Perspective

Insulin Resistance in HIV Infection: Drugs, Host Responses, or Restoration to Health?

Protease inhibitors (PIs) are widely assumed to be associated with a syndrome of insulin resistance accompanied by hyperlipidemia and fat redistribution. Insulin resistance in HIV infection has numerous other causes, however, which include not only the direct effects of antiretroviral drugs but also factors such as aging and restoration to health accompanied by fat accumulation. Studies of PIs in HIV-infected and noninfected patients indicate that some of these drugs are associated with reduced insulin sensitivity (greater acute versus chronic effects) that may be due to direct blockade of the insulin-sensitive glucose transporter in muscle and fat cells. Other studies have shown that insulin levels increase over time with antiretroviral therapy, likely the result of improved health, fat accumulation, and aging, and that increases in visceral fat and upper trunk fat are associated with a higher risk of insulin resistance in HIV-infected and -uninfected individuals alike. This article summarizes a presentation on insulin resistance in HIV infection made by Carl Grunfeld, MD, PhD, at the 10th Annual Ryan White HIV/AIDS Program Clinical Update in Phoenix in June 2007. The original presentation is available as a Webcast at www.iasusa.org.

Protease inhibitors (PIs) are widely assumed to induce a syndrome of insulin resistance accompanied by hyperlipidemia and fat redistribution that resembles the metabolic syndrome with its increased risk of cardiovascular disease. Researchers now believe, however, that numerous factors contribute to the metabolic alterations observed in HIV-infected patients and that some of these factors may be overlooked if only a single cause is assumed.

Insulin Resistance

Insulin resistance exists, but it cannot be diagnosed accurately in the clinic. Clinical insulin assays are, in short, terrible for providing absolute measurements of insulin; these assays were developed as a clinical tool to detect inappropriate insulin levels during hypoglycemia by assessing whether insulin levels change during fasting. (Research insulin assays may work better.) Many studies assess insulin resistance using a homeostasis model assessment of insulin resistance (HOMA-IR), which is calculated as follows: insulin concentration (µU/mL) multiplied by the result of glucose concentration (mmol/L) divided by 22.5; a score of higher than 4 indicates insulin resistance, which is useful in epidemiologic studies. Note, however, that the calculation depends on measuring insulin level and therefore does not work using clinical laboratory measurements. Similar calculations can be derived from results of glucose tolerance testing. The current gold standards are the insulin tolerance test and the euglycemic-insulin clamp technique, the latter of which measures insulin-mediated glucose disposal (glucose infusion rate divided by insulin level, or M/I). Neither is appropriate for use in the clinic. The bottom line is that insulin resistance is inferred rather than accurately measured in a given patient.

A diagnosis of insulin resistance portends an unfavorable outcome. Insulin resistance is the first step toward diabetes, but it must be accompanied by a (largely genetically determined) reduction in insulin secretion. Insulin resistance is one of the World Health Organization (WHO) criteria for metabolic syndrome, but the WHO criteria are rarely used because of the need to perform insulin clamp studies to make the diagnosis (Kahn et al, Diabetes Care, 2005). Epidemiologically, insulin resistance is strongly linked with coronary artery disease, and debate exists over whether it is the prime causal factor or a risk marker. Factors known to cause insulin resistance outside the setting of HIV infection include obesity, especially visceral obesity; physical inactivity; the use of some drugs (eg, glucocorticoids and niacin); and acute bacterial infection. Keep in mind, however, that approximately 20% of healthy, thin individuals have insulin resistance.

Insulin Resistance in HIV Infection: Effects of Protease Inhibitors

Studies of acute HIV infection usually show insulin resistance and hyperglycemia (with hypoglycemia appearing during sepsis). Early studies of the insulin profile in HIV infection (Hommes et al, Metabolism, 1991) were remarkable in that no insulin resistance or hyperglycemia was observed; in fact, patients were often thin, and clamp studies indicated increased insulin sensitivity. In 2000, Mulligan and colleagues reported findings in a study that assessed changes in glucose and insulin before and approximately 3 months after the addition of a PI (indinavir, saquinavir, or ritonavir) or lamivudine to stable antiretroviral therapy and compared those results to those in patients maintained on a stable regimen that did not include a PI or lamivudine (control). As shown in Figure 1, patients receiving a PI had a clinically trivial but nonetheless remarkable increase in glucose concentrations over the short study period, as well as a doubling in insulin concentrations; also, no change in body fat distribution (limb fat and trunk fat) was evident (Mulligan et al, JAIDS, 2000). These findings indicate that
related to restoration of health or a direct result of the PI. These studies again showed no alteration in visceral or subcutaneous fat with PI administration. Indinavir, but not lopinavir/ritonavir, was associated with statistically significant increases in fasting glucose and insulin concentrations (Figure 2; Noor et al, *AIDS*, 2001; Lee et al, *AIDS*, 2004).

These findings thus suggest that the effects of at least some PIs on metabolism do not depend on antiretroviral therapy–related restoration of health and improved immune response or on changes in body composition. This is not to say, however, that metabolic changes related to body composition factors do not also occur. Clamp studies in the patients receiving indinavir showed a statistically significant decrease in insulin sensitivity; results of 2-hour oral glucose tolerance testing showed a statistically significant increase in glucose levels, with 1 patient meeting the criterion for diabetes and 2 patients meeting the criterion for impaired glucose tolerance (Figure 3). However, the insulin resistance observed in these patients was not classic insulin resistance because no resistance to the effects of insulin on lipid metabolism was observed. Measurement of free fatty acid levels during oral glucose tolerance testing showed that levels were normally suppressed in both indinavir and lopinavir/ritonavir recipients (Figure 4); similar findings were made in clamp studies.

The findings indicating normal lipid kinetics in these subjects are of particular interest given in vitro findings indicating that PIs bind to and block the insulin-sensitive glucose transporter (GLUT4; Hruz, *Am J Infect Dis*, 2006). Protease inhibitors decreased insulin-stimulated glucose transport in fat cells with no blockade of any aspect of insulin activation (eg, phosphorylation, lipid metabolism). The direct effect on GLUT4 was supported by showing that glucose transport was blocked in non-insulin-sensitive cells transfected with GLUT4. These effects of PIs were evident within minutes of exposure.

Dr Grunfeld and colleagues therefore examined the effects of single doses of PIs in healthy HIV-seronegative patients. As shown in Figure 5, every patient exhibited insulin resistance (reduced M/I), with the reduction in glucose infusion rate during the clamp study evident within 30 minutes. Glucose disposal during the hyperinsulinemic clamp is caused by insulin increasing glucose transport by increasing the activity of GLUT4 in muscle and fat. Studies of other PIs showed that single-dose ritonavir—but not ampranavir—reduced M/I (Figure 6), and that 10 days of lopinavir/ritonavir also reduced M/I. The picture that has emerged from these studies is that the effects caused by some PIs of increasing insulin resistance are strong in the short term and reduced with long-term dosing (Lee et al, *Curr HIV/AIDS Rep*, 2000). The greatest effects are observed with indinavir and full-dose ritonavir, the drugs in use when diabetes began to appear in HIV-infected patients.

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**Figure 1.** Changes in plasma glucose and insulin levels in HIV-infected patients after adding a protease inhibitor (PI) (indinavir, n = 16; saquinavir, n = 2; or ritonavir, n = 2) or lamivudine (n = 9) to stable treatment containing neither (control, n = 12). Asterisks indicate statistically significant difference. Adapted from Mulligan et al, *JAIDS*, 2000.

**Figure 2.** Plasma glucose and insulin levels before and after 4 weeks of protease inhibitor treatment in healthy HIV-seronegative patients. Adapted from Noor et al, *AIDS*, 2001, and Lee et al, *AIDS*, 2004.

whereas PIs do cause some metabolic changes, the changes are not mediated by alteration of body composition.

Dr Grunfeld and colleagues thus performed studies in which indinavir or lopinavir/ritonavir were administered to healthy HIV-seronegative patients to determine whether the metabolic effects in HIV-infected patients might be
Average Ritonavir 100 20 200 180
Indinavir 120 180 150
Indinavir 40 180 60 160
Amprenavir 150
Average 120 120 30 80 60 90 90 60 140 30
Mean

Mean long-term follow-up of more than 5 years showed that all groups had a statistically significant increase in insulin levels over time (Figure 7). Short-term follow-up among nonrandomized patients receiving didanosine/stavudine versus abacavir/ lamivudine showed a statistically nonsignificant greater increase in the patients receiving nucleoside analogue reverse transcriptase inhibitors (nRTIs) than in patients receiving NNRTIs (nRTIs are themselves associated with specific effects on metabolism that are not discussed here; Shlay et al., JAIDS, 2005; Shlay et al., JAIDS, 2007).

The factors causing increased insulin resistance in these treated patients, which appear to overwhelm the changes produced by PIs, are likely related to changes such as improved health and gaining of body fat, as well as aging. In the Fat Redistribution and Metabolism (FRAM) study (Grunfeld et al., JAIDS, 2007), Dr Grunfeld and colleagues assessed metabolic and body composition profiles in nondiabetic HIV-infected patients and healthy controls. Glucose levels were similar in male and female patients and controls; HOMA-IR levels were somewhat higher in HIV-infected women, but not in HIV-infected men, compared with controls. Multivariate analysis showed that being in the upper tertiles for visceral fat and upper trunk fat was associated with a markedly increased risk of having a HOMA-IR value higher than 4 (Table 1). The relationship between fat deposits and insulin resistance as assessed by HOMA-IR values above 4 is stronger in controls than in HIV-infected subjects because other factors, such as antiretroviral drugs, contribute to insulin resistance in patients with HIV infection that are not operative in controls. Factors predictive of greater visceral fat were male sex, white race, increasing age, not smoking, and reduced physical activity (Table 2).

Figure 4. Comparison of free fatty acid levels during oral glucose tolerance testing in healthy HIV-seronegative patients receiving 4 weeks of indinavir or lopinavir/ritonavir. Adapted from Noor et al, AIDS, 2001, and Lee et al, AIDS, 2004.

Other Factors in Insulin Resistance: Restoration of Health, Fat, and Aging

The effects of indinavir on insulin resistance are greater in HIV-infected patients than in noninfected patients, indicating that factors in addition to the potential blocking of insulin-mediated glucose transport are operative in HIV infection. That such factors are active in addition to the specific drug effect of some PIs is supported by long-term data. In the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study, patients in whom a PI was added to treatment had an early increase in insulin levels compared with those adding a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) or PI plus NNRTI treatment; however, follow-up of more than 5 years showed...
Should Insulin Resistance Be Treated?

Insulin resistance in HIV-infected patients is treatable with lifestyle modification or drug therapy. The “prediabetic” use of antidiabetic drugs is not currently approved by the US Food and Drug Administration. Small studies of metformin and rosiglitazone in HIV-infected patients with insulin resistance have shown statistically significant decreases in insulin area-under-the-curve concentration with both drugs (Hadi gan et al, JAMA, 2000, and Hadigan et al, Ann Intern Med, 2004). The Diabetes Prevention Program study in individuals from the general population with impaired fasting glucose or impaired glucose tolerance showed that a rigorous lifestyle intervention (diet and exercise) was associated with a 68% reduction in incidence of diabetes compared with a 31% reduction with metformin treatment; the thiazolidinedione troglitazone was discontinued from this study (and removed from the market after reports of severe and fatal hepatotoxicity) but was associated with reductions in incidence of diabetes at early time points in the study.

Other data also indicate the benefit of thiazolidinedione treatment in “preventing” diabetes in individuals with impaired fasting glucose and impaired glucose tolerance. However, an increased risk of myocardial infarction and of bone fracture in women has been reported with rosiglitazone treatment, and both rosiglitazone and pioglitazone (the 2 thiazolidinediones currently on the market) have been associated with lower bone mineral density. Whether treatment of insulin resistance before development of diabetes is associated with long-term benefits has yet to be determined.

Table 1. Effect of Tertile of Visceral Adipose Tissue and Upper Trunk Fat on Risk for Insulin Resistance (HOMA-IR > 4) in Healthy Control and HIV-infected Patients in Fat Redistribution and Metabolism Study

<table>
<thead>
<tr>
<th>Visceral Adipose Tissue</th>
<th>Controls</th>
<th>HIV-infected Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>P Value</td>
</tr>
<tr>
<td>3rd vs 1st tertile</td>
<td>12.1</td>
<td>.0002</td>
</tr>
<tr>
<td>2nd vs 1st tertile</td>
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<td>.31</td>
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<table>
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<tr>
<th>Upper Trunk Fat</th>
<th>Controls</th>
<th>HIV-infected Patients</th>
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<tbody>
<tr>
<td>3rd vs 1st tertile</td>
<td>9.0</td>
<td>.001</td>
</tr>
<tr>
<td>2nd vs 1st tertile</td>
<td>2.4</td>
<td>.20</td>
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</tbody>
</table>

HOMA-IR indicates homeostasis model assessment of insulin resistance.

*The model controls for ethnicity, age, sex, alcohol use (HIV group only), current “crack” and other cocaine use (HIV group only), physical activity (control group only), and adequacy of food (control group only).

*Tertiles of control group are used as reference to directly compare HIV group with control group.

Conclusions

The development of insulin resistance in HIV-infected patients is multifactorial, with causes including restoration to health, direct drug effects of PIs and nRTIs, increased visceral adipose tissue, age, and inactivity. Insulin resistance is hard to diagnose accurately but can be inferred. Treatment of insulin resistance is similar in HIV-infected patients and uninfected individuals, but the long-term value of initiating treatment before the development of diabetes is unknown.
Table 2. Effects of Subject Characteristics on Visceral Adipose Tissue in Fat Redistribution and Metabolism Study

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Percent Effect</td>
<td>P Value</td>
</tr>
<tr>
<td>Ethnicity, vs White</td>
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<td></td>
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<tr>
<td>African American</td>
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<td>.001</td>
</tr>
<tr>
<td>Hispanic</td>
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<td>.74</td>
</tr>
<tr>
<td>Age, per decade</td>
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<td>&lt;.0001</td>
</tr>
<tr>
<td>Current Smoker</td>
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<td>.003</td>
</tr>
<tr>
<td>Physical Activity, vs 1st Quartile (least)</td>
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<td></td>
</tr>
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<td>2nd quartile</td>
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<td>.82</td>
</tr>
<tr>
<td>4th quartile</td>
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<td>.020</td>
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Suggested Reading


Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in women with HIV infection. JAIDS. 2006;42:562-571.

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