CHAPTER

28

HIV & Diabetes – A Double Trouble

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INTRODUCTION

Patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are increasing in number, partly due to improved screening,earlier diagnosis, better methods of treatment, and greater accessibility to, as well as acceptance of therapy. The treatment of HIV-1 infection with combined antiretroviraltherapy (cART) has significantly altered the natural history of this life-threatening condition. Immunocompetence has come at significant metabolic cost, however, because cART is associated with a range of metabolic complications, including insulin resistance, glucose intolerance, type 2 diabetes mellitus, dyslipidemia, and changes in body fat compartmentalization (lipodystrophy).[1] cART-associated lipodystrophy in HIV infection is now the commonest form of lipodystrophy. These metabolic complications have rapidly translated into increased risk for type 2 diabetes and cardiovascular disease.[1] These diseases will present new challenges in the management of HIV infection.

EPIDEMIOLOGY

The prevalence of DM in HIV-infected patients has been reported to range from 2% to 14% and varies by the composition of the cohort studied, howDM diagnosis is ascertained, and how DM risk factors are accounted for in the analysis .[2–5] There is conflicting evidence on whether HIV infection is an independent risk factor for DM, with some studies showing increased risk[2,6,7] and others showing no independent effect of HIV on DM or showing an inverse effect.[4,8,9]

Despite the conflicting evidence on the independent role of HIV in DM, certain factors are clearly associated with DM, including increasing age, obesity, and genetic factors. Other factors influence DM incidence in the general population but are more common in HIVinfected patients: hepatitis C virus infection,[10] use of certain medications (atypical antipsychotics, corticosteroids), opiate use, and low testosterone.[11] Furthermore, ART-associated lipoatrophy[4] and visceral fat accumulation/ lipohypertrophy[3,12] and HIV-related inflammation (increased proinflammatory cytokines and/or free fatty acids)[13,14] are DM risk factors in HIV-infected patients.

DIAGNOSIS OF DIABETES

Table 1 shows the current American Diabetes Association (ADA) definitions of DM and prediabetes.[15]

Data are accumulating that HbA_1c may underestimate glycemia in HIV-infected individuals. Although the degree of discordance has varied, higher mean corpuscular volume, nucleoside reverse transcriptase inhibitor use (specifically abacavir), and lower CD4 count have been associated with discordance.[16-20]

DIABETES AND HIV: CLASSIFICATION

Three subgroups of patients with diabetes and HIV can be identified:

1. Patients with preexisting diabetes who contract HIV,
2. Those who are diagnosed to have diabetes at onset of HIV infection, and
3. Others who develop hyperglycemia after start of therapy.

These subgroups need to be managed differently, as the mechanisms of metabolic dysregulation vary in them.

Aetiopathogenesis

Impaired glucose tolerance, and insulin resistance are noted to precede weight loss in patients with HIV.[21-25] Insulin resistance, rather than insulin deficiency, is usually implicated in the pathogenesis of diabetes in HIV-infected patients. According to earlier reports, evidence of islet cell autoimmunity, or beta cell destruction has not been seen in HIV patients.[26] Autoimmune diabetes, however, has recently been reported to develop in some HIV-infected

Table 1: Definitions of Prediabetes and Diabetes

	HbA1c	FBS	RBS	OGTT
Diabetes	>=6.5%	>=126mg/dL(>=7.0mmol/L)	>=200mg/ dL(>=11.1mmol/L) with polyuria & polydipsia	>=200mg/ dL(>=11.1mmol/L)
Prediabetes	5.7%-6.4%	100-125mg/dL(5.6-6.9mmol/L)	-	140-199mg/dL(7.8-11.1mmol/L)
Normal	<5.7%	<=99mg/dL(<=5.5mmol/L)	-	<=139mg/dL(<=7.7mmol/L)

patients after immune restoration during HAART. The postulate is that recovery of immune function predisposes to autoimmune disease, in the form of type 1 diabetes (T1DM).[27] The type of diabetes associated with HIV may be classified as type 2 diabetes (T2DM), rather than T1DM, in the vast majority of patients.

Viral factors which contribute to diabetes risk are an increase in viral burden of 0.5 log over a 6 month period, a lower CD4 count, and longer duration of HIV infection.[21] In general, people with severe, long-standing HIV infection are more prone to developing diabetes

Coexistent hepatitis C virus (HCV) infection with HIV infection seems to increase diabetes risk in some but not in all studies. HCV infection is associated with increased insulin resistance.[28] A retrospective study of 1230 HIV-infected Cart recipients (50% coinfected with HCV) offers valuable insights. Diabetes mellitus prevalence was doubled in those coinfected with HCV, 5.9% compared with 3.3% in subjects with HIV infection alone.[29] Incident cases of diabetes mellitus were more common in those with HCV coinfection: 5.8% vs 2.8%; the incidence of hyperglycemia per 100 person-years was 4.9 in those with HCV coinfection vs 2.3 in those with treated HIV infection alone.[29] In contrast, the Swiss HIV Cohort Study of 6513 subjects did not find HCV coinfection a risk factor incident diabetes mellitus.[30]

HIV is also associated with various endocrine abnormalities. These include deficiency of growth hormone, as well as growth hormone resistance. Growth hormone deficiency may contribute to insulin resistance in HIV-infected patients.[31]

The increased accumulation of visceral fat, with wasting of subcutaneous fat, noted in these patients, creates higher levels of inflammatory cytokines such as TNF α. This in turn leads to diabetes or impaired glucose tolerance by increasing insulin resistance.[32]

HIV-infected subjects with metabolic syndrome show disturbances in inflammation and adipokines: they have higher CRP (5.5 ± 7.0 vs. 3.9 ± 6.0 mg/l) and leptin (9 ± 9 vs. 4 ± 6 ng/ml) and lower adiponectin(12 ± 8 vs. 15 ± 10 μg/ml) levels. This may contribute to the pathogenesis of diabetes.[33]

The major contributor to hyperglycemia in HIV/AIDS, however, is iatrogenic. A recent analysis has found that diabetes is four fold more common in HIV-infected men exposed to highly active anti retroviral therapy (HAART) than in HIV seronegative men.[34] HAART based on the use of Class of drugs Protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) have been linked with development of diabetes mellitus.

PIs have been shown to increase insulin resistance and reduce insulin secretion, by interfering with GLUT-4 mediated glucose transport. Risk factors for development of diabetes with PI therapy include positive family history of diabetes, weight gain, lipodystrophy, old age and hepatitis C infection.[35] PIs interfere with cellular retinoic acid-binding protein type 1 (CRABP 1) that interacts with peroxisomal proliferator-activated receptor (PPAR) γ. Inhibition of PPAR-γ promotes adipocyte inflammation, release of free fatty acids and insulin resistance.[36] Hyperglycemia resolves in almost all patients when PIs are discontinued.[36] All PIs do not have the same metabolic effects. Indinavir induces insulin resistance with no effect on lipid metabolism, whereas lopinavir and ritonavir increase fasting triglycerides and free fatty acids, but do not worsen insulin sensitivity. Indinavir and retonavir both block GLUT -4, but no such effect is noted with amprenavir, and atazanzvir. This implies that there is no class effect of PIs on diabetes, and that various PIs should be studied individually with respect to their metabolic effects.[36]

The other class of drugs which is used is the nucleoside analogs (reverse transcriptase inhibitors) (NRTIs). The risk is highest with stavudine, but is also significant with zidovudine and didanosine. Proposed mechanisms include insulin resistance, lipodystrophy, and mitochondrial dysfunction.[37] These mechanisms may be evident only in HIV-infected persons treated for long periods of time with NRTIs.[37]

This does not mean that HAART should not be prescribed to patients with HIV and diabetes. One should be aware of the adverse metabolic effects of these drugs, and take proactive steps to prevent and manage these.

Anti-retroviral drugs are not the only iatrogenic culprits in HIV-associated diabetes. Drugs used to manage comorbid conditions associated with AIDS may also cause diabetes. Pentamidine, which is used to prevent and treat P. carinii associated pneumonia, can cause β-cell toxicity, with acute hypoglycemia followed by later diabetes. Megesterol acetate, which is used as an appetite stimulant, predisposes to diabetes because of its intrinsic glucocorticoid like activity, increased caloric intake and weight gain.[38]

Screening for Diabetes

Patients with HIV should be screened for diabetes at diagnosis, at onset of HAART therapy, and three to six months after HAART. While certain professional bodies advise fasting blood glucose as a screening tool,[39] the predominant role of insulin resistance in the development of the illness implies that postprandial glucose values, or an oral glucose tolerance test, should also be performed as part of screening procedures.A1c has not been recommended as a diagnostic test in HIV/AIDS.

DIABETES MANAGEMENT

Initial Management

Lifestyle modification have a meaningful impact on glucose control and the course of DM.

Medication Therapy

Oral- Hypoglycaemic Drugs

The first-line medication for DM is metformin . Special caution should be used when metformin is coadministered with dolutegravir, as dolutegravir increases metformin

concentration.[40]

After lifestyle modification and metformin, if a patient is still not at goal, there are multiple treatment options like sulfonylureas, thiazolidinediones, incretins (GLP-1 analogues and DPP 4 inhibitors) gliflozins and meglitinides.

Levels of thiazolidinediones may increase when used with CYP2C8 inhibitors (many PIs). It should monitor carefully. Concern regarding gliptin use in HIV infected individuals was raised, as gliptins have molecular targets on immune cells; however, a small study revealed no changes in CD4 or HIV RNA among treated HIV-infected patients taking sitagliptin.[41] Of note, saxagliptin interacts with strong cytochrome P450 3A4/5 inhibitors (eg, ritonavir), and saxagliptin dose should be reduced when used in combination.[42] No interactions between ART and dapagliflozin are expected; however, if UDP-glucuronosyltransferase enzyme inducers (eg, ritonavir) must be coadministered with canagliflozin, clinicians could consider increasing the dose to 300 mg.[43] When used with CYP3A4/CYP2C8 inhibitors (many PIs), meglitinides (repaglinide/ nateglinide) levels may increase. Monitor carefully. Efavirenz (EFV) and Etravirine (ETR) may increase nateglinide .

Insulin

Insulin is the preferred choice for management of diabetes with HIV. Insulin has an anabolic effect, is known to reduce inflammatory markers such as TNFalpha, does not have any interactions with antiretroviral or other drugs, is not contraindicated with renal or hepatic dysfunction, does not reduce appetite or cause gastrointestinal side effects, can correct both insulin deficiency and resistance when given in appropriate doses, and does not increase the risk of cardiovascular disease.[44]

Changes in HAART

PI-based regimes should be avoided in patients at high risk of developing diabetes, e.g., those with a history of gestational diabetes, a positive family history of diabetes, or impaired glucose tolerance on screening. Indinavir should be avoided, and replaced with less toxic drug.

Management of Pre-Existing Diabetes

Pre-existing T2DM may continue to be managed, after diagnosis of HIV, with the same drug therapy that was being used prior to detection of HIV. Patients should be informed about the chances of worsening hyperglycemia, and educated about the features of ketosis and lactic acidosis. In case glycemic control deteriorates, insulin should be initiated, rather than increasing dosage or number of OADs.

CONCLUSION

Diabetes mellitus is a prevalent chronic condition with many deleterious effects, which may be accentuated among patients with both DM and HIV. Clinicians should perform regular DM screening in HIV-infected patients. The effective management of diabetes in HIV-infected patients requires a thorough understanding of pathophysiology and pharmacology. The choice should be based on the etiopathogenesis of the disease. In treating DM, lifestyle changes are critical, as a 5%-10% weight loss can have important metabolic effects. If drug treatment is required, metformin is first line therapy. Decisions regarding second and third line drugs should be individualized. Insulin is a safe and effective method of treating all these patients irrespective of type of diabetes.

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