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Glycemic Control in HIV Patients

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Abstract
Purpose of Review Glycemic alterations are highly prevalent in HIV-infected and non-HIV-infected patients. Our purpose was to review the etiology, diagnosis, and management of dysglycemia to improve the treatment in the HIV population.
Recent Findings Fourteen percent of HIV patients have diabetes. Etiology factors can be divided in environmental factors (weight, age, smoking), as well as factors merely associated to HIV, such as viral effects, growth hormone deficiency, antiretroviral therapy, lipodystrophy, hepatic steatosis, and hepatitis C co-infection. Diabetes diagnosis is comparable to those uninfected, being the only exception the glycosylated hemoglobin criteria. However, treatment differs due to drug interactions between oral antidiabetic drugs and antiretrovirals. Lifestyle modifications in diet and exercise remain essential as a complement to the pharmacological treatment.
Summary We reviewed current information about epidemiology, etiology, diagnosis, and management of glycemic alterations in HIV-infected patients.

Keywords HIV · Dysglycemia · Insulin resistance · Diabetes mellitus · HAART

Topical Collection on *Nutrition*

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Introduction

Diabetes mellitus (DM) is becoming more common. From 1980 through 2014, the number of Americans with the disease, increased fourfold, from 5.5 million to 22.0 million [1]. Human immunodeficiency virus (HIV), on the other hand, decreased its prevalence, dropping 19% of new diagnoses from 2005 to 2014 [2]. Nevertheless, DM prevalence estimates in HIV-infected patients is up to 14% [3••]. This increased number of unexpected consequences of chronic illness has been seen since the introduction of highly active antiretroviral therapy (HAART) [4••].

The mechanisms underlying dysglycemia and the relationship of the glucose metabolic disorders to those of lipid metabolism and fat redistribution, ethnicity, diet, and specific HAART agents are multifaceted, complex and, to some degree, enigmatic [4••].

Lipodystrophy syndrome or HIV metabolic syndrome is characterized by alterations in the lipid and glucose metabolism, excess and redistribution of body fat, and hypertension. Despite the HAART bringing many benefits to carriers of the HIV, metabolic changes can occur as side effects, increasing cardiovascular risks and insulin resistance (IR) [5].

Our goal is to review key issues in the development of dysglycemia in HIV-infected patients in order to prevent, diagnose, and treat correctly those alterations with lifestyle modifications and considering drug interactions between oral anti diabetic drugs (OADs) and HAART.

Epidemiology

The risk of DM in HIV-infected patients has been through an ongoing scrutiny probably due to the fact that three subgroups of patients with diabetes and HIV can be identified: patients

with preexisting diabetes who contract HIV, those who are diagnosed to have diabetes at onset of HIV infection, and others who develop hyperglycemia after start of therapy [6•]. There is a lack of prevalence studies among these subgroups. An analysis conducted in the Multicenter AIDS Cohort Study showed that 14% of HIV-infected men using HAART at the baseline visit had prevalent DM and that the rate of incident DM was 4.7 cases per 100 person-years among HIV-infected men using HAART compared with 1.4 cases per 100 person-years among HIV seronegative men [7].

The prevalence of diabetes among HIV-infected persons who are not receiving antiretroviral therapy is unknown. A cross-sectional survey carried out in China analyzed 2006 newly diagnosed HIV patients and found out that 10.52% had diabetes. They also found that the prevalence of diabetes increased with being a minority ethnicity, increasing age, and decreasing CD4 count [8].

Another study, examined metabolic syndrome prevalence in 788 HIV-infected adults that had received HAART at some point and found a 14% prevalence by the International Diabetes Federation (IDF) criteria and 18% by the US National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria [9]. Current HAART type and duration were similar in those with and without metabolic syndrome for nucleosidase reverse transcriptase inhibitors (NRTIs) and non-nucleosidase reverse transcriptase inhibitors. Protease inhibitor (PI) use was associated with a significantly higher prevalence of metabolic syndrome and among these patients; prevalence of diabetes was five- to ninefold greater in those with metabolic syndrome [9]. These findings are relevant because the high prevalence of diabetes and metabolic syndrome puts HIV patients at a higher risk of myocardial infarction [4••].

Etiology and Mechanisms

The etiology of glycemic alterations and associated defects in insulin action and secretion in HIV-infected patients is broad (Fig. 1), with new information continually surfacing [4••]. To better understand the mechanisms, two conditions must be differentiated: an HIV infection without treatment and the other one with HAART.

HIV Infection Without HAART

In a recent study of the proteomic composition of HIV-1-infected CD4 cells, an increase in the concentration of fatty acid synthase (FASN) after HIV-1 infection was found [10]. Other study reported a dysregulation of multiple pathways of lipid metabolism [11]. These findings illustrate the viral effect of the HIV infection on lipid metabolism [12].

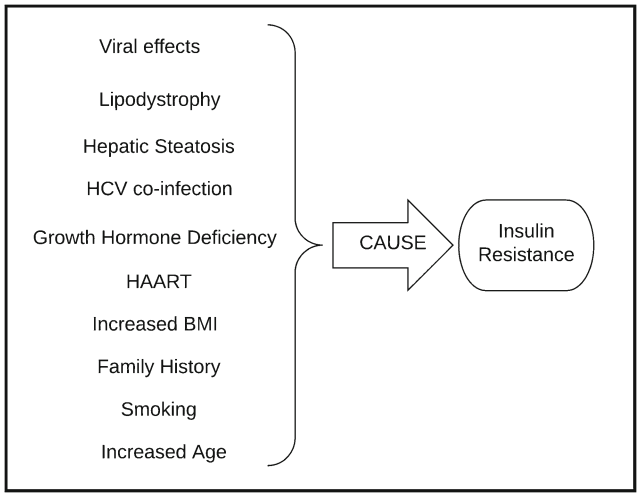

Fig. 1 Etiologic factors for insulin resistance in HIV-infected patients

HIV viral effects can lead to disorders in lipid metabolism and thus produce IR, dysglycemia, and diabetes. Insulin resistance, rather than insulin deficiency, is usually implicated in the pathogenesis of diabetes in HIV-infected patients. However, autoimmune diabetes has recently been reported to develop in some HIV-infected patients after immune restoration during HAART. It is important to notice that DM type 2 is the most frequent in these patients, yet DM type 1 can also be present [6•].

HIV Infection With HAART

Dysglycemia is a significant metabolic side effect associated with HAART. Numerous studies suggest that environmental risk factors such as positive family history, increased body mass index (BMI), smoking, and increased age are more important than HAART in its development [13•]. However, antiretroviral therapy may also contribute to iatrogenic cause of IR [6•].

The main effect of HAART is to suppress viral replication, allowing the individual's immune system to recover and protect against the development of acquired immune deficiency syndrome (AIDS) and death. Nonetheless, long-term HAART induces metabolic abnormalities, including dysregulation of glucose metabolism, dyslipidemia, and/or lipodystrophy [14, 15]. Some studies have shown that patients on a combination of antiretrovirals are more likely to develop glucose intolerance and diabetes mellitus compared to controls [16, 13•].

Lipodystrophy (increased visceral adiposity and peripheral lipoatrophy) has profound defects in lipid turnover kinetics and prompts severe IR and dysglycemia. HIV patients with lipodystrophy have decreased insulin-stimulated glucose disposal, increased intramyocellular lipid, impaired skeletal muscle glucose uptake, increased fasting plasma levels of free fatty acids and insulin, and a higher percentage of hepatic fat, which leads to the development of hepatic steatosis [4••].

The prevalence of hepatic steatosis in HIV-infected patients is high, especially in patients with chronic hepatitis C virus (HCV) or on NRTIs [4••, 17].

Protease inhibitors, which have been extensively used as antiretroviral agents, have been shown to increase IR and reduce insulin secretion, by interfering with glucose transporter type 4 (GLUT-4) [6•]. Other PI-associated effects include alterations in gene expression, altered adipocyte differentiation, and decreased lipid metabolism [18•] through decreasing expression of the transcription factor SREB1c. This factor may induce lipolysis or block adipogenesis by restraining the expression of critical regulators of lipid metabolism, such as lipoprotein lipase and FASN [4••].

Nucleoside reverse transcriptase inhibitors are nucleoside analogues designed to inhibit HIV reverse transcriptase, DNA polymerase, and the DNA polymerase active in mitochondrial replication [19]. This mitochondrial dysfunction slows the Krebs cycle and decreases pyruvate fatty acid metabolism. As a result, glucose clearance decreases independently of insulin content; in other words, IR appears [18•]. It is proposed that PIs confer acute metabolic risks, while NRTIs confer cumulative risks of diabetes in pre-disposed and exposed persons. Thus, the exposure to a combination of NRTIs and PIs has shown to be an additional risk factor for onset of diabetes [20].

The adipose tissue plays a critical role in the maintenance of normal glucose homeostasis and inflammation [21•]. Changes in fat mass (lipoatrophy and/or lipohyperthrophy) or adipocyte function are strongly associated with HIV metabolic syndrome [22].

Leptin, a hormone secreted by the adipose tissue, presents low concentrations in unregulated insulin-deficient diabetes [23]. Hypoleptinemia, hypertriglyceridemia, and hyperinsulinemia can be observed in HIV patients with lipoatrophy and six or more months of HAART treatment [4••]. Leptin deficiency may affect insulin sensitivity through several mechanisms studied primarily in mice. In animal models, leptin signaling regulates hepatic insulin sensitivity, inhibits gluconeogenesis, and attenuates glucose-stimulated insulin secretion. In general, its effects on insulin sensitivity appear to be beneficial [13•], although it is important to mention that long-term HAART, when not accompanied by fat redistribution, does not seem to affect serum leptin concentrations [13•].

Adiponectin has anti-inflammatory effects. It is an adipocyte-secreted protein that links visceral adiposity with IR and atherosclerosis. Its circulating concentrations are lower in obese than in normal weight humans. Thus, low circulating adiponectin concentrations are predicting of the development of insulin resistance, type 2 DM and cardiovascular disease [23]. Adiponectin levels are low in HIV-infected individuals with lipodystrophy and hypertriglyceridemia. Hypoadiponectinemia is seen in HIV-infected patients even prior to the initiation of HAART, though it worsens after initiation [4••].

HIV is also associated with various endocrine abnormalities, including those of the growth hormone axis. These include deficiency of growth hormone (GH), as well as GH resistance. GH deficiency may contribute to insulin resistance in HIV-infected patients [3••, 24] and it is also associated with both HIV lipodystrophy and IR [4••].

The result of all factors is the attenuation of insulin sensitivity. HIV patients with metabolic syndrome due to HAART are usually characterized by euglycemic hyperinsulinemia, and IR. However, diabetes mellitus may develop with the progression of time [13•].

Diabetes and Prediabetes Definitions

According to the American Diabetes Association (ADA), the definition of both terms is practically the same for non-HIV-infected patients (Table 1) [25••], the only exception being the glycosylated hemoglobin (HbA1c) criteria, as there is data that concludes that HbA1C may underestimate blood glucose levels in HIV-infected patients [26]. A prospective study in 2009 determined the relationship between HbA1C and glycemia in HIV infection. A total of 100 HIV-infected patients with type 2 DM (70%) or impaired fasting glucose (23%) were compared to 200 controls with non-HIV-infected type 2 DM and demonstrated that HbA1C levels were discordant with blood glucose levels in patients HIV-infected, especially those who were taking NRTIs [26].

Due to all the risk factors of developing IR, dysglycemia, and/or diabetes, it is recommended that every HIV patient should be screened for diabetes and prediabetes for 6 to 12 months before initiating antiretroviral therapy, and 3 months after initiating treatment. If initial results are normal, fasting glucose should be repeated annually as a screening process [25••, 27].

Diabetes Management

Treatment of type 2 DM in HIV-infected patients varies slightly from the general population [6•]. Nevertheless, therapeutic goals are the same as for the non-HIV-infected population [17]. In addition, the type of HAART must be considered when dysglycemia appears, because as discussed above, PIs and NRTIs can alter glucose and fat metabolism, prompting lipodystrophy, IR, and DM. When appropriate, literature suggests that changes in the type of antiretroviral prescribed should be made in order to achieve euglycemia in high-risk

Table 1 Definitions of prediabetes and diabetes according to ADA

	Fasting plasma glucose (mg/dL)	Random plasma glucose (mg/dL)	HbA1C%[a] (%)	Oral glucose tolerance test (mg/dL)
Diabetes	≥126	≥200	≥6.5	≥200
Prediabetes	100–125	–	5.7%–6.4	140–199
Normal	≤99	–	<5.7	≤139

All parameters should be repeated for confirmation of the diagnosis

[a] Glycosylated hemoglobin

patients [4••], especially, with chronically exposed patients to this treatment [28].

Features of Diabetes Management in HIV Patients

Statins

There are two important disorders associated with type 2 DM, "hypertension and dyslipidemia." These, need to be treated with both pharmacological and non-pharmacological measures in order to be successful at glycemic controls. Dyslipidemias are common in HIV-infected patients with HAART; thus, it is important to add statins as part of the treatment. However, caution should be taken with certain statins, since simvastatin is contraindicated in patients who use PIs, due to the common cytochrome P450 isozyme pathway for metabolism. A safer option for these patients would be atorvastatin and rosuvastatin [6•].

Lifestyle Modification

Weight gain has been seen after the first year of starting antiretroviral treatment; a study published in 2016 whose objective was to understand the weight gain and incident diabetes among HIV-infected veterans initiating antiretroviral therapy compared to uninfected individuals found that for each 5 lb of gained weight, HIV-infected patients had a 14% increased risk of type 2 DM (HR, 1.14; 95% CI, 1.10–1.17) and uninfected individuals had 8% increased risk (HR, 1.08; 95% CI, 1.07–1.10) ($p < 0.01$ for interaction) [29].

A registered dietitian should be consulted for specialized dietary needs, especially in weight-control diets. Evidence has shown that energy-restricted patterns improve metabolic abnormalities and may be appropriate in adults who need those changes [27]. Patients should follow a balanced macronutrient composition pattern consisting of 50–60% carbohydrate, 20–30% fat, and between 15 or 20% protein. Simple sugars must be avoided and preferred high fiber complex carbohydrates, distributed evenly among meals and snacks and consumed in combination with protein or fat [27]. There is not a one-size-fits-all eating pattern for individuals with diabetes [25••].

Regular physical activity is associated with reduced risk of inflammation-associated disease, including dementia, cancer, cardiovascular disease (CVD), and IR. In contrast, prolonged physical inactivity is associated with visceral adipose tissue accumulation, elevation of multiple pro-inflammatory cytokine levels [21•], lower CD4 count, and presence of lipodystrophy [30]. Aerobic exercise leads to improvements in BMI, subcutaneous adipose tissue in triceps, and waist-to-hip ratio [31], which at long term also may improve IR in HIV patients with dysglycemia. Thus, regular physical activity should be encouraged. As in all patients with diabetes, recommendations state that at least 150 min of moderate to vigorous activity should be performed every week, with no more than two consecutive days without exercise. Patients should also decrease time spent in sedentary behavior, and prolonged sitting should be interrupted every 30 min for blood glucose benefits [3••, 25••].

Nutrition therapy has an integral role in overall diabetes management [25••]. In general, patients with diabetes should be educated to prevent acute complications, increase adherence to treatment, and reduce long-term complications. It is essential to insist on blood glucose self-monitoring, diet adjustment, and a physical activity plan, all with the purpose of improving blood glucose and reducing CVD risk [18•]. Smoking cessation should be encouraged in all patients, as well as moderation of alcohol consumption [3••].

Oral Antidiabetic Drugs

The drugs of choice to treat diabetes in HIV-infected patients are metformin and thiazolidinedione. These have been shown to delay the development of diabetes through controlling IR [18•].

Metformin was associated with a reduction in visceral and subcutaneous abdominal fat [18•, 32]. Its use should be avoided in combination with stavudine, since it may increase the risk of lactic acidosis. Other drugs such as abacavir, lamivudine, and tenofovir may be used instead [6•]. Caution also should be taken with the integrase inhibitor, dolutegravir, as it may increase plasma concentration of metformin and might require a reduction in its dose [32].

There are currently no large trials exploring the use of sulfonylureas, meglitinides, GLP-1 analogues, or alpha-glucosidase inhibitors in HIV patients with HAART, but case reports have demonstrated control of diabetes, and the

decision to use them in HIV patients should be individualized [3••, 4••].

Insulin

Insulin is the drug of choice, due to its numerous advantages in these patients. It has anabolic effects, reduces inflammatory markers, and does not have interactions with HAART or other drugs; it is not contraindicated in renal failure or liver dysfunction and does not reduce appetite or cause gastrointestinal side effects. It can correct both insulin deficiency and resistance and does not increase the risk of CVD [6•].

Insulin initiation is essential in order to follow American Diabetes Association (ADA) recommendations. First, in those patients with HbA1C ≥9%, basal insulin 10 U/day or 0.1–0.2 U/Kg/day in combination with metformin, until obtaining therapeutic target, uses fasting blood glucose and adjusting doses once or twice a week according to blood glucose values [25••].

In some cases, basal insulin is not sufficient to reach targets in patients with severe opportunistic infections [6•]. In addition, if HbA1C is not controlled, combined injectable therapy should be considered (adding prandial short acting insulin) with basal bolus at 0.1 U/Kg or 10% of the total basal dose [25••].

Conclusions

There are many causes of glycemic alterations among HIV-infected patients. Several metabolic pathways that ultimately lead to increased IR have been described, mainly related to impaired lipid metabolism. It is important to consider antiretroviral treatment as the main cause of glycemic disorders and to assess the cycling of these medications when needed. We must understand the metabolic and inflammatory effects of the virus itself and maintain better virological control. All HIV-infected patients should undergo screening for prediabetes and diabetes as recommended by the ADA to initiate treatment and in a timely manner when they require it. The drugs of choice are ADOs (metformin and thiazolidinedione); thus, consideration should be given to the interactions they have with antiretrovirals. Insulin is the best choice due to numerous advantages; therefore, it is advisable to adhere to the ADA's proposed injecting therapy algorithm, whether combined or not. Modifiable factors such as BMI control, physical activity, avoidance of smoking, and glycemic auto-monitoring have enormous effects on glycemic control. Consequently, lifestyle modifications are strongly encouraged.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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