence rates of 12% based on dual-energy x-ray absorptiometry (DEXA) scans. A prevalence rate of 16% was shown in women based on self-assessment in a preliminary study. At the current time, no consensus exists for the most appropriate terminology to describe and define the metabolic changes and body fat abnormalities that have been observed.

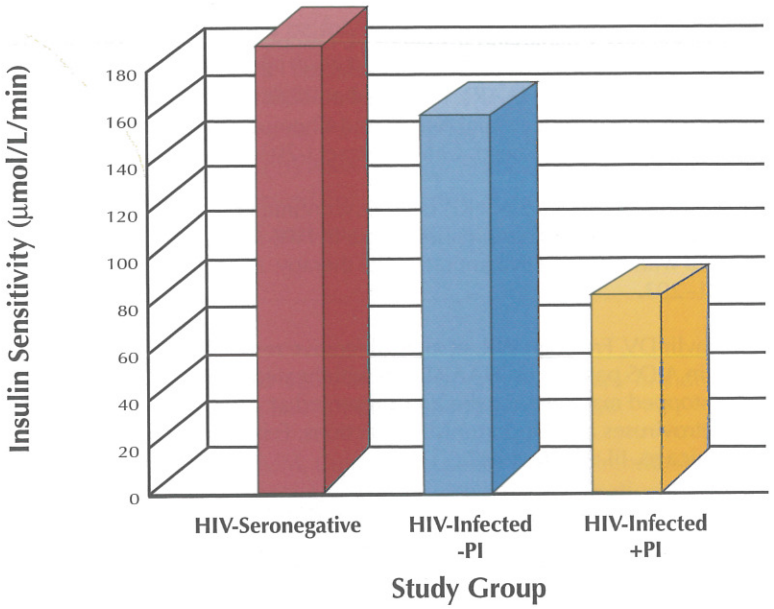

Figure 1. *Insulin sensitivity among HIV-seronegative controls (n=180) and patients with HIV infection receiving antiretroviral regimens containing a protease inhibitor (+PI; n=13) or not containing a protease inhibitor (-PI; n=61). Adapted from Walli R, et al.* AIDS. *1998.*

POTENTIAL PATHOPHYSIOLOGIC MECHANISMS

A number of mechanisms have been proposed to account for HIV lipodystrophy syndrome. Carr and Cooper have posited that abnormalities in fat redistribution result from protease inhibitor suppression of chylomicron and triglyceride uptake by the endothelial lipoprotein-related peptide (LRP)-lipoprotein lipase complex and inhibition of CRABP-1 (cis-retinoic acid binding protein-1)-mediated adipocyte differentiation and apoptosis, resulting in increased peripheral fat deposition and redistribution. However, a number of other groups have observed the syndrome in protease inhibitor-naive patients. It has thus been suggested that pathophysiologic mechanisms may include interaction of underlying metabolic abnormalities due to HIV disease itself and weight gain resulting from potent antiretroviral therapy. For example, hypertriglyceridemia has long been associated with HIV disease, and may worsen in association with weight gain and use of potent therapy.

Other potential mechanisms contributing to the observed metabolic abnormalities in HIV lipodystrophy syndrome include the effects of cytokines and/or hormonal factors. The buffalo hump and centripetal fat deposition observed in the syndrome are similar to the clinical picture of Cushing's syndrome, which is associated with hypercortisolemia. The association of the syndrome with elevated cortisol levels, however, remains unclear, with some studies indicating elevated serum and urine cortisol levels and other studies indicating primarily normal levels and appropriate