Insulin and Carbohydrate Dysregulation

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Patients with human immunodeficiency virus receiving highly active antiretroviral therapy (HAART) may experience abnormal body composition changes as well as metabolic abnormalities, including dyslipidemia, increases in triglycerides, low high-density lipoprotein cholesterol levels, and abnormal carbohydrate metabolism, ranging from insulin resistance with and without glucose intolerance to frank diabetes. Whether the body composition changes (i.e., increased visceral adiposity and fat wasting in the peripheral tissues) are linked to abnormalities in carbohydrate metabolism is unclear. The use of HAART with and without therapy with protease inhibitors (PIs) is related to carbohydrate abnormalities and changes in body composition. Regimens that include PIs appear to have a higher incidence of insulin resistance (up to 90%) and diabetes mellitus (up to 40%). The etiology of these abnormalities is not well understood; what is known about insulin and carbohydrate dysregulation with HAART is discussed.

Since the late 1990s, many reports have been published that have described insulin and carbohydrate abnormalities in HIV patients receiving highly active antiretroviral therapy (HAART) [1, 2]. As with other metabolic abnormalities, the prevalence of diabetes, impaired glucose tolerance (IGT), and insulin resistance (IR) is not precisely known. How these abnormalities relate to protease inhibitor (PI) therapy or other components of HAART is likewise not fully understood. Here, I discuss these issues, along with nutritional interventions and considerations for switching antiretroviral therapies.

PREVALENCE

Existing data suggest that patients receiving therapy with PIs have a greater incidence of IR (~30%–90%) than patients receiving non–PI-containing regimens (up to 20%) [2–4]. However, many patients receiving PIs do not have glucose intolerance, and most are not overtly diabetic. The incidence of frank hyperglycemia and diabetes mellitus is 1%–11% [5–8], with the higher estimates including diabetes (up to 40%) detected by oral glucose tolerance testing (oGTT) [6]. In addition to the 7% prevalence of diabetes among PI recipients, an additional 16% had IGT [6]. Another study reported that 5 (13%) of 38 PI recipients had diabetes and 18 (47%) of 38 had IGT detected by oGTT, whereas 4 (24%) of 17 PI-naive subjects had IGT and none had diabetes [5]. In contrast, IR has been reported in treatment-naive patients (D. Hardin, personal communication) as well as in patients receiving non–PI-containing regimens before HAART.

In one large-cohort study comparing 75 HIV-infected women experiencing wasting with 30 healthy controls, significant hyperinsulinemia was present in association with HIV infection unrelated to PI therapy [9]. Nonetheless, cross-sectional studies strongly implicate PI therapy as a significant cause of IR in HIV-infected patients [3]. However, all PIs may not have the same effects on carbohydrate metabolism. Dube et al. [10] showed that amprenavir-based therapy for 8 weeks had little effect on glucose metabolism but was associated with increases in cholesterol. These rates of diabetes in HIV-positive patients are higher than the incidence of diabetes in the general population of the United States, which is 6% [11]. This implies that large
numbers of HIV patients may be at risk for the complications of diabetes mellitus, which has significant health care consequences.

It is uncertain how individual patients should be evaluated for abnormalities of carbohydrate and insulin metabolism. For example, glucose or free fatty acid levels are insensitive measures of IR. Even with severe IR, if the pancreas is functional, insulin levels rise to counter the increased IR. Similarly, oral or intravenous glucose tolerance tests indicate whether insulin output can increase sufficiently to clear a glucose load, but unless insulin levels are measured, these tests will not identify IR. Measures of insulin and C-peptide levels in relation to glucose levels or insulin-glucose clamp techniques are needed to assess and monitor the progression of IR.

In patients receiving PIs, as well as in patients receiving non-PI-containing regimens and who have normal fasting glucose, severe IR can be demonstrated on the basis of the glucose clamp technique and is similar to that in patients with type 2 diabetes mellitus [12]. Thus, standardized assessments are needed to determine the true prevalence of IR and carbohydrate metabolism abnormalities. Until that time, practitioners may elect to measure fasting insulin, C-peptide, and glucose levels to assess insulin sensitivity, although exact guidelines that differentiate normal from abnormal/IR do not exist. In addition, oGTT may be helpful in those patients with borderline fasting glucose levels (≥110 mg/dL) to assess these patients for diabetes mellitus as well as IGT. It is possible for patients to have normal fasting glucose levels but still have IGT that the oGTT would detect. Therefore, oGTT may be the best test. The addition of insulin level measurements would evaluate the patients for IR as well.

POTENTIAL FOR MORBIDITY AND MORTALITY

The potential consequences of IR in this patient population may be inferred from experience with diabetes and obesity in HIV-uninfected persons. Hyperinsulinemia was shown to be an independent risk factor for ischemic heart disease apart from its effects on lipids and endothelial cell function [13]. In addition, IR is associated with a dyslipidemia that is also atherogenic [14]. The primary dyslipidemia associated with IR is elevation of serum triglycerides due to reduced activity of lipoprotein lipase [15]. In addition, high-density lipoprotein cholesterol levels are consistently low secondary to decreased production and increased catabolism, but levels of low-density lipoprotein cholesterol usually are not markedly elevated [15]. The low levels of high-density lipoprotein cholesterol in the HIV-infected population may be the more important finding. IR induces high levels of plasminogen activator inhibitor type 1, which may predispose patients to thrombosis. IR is also linked to elevated fibrinogen and factor VIII levels, which may reflect endothelial cell dysfunction [14, 15]. Thus, there are multiple mechanisms by which IR can lead to atherosclerosis.

In terms of assessing patients, it has been shown from studies in patients with type 2 diabetes mellitus that IGT is more predictive of cardiovascular disease risk [16]. Therefore, in the HIV-positive patients, oGTT may be an important screening tool not only for assessing whether patients have diabetes or IGT, but also for assessing whether they are at increased risk for cardiovascular disease.

In addition to an increased risk of atherosclerosis, HIV-infected individuals with IR may also be more at risk for abnormalities in body fat. As indicated above, one important issue is whether body fat changes are independent of the metabolic changes. Data from Mulligan et al. [17] suggest that IR precedes changes in body fat in HIV-positive patients initiating PI therapy. In one cohort study of PI use and HIV lipodystrophy (loss of fat from the periphery and increased truncal fat), subjects receiving PIs had greater homeostasis model assessment (HOMA) IR values [6]. Increasing lipodystrophy severity was associated with a trend for increasing values of HOMA-IR (P = .05) and was predicted by higher antecedent fasting C-peptide and triglyceride levels, suggesting that body shape and metabolic abnormalities may be linked [6].

These data are similar to findings by the LIPOCO study, which showed that in patients who received both nucleoside reverse transcriptase inhibitors (NRTIs) alone or regimens that included PIs, both groups had body fat changes and significant IR [18]. In addition, Carr et al. [19] reported that patients who had lipodystrophy while receiving PIs plus NRTIs as well as those receiving only NRTIs had elevated C-peptide levels, this providing some evidence of carbohydrate dysregulation. Not all studies [20] that evaluated patients who received NRTIs only and who developed abnormal body fat distribution assessed carbohydrate metabolism. Therefore, long-term prospective studies, particularly in therapy-naive patients, are needed to assess whether the changes in body composition are linked to IR, as in the classic syndromes of lipodystrophy [21]. The data do imply, however, that both PIs and NRTIs cause a lipodystrophy syndrome that includes IR [19, 20].

PATHOGENESIS

The etiologies of both the IR and the body composition changes are unclear. It is likely that multiple factors play a role. These include direct drug toxicity (not all drugs in every class have the same effects, so it can be drug specific), changes in the immune system brought about by the successful treatment of patients with HAART, and the genetic predisposition of the individual and perhaps the HIV infection itself [22, 23]. Our group reported that in patients (receiving PIs and/or NRTIs) with the fat-redistribution syndrome, IR was highly correlated
to the circulating levels of the soluble type 2 receptor for TNF-α (TNFR-2) \[12\]. Another group of investigators \[22\] also found that both serum levels of TNF-α and TNFR-2 were elevated in patients with lipodystrophy. These authors reported that after PI administration, there was an increase in the percentage of absolute numbers of T cells synthesizing TNF-α observed in all patients. In women receiving antiretroviral therapy who developed lipodystrophy, IL-12 synthesis was increased, but not TNF-α. These studies suggest that inflammation may play a role in the pathogenesis of this syndrome. Certainly, cytokines, including TNF-α, have been shown to increase serum free fatty acids and can interfere with the insulin signaling cascade, thus inducing IR and hyperglycemia. This has been well documented in obese patients with type 2 diabetes mellitus \[24, 25\].

In terms of direct drug toxicity, recent data from Bastard et al. \[26\] demonstrated that in adipose tissue from HIV-positive patients, there was a decrease in the mRNA concentrations of the adipogenic differentiation factors, peroxisome proliferators-activated receptor (PPAR) gamma and the 1c isoform of sterol regulatory element–binding protein 1. In addition, leptin was lower and expression of TNF-α was increased. These abnormalities, taken together, could explain the loss of peripheral fat and the resultant IR. Brinkman et al. \[27\] postulated that the NRTI-related syndrome may be the result of mitochondrial toxicity with impairment of hepatic glycogen and fat oxidation, leading to increased oxidation of peripheral energy stores and to lipolysis. However, it is not clear how this would explain the mixed syndrome of fat accumulation and IR seen in some patients receiving NRTIs. It would seem likely that all these factors may be operative in patients on HAART to cause these body composition and metabolic complications. Careful prospective studies that focus on pathogenesis as well as clinical manifestations are needed to answer some of these questions and direct targeted therapies.

**NUTRITIONAL INTERVENTIONS**

Although the etiology of abnormalities in glucose and insulin sensitivity has not been fully established, appropriate aspects of management can be initiated. Patients need to be assessed for risk factors for IR and diabetes mellitus as well as for atherosclerosis (e.g., family history, inactivity, smoking, and body mass index [weight in kilograms divided by height in meters squared as indicator of obesity], hypertension, and dyslipidemia). Risk factors need to be modified where possible. Diet and exercise, mainstays of therapy for type 2 diabetes mellitus \[28\], are also appropriate for HIV-related IR and diabetes. Thus, following recommendations of the American Diabetes Association for diet and exercise should be appropriate for persons with HIV. In brief, diet should be composed of 50%–60% carbohydrates (mostly complex carbohydrates) and protein intake of 10%–20% of all calories; total fat intake should be restricted to 30% of total calories (with saturated fat limited to 10% of total calories and total cholesterol intake <300 mg/dL). A word of caution about exercise, particularly in older patients: it may be wise to assess the cardiac status of the patient before starting an exercise program, particularly if the patient has other risk factors for coronary artery disease.

Medical nutrition therapy is integral to total care and management. Achieving nutrition-related goals requires a coordinated team effort that includes the patient. Because of the complexity of nutrition-related issues, a registered dietician or other qualified nutrition professional knowledgeable and skilled in implementing diabetes medical nutrition therapy should provide nutrition care and education.

A number of factors should be considered in deciding on specific interventions. As noted above, IR alone (without hyperglycemia) is a major risk factor for atherosclerosis. Hyperglycemia only minimally increases the risk for atherosclerosis above that of IR, but IGT, as noted above, may reflect cardiovascular disease risk \[16\]. Thus, interventions may be appropriate when there is evidence of elevated insulin levels or IGT. If the patient has diabetes mellitus (defined by fasting glucose values \(\geq 126\) mg/dL or random levels \(\geq 200\) mg/dL), then diet, exercise, and—if necessary—drug therapy and/or insulin may be required.

Drug therapy in HIV-positive patients with diabetes mellitus should be that recommended for type 2 diabetes mellitus. Part of the current guidelines for HIV-uninfected patients with type 2 diabetes mellitus is that they be treated with oral agents to reduce the hyperglycemia and secondarily to improve insulin sensitivity. The 2 major classes of oral agents are the insulin secretogogues (the major class being the sulfonylureas) and the insulin-sensitizing agents (biguanides [metformin] and the thiazolidinediones [TZDs]) \[29\]. There are few studies in HIV-positive patients that assess either of these classes of agents. However, the insulin-sensitizing agents may have an advantage in HIV-positive patients both to ameliorate the IR and to decrease visceral adiposity.

Metformin therapy has been studied both in an open-label nonplacebo controlled study \[30\] and more recently in a randomized, controlled trial \[31\]. In both studies, metformin significantly improved IR, and there was a trend toward decreased visceral adiposity as measured by CT scan; however, metformin also decreased peripheral fat. Patients treated with metformin demonstrated significant weight loss, reduced waist circumference, and decreased diastolic blood pressure. Only in the open-label study did serum triglyceride levels decrease.

In a subsequent study, a subanalysis from the randomized clinical trial with metformin \[32\], metformin therapy significantly decreased plasminogen activator inhibitor 1 and tissue...
type plasminogen activator antigen concentrations, both known to be associated with increased cardiovascular disease risk, suggesting that metformin may improve associated cardiovascular disease risk in this patient population. Importantly, at least over 3 months, metformin did not result in any increase in lactic acidosis, which is a potential side effect of this drug [33], and, interestingly, the patients randomized to metformin therapy had higher baseline lactate levels than did patients receiving placebo [31]. There are small studies exploring the use of the TZDs. Theoretically, TZDs are ideally suited to treat the metabolic abnormalities observed in HIV-positive patients with fat redistribution and IR. The TZDs stimulate adipocyte differentiation; thus, they have the potential to decrease visceral adiposity and to increase subcutaneous adipose tissue as well as to improve IR. Walli et al. [34] studied a small cohort of HIV-positive patients who received therapy with troglitazone, but as a result of the potential liver toxicity with this agent, troglitazone is no longer available. Other TZDs, rosiglitazone and pioglitazone, are now available; they are associated with less liver toxicity and fewer drug-drug interactions.

In a small pilot study of 9 HIV-positive patients with documented IR and fat redistribution, rosiglitazone 8 mg/d was administered for 6–12 weeks [35]. IR improved by 59%, subcutaneous fat increased by 23%, and visceral adiposity decreased by 21%. These results are promising. However, Sutinen et al. [36], in a placebo-controlled trial that used rosiglitazone therapy in HIV-positive patients with diabetes, did not find changes in fat redistribution, although a significant improvement in IR was observed. Nonetheless, these drugs hold promise, although more studies are needed to assess their long-term safety and efficacy in HIV-positive patients.

CONSIDERATIONS FOR SWITCHING ANTIRETROVIRAL THERAPIES

Decisions about when to switch antiretroviral therapy for patients with IR and/or hyperglycemia should be individualized. For patients receiving PI-containing regimens who develop hyperglycemia that is difficult to control, switching antiretroviral therapy should be considered, especially if it includes a PI. IR improved after substituting nevirapine for PI therapy in non-NRTI–naive patients in one published study [37] but not in other studies presented in abstract form [38–40]. Improvement in insulin sensitivity measured by intravenous insulin-tolerance testing occurred after the substitution of abacavir for a PI [41]. However, a recent study by Carr et al. [42] demonstrated that the elimination of PIs from the therapeutic regimen failed to increase peripheral fat accumulation or to improve insulin sensitivity. Virologic relapse rates after substitution of a non-NRTI or abacavir for a PI have not been high to date, but longer follow-up is needed. Clinicians thus must weigh the potential benefits of reduced IR with the risks of virologic relapse and new drug toxicities.

References


