Diabetes and the metabolic syndrome in HIV

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When the antiretroviral (ARV) rollout finally began in 2004, it was a huge victory for the health sector and South Africa.1 Almost 10 years later, we find ourselves facing new challenges in HIV-positive patients. As patients survive longer into middle age with the use of antiretroviral therapy, they are becoming more prone to non-HIV related diseases such as type 2 diabetes, hypertension, dyslipidaemia and an increased risk of cardiovascular disease. In the long term these conditions are associated with significant morbidity and mortality and need prompt diagnosis and treatment.2

There are three categories of diabetic patients in the HIV-positive population:

- highly active antiretroviral therapy (HAART)-naive, HIV-positive patients who develop diabetes after becoming infected with HIV;
- Diabetic patients who had diabetes prior to becoming HIV infected;
- HIV-positive patients who develop diabetes after antiretroviral therapy has been initiated.

The time of HIV infection is difficult and almost impossible to determine. Identifying more patients at the onset of HIV infection would allow larger numbers of patients to be recruited and studied for the effects of HIV on glucose homeostasis. There have been several studies on the development of diabetes and insulin resistance secondary to antiretroviral therapy. But there is limited research on a possible link between HIV itself and the consequent development of diabetes.3

Insulin resistance may have an HIV disease-associated component. Earlier studies show that HIV-infected HAART-naive patients may have higher rates of insulin clearance and increased insulin sensitivity in peripheral tissues compared to a non-infected person.4

Lipodystrophy occurs usually in patients on particular antiretroviral drugs, but can occur in the ARV-naive patient. There is evidence that HIV 1 infection contributes to the development of the lipodystrophic phenotype, interfering with some key genes of adipocyte differentiation and mitochondrial function.5

Lipodystrophy presents with fat loss on the face, buttocks, arms and legs. There is also fat accumulation in certain areas. Patients develop hepatic steatosis, central obesity, fat deposits in their upper backs (interscapular fat pad) and increase in breast size. Lipodystrophy does not progress, but usually does not reverse once causative antiretroviral therapy has been stopped. Generalised lipodystrophy is associated with severe insulin resistance and is often accompanied by dyslipidaemia.6

The metabolic syndrome has various definitions and criteria. Essential components consist of diabetes or impaired glucose tolerance, hypertension, dyslipidaemia (hypertriglyceridaemia and low high-density lipoprotein cholesterol) and obesity—central obesity (increased waist:hip ratio or a body mass index > 30kg/m2). Patients on antiretroviral therapy are at high risk of developing the metabolic syndrome and its complications.7

Antiretroviral therapy is associated with diabetes and impaired glucose tolerance, dyslipidaemia and lipodystrophy. Hence the link between antiretroviral exposure and the metabolic syndrome is not surprising. Other factors besides antiretroviral therapy that predispose patients to diabetes and the metabolic syndrome should be taken into consideration:

- the age of the patient (≥ 50 years increases risk);
- obesity, some contributing factors being sedentary lifestyle and poor dietary habits;
- ethnicity: Asian and the black population are at increased risk;
- positive family history of diabetes, hypertension, dyslipidaemia.4

Antiretroviral therapy involved in the development of diabetes and the metabolic syndrome

Most commonly, the most marked effects are caused by nucleotide reverse transcriptase inhibitors (NRTIs), especially stavudine, and protease inhibitors. Protease inhibitors may cause fat redistribution, hyperlipidaemia, insulin resistance and hyperglycaemia. They have varying effects on glucose and lipid metabolism and need to be assessed individually. The mechanisms of these metabolic changes have not yet been fully clarified. There is likely to be a multifactorial aetiology.8

Lopinavir/ritonavir increases fasting triglyceride and free fatty acid levels, but has little or no effect on insulin sensitivity. Indinavir may induce insulin resistance by blocking insulin-mediated glucose disposal by direct blockade of GLUT-4. However there is no effect on lipid metabolism.4,5

Protease inhibitors are associated with reduced adiponectin secretion and induced expression of interleukin 6. This may contribute to the inhibition of insulin-stimulated glucose uptake.9

Common drugs altering lipid profiles are stavudine, zidovudine, efavirenz, lopinavir/ritonavir and earlier protease inhibitors. Drugs with a cleaner lipid profile are lamivudine, emtricitabine, nevirapine, tenofovir and atazanavir.10

Management of diabetes in the HIV-positive patient

- Making the diagnosis with SEMDSA guidelines. No screening guidelines are in place for patients exposed to antiretroviral therapy. Various factors need to be considered: risk factors, choice of antiretroviral drug in a known diabetic patient, if and when to switch antiretroviral therapy in a patient showing signs of impaired glucose tolerance or insulin resistance.4

- Patient education at diagnosis is vital and regular ongoing education is necessary. These patients are already on antiretroviral therapy and are trying to cope with HIV, antiretroviral therapy and side effects. Adding more medication with further side effects and more responsibility for another condition requires

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a good understanding of their diabetes as well as all the other problems encountered in the metabolic syndrome.

- General measures: modify risk factors such as hypertension and dyslipidaemia. Check blood pressure quarterly and do an annual lipid profile. Self monitoring of sugar levels where possible. Advise patient to be careful with the sharps they’re using. Check HbA1c, level two to four times per annum. Aim to keep HbA1c < 7%.

Annual eye examination by an ophthalmologist or optometrist. Foot care: refer to a podiatrist when necessary. Patients with diabetes and HIV may be prone to peripheral neuropathy. This may be compounded by TB treatment and antiretroviral therapy.

Screen for diabetic nephropathy. These patients may also have HIV-associated nephropathy.

- Lifestyle modification: dietary modification. Refer patients to a dietician to provide adequate nutritional support and dietary education. Exercise and weight loss (in the patient with a raised body mass index) have positive effects on metabolic parameters in HIV-positive patients. It may improve blood pressure and lipid profile and increase insulin sensitivity. Cessation of smoking as this is a major risk factor for cardiovascular disease.7,10,11

Drug management of diabetes mellitus

The aim of treatment is to reduce mortality and morbidity of diabetes-related complications.

What are the indications for a lipid-lowering agent? The use of statins should be universal in diabetics. Consider drug interactions with antiretroviral therapy, particularly protease inhibitors. Fibrates are the agents of choice with hypertriglyceridaemia and have some effect against hypercholesterolaemia. They are safe to use with protease inhibitors. Many statins have significant drug interactions with protease inhibitors, leading to elevated levels of statins, resulting in potential toxicity. Pravastatin and low-dose atorvastatin are safe to use with protease inhibitors.

Other important medications include ACE inhibitors or angiotensin receptor blockers (ARBs) which are renoprotective, aspirin10,12,13 and oral hypoglycaemic agents, such as biguanides, thiazolidinediones and insulin secretagogues.

Biguanides: Metformin improves insulin resistance or glucose intolerance. There is a possible risk of lactic acidosis, but it is not contra-indicated in patients on antiretroviral therapy. Patients receiving nucleotide reverse transcriptase inhibitor (NRTI) therapy for longer than six months are usually at higher risk for lactic acidemia. Stavudine, zidovudine and didanosine are the drugs most commonly associated with raised lactate levels. Check renal function first. Educate patients about symptoms of lactic acidosis.

Thiazolidinediones increase insulin sensitivity and reduce insulin resistance. Do liver function tests (LFTs) before using pioglitazone or rosiglitazone. Avoid these drugs if LFTs are impaired: > 2.5 upper limit of normal.

Insulin secretagogues such as sulphonylureas may not be effective in severe insulin resistance.

Change to subcutaneous insulin therapy if diabetes remains uncontrolled. Insulin does not have any drug interactions with antiretroviral therapy or other drugs and it is not contra-indicated in hepatic or renal dysfunction. Insulin is always the safe option if there is any doubt.3,4

Type 1 diabetes is usually more difficult to manage with or without HIV. Most of these patients are adolescents. Various issues need to be addressed. These patients need more extensive counselling, support and the involvement of caregivers. Compliance, substance abuse and sexual issues are some of the points that need to be addressed. A multidisciplinary approach is important where the social worker, caregiver, teachers at school, doctors and many others need to be involved.10,14

Conclusion

HIV and diabetes are chronic diseases which significantly impact on a patient’s lifestyle and wellbeing. It can be overwhelming to deal with. One has to understand the glucose disturbances that can occur with antiretroviral therapy, screen patients appropriately for impaired glucose tolerance and diabetes, altering HIV therapy when necessary, and take into account all other metabolic disturbances associated with antiretroviral therapy, which put patients at high risk of cardiac disease. These modifiable cardiovascular risk factors will have a significant impact on healthcare and patients in the near future.14,16

References