American Journal of Infectious Diseases 2 (3): 184-186, 2006
ISSN 1553-6203

Abnormal Glucose Regulation and Treatment Strategies for Insulin Resistance HIV-Infected Patients

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Abstract: HIV-infected patients receiving highly active antiretroviral therapy often demonstrate abnormalities in glucose regulation, in association with changes in fat distribution[1,2]. In the majority of cases, these abnormalities are best characterized by insulin resistance and impaired glucose tolerance, rather than overt diabetes mellitus and fasting hyperglycemia. Insulin resistance may result from direct effects of antiretroviral therapy, changes in fat distribution or abnormal regulation of fat metabolism and adipocytokines. Use of insulin sensitizing agents may be rationale to reduce cardiovascular risk and improve related metabolic and body fat abnormalities in HIV-infected patients.

Key words: HIV-infected patients, abnormalities, insulin resistance, glucose regulation

INTRODUCTION

Mechanisms of insulin resistance: The mechanisms of abnormal glucose regulation in HIV-infected patients may include direct effects of antiretroviral therapies and/or related effects of abnormal fat redistribution (increased visceral fat, decreased subcutaneous fat), dyslipidemia, increased lipolysis and altered adipocytokines. Protease inhibitors have been shown to decrease glucose uptake in adipocytes *in vitro* and may act similarly *in vivo*, as demonstrated recently by Noor *et al*.[3]. In a recently completed study, insulin sensitivity declined by approximately 25% in response to acute dosing with a protease inhibitor[4]. In contrast, other studies have demonstrated strong correlations between changes in fat redistribution independent of PI therapy[5]. In particular, decreased insulin sensitivity has been associated with fat loss in the extremities, as well as increased waist circumference and WHR[5,6].

New data suggests that accumulation of lipid within the intramyocellular (IMCL) compartment may also contribute to glucose intolerance. In this regard, increased lipolysis and deposition of fatty acids within the myocytes may interfere with insulin signaling through effects on PI3-kinase. Indeed, recent data demonstrate that inhibition of lipolysis acutely improves insulin sensitivity, perhaps as a result of this mechanism[7]. In addition, decreased adiponectin has been demonstrated in association with reduced extremity fat and increased visceral adiposity in HIV-infected patients[8]. Adiponectin increases the oxidation of fat within the muscle. Reduced levels of adiponectin are associated with decreased insulin sensitivity and this mechanism may also contribute to altered glucose regulation in HIV-infected patients. Taken together, the data to date indicate that abnormalities in glucose and insulin regulation among HIV-infected patients are likely multifactorial in etiology.

Prevalence of impaired glucose tolerance and diabetes mellitus: What is the prevalence of impaired glucose tolerance among HIV-infected patients receiving HAART and among those with fat redistribution? Carr *et al* demonstrated an 8% prevalence of diabetes mellitus among HIV-infected patients receiving HAART[2]. Hadigan el al. demonstrated an 6-fold increase risk of impaired glucose tolerance (glucose > 140 mg dL^{-1} on a two hour 75 gram glucose tolerance test) among HIV-infected patients with clinical and subjective evidence of fat redistribution compared to age and BMI-matched subjects from the Framingham Offspring Cohort (30 vs. 5%). Subjects with abnormal fat redistribution also had an increased prevalence of diabetes mellitus (8% vs. 0.5%) compared to the Framingham subjects[1]. Insulin levels were markedly increased, suggesting insulin resistance rather than pancreatic insulin deficiency. Forty-three percent of the subjects screened met the newly defined ATP-III definition of the metabolic syndrome[9]. Brown demonstrated that diabetes mellitus was 3.1 times more likely to develop over 3 years in HIV-infected men receiving combination antiretroviral therapy compared to control subjects in a longitudinal cohort study[10].

Rationale for the treatment of insulin resistance and impaired glucose tolerance: Recent data suggests that hyperinsulinemia contributes independently to CAD[11]**.** The mechanisms of this effect are not known, but may related to changes in endothelial function and/or associated dyslipidemia or impaired fibrinolysis. In addition, significant data now suggests that impaired

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glucose tolerance confers an increased risk of CAD. In the Paris Prospective Study, Eschwege *et al*. demonstrated an increased risk of CAD among patients with IGT compared to normal glucose tolerance[12]. Although similar studies have not been performed among HIV-infected patients, there is increasing concern that abnormalities in glucose homeostasis may similarly confer increased CAD risk in the HIV population.

Strategies to improve insulin sensitivity: General strategies to improve insulin sensitivity include weight loss (for the viscerally obese), exercise and use of insulin sensitizers. Among HIV-infected patients with insulin resistance, recent studies suggest that use of insulin sensitizing agents, including exercise (in the form of aerobic and resistance training) metformin and/or the glitazones (thiazolidinediones which bind and activate PPAR gamma) may be useful to modify cardiovascular risk, improve glucose control and potentially redistribute body fat. In a recently published study, Hadigan *et al*. demonstrated improved insulin, blood pressure, waist circumference and CHD risk markers of impaired thrombolysis (TPA and PAI-I) in patients treated with metformin for 12 weeks[13,14]. Sustained benefits over 9 months on insulin and CHD markers were seen in a recently published 9-month open label extension[15].

Treatment with metformin is best reserved for those patients with truncal and/or visceral obesity and not subjects with primary lipoatrophy, in whom agents to restore subcutaneous fat may be more beneficial. Metformin should never be given to patients with creatinine > 1.4 mg dL^{-1} and or significant liver dysfunction. Lactic acidosis is a potential concern, but has not been demonstrated in any prior study published to date among HIV-infected patients. Metformin therapy must be considered investigational at the current time, although its use in selected patient populations of HIV-infected patients (impaired glucose tolerance, insulin resistance, increased central adiposity) has proven promising in reducing CHD risk indices and decreasing truncal fat.

Exercise may improve the effects of insulin sensitizing agents and be useful in combination with pharmacologic therapy. In a recent study, Driscoll *et al*. investigated the effects of metformin alone or in combination with progressive resistance and aerobic training three times a week over 3 months[16]. Treatment with combination metformin and exercise resulted in a greater improvement in WHR and insulin than metformin alone. One potential mechanism of this added effect may a reduction in fat within the muscle. Driscoll *et al*.[17] demonstrated that combined metformin and exercise reduce fat within the muscle more than metformin alone. The improvement in fat within the muscle was a significant predictor for improved insulin levels. As discussed above, abnormal lipid deposition within the muscle may contribute to reduced glucose uptake due to inhibition of IRS-1 associated PI3-kinase.

Recent attention has focused on the glitazones, agents that stimulates PPAR gamma and increase glucose uptake into the muscle. In addition, the glitazones increase subcutaneous adipogenesis. Rationale for the use of glitazones was suggested by the recent observations of PI-induced inhibition of SREBP and PPAR gamma signaling in HIV-infected patients[18]. In addition, thiazolidinediones increase adiponectin, which may further contribute to increased insulin sensitivity through increased lipid oxidation.

Arioglu *et al*.[19] demonstrated in non-HIV infected patients that a glitazone agent can increase subcutaneous fat in patients with congenital or acquired non HIV lipodystrophy. Similarly, recent preliminary studies in HIV-infected patients demonstrate that rosiglitazone can increase extremity fat as assessed by DEXA[20]. Other studies suggest that such agents may decrease liver fat and improve liver function[21]. Three randomized, placebo-controlled trials of rosiglitazone in HIV-infected patients have recently been published[21-23]. Sutinen and Carr *et al*.[21,22] studied HIV-infected patients with evidence of fat atrophy, but did not *a priori* select patients for insulin resistance. Although insulin levels improved in both studies, subcutaneous fat did not increase. In contrast, Hadigan *et al*.[23] performed a randomized, placebo-controlled study of HIV-infected patients with insulin resistance and fat atrophy. Hadigan *et al*. demonstrated improved insulin sensitivity using the hyperinsulinemic euglycemic clamp procedure and a 24% increase in mid thigh extremity fat as determined by cross-sectional CT scan. In addition, adiponectin increased significantly, as also shown by Carr *et al*.[22]. Of note, rosiglitazone was associated with an increase in LDL in the three randomized studies performed to date[21-23]. This effect has been previously demonstrated in non HIV-infected patients receiving thiazolidinediones and may be improved with use of other agents including pioglitazone, or in combination with lipid lowering therapy.

Liver function improved in one study and did not worsen in the others. However, idiosyncratic liver dysfunction in response to glitazone administration is possible with this class of agents. Nonetheless, glitazones remain a promising class of agents to potentially increase subcutaneous fat and improve metabolic indices in HIV-infected patients. Further studies of the glitazones are now underway, including an ACTG study in which both rosiglitazone and metformin are being investigated alone and in combination.

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