Insulin resistance in HIV disease: aetiopathogenesis and treatment

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Introduction

When AIDS was first recognised in 1981, in the US, not much was known about this new condition which a few years later became a pandemic unprecedented in the history of man. Since then, more than 20 million deaths have been attributed to HIV/AIDS with new HIV infections on the increase, particularly in sub-Saharan Africa.[1] However, the advent of highly active antiretroviral treatment (HAART) has transformed HIV infection from an inexorably fatal disease, a death sentence, to a chronic condition marked by reduced morbidity and mortality.[2–4] This combination of three or more antiretroviral drugs for HIV treatment was introduced into clinical practice in the mid-1990s. However, there are long-term side-effects associated with HAART.[5,6] Metabolic changes are common and include insulin resistance (IR),[6,7] a state in which a given concentration of insulin produces a less- than-expected biological effect. It has also been arbitrarily defined in diabetes as a requirement of >200 units of insulin per day to achieve glycaemic control or to prevent ketosis.[8] Insulin resistance is a multifaceted syndrome that plays a significant pathogenic role in type 2 diabetes, hypertension, dyslipidaemia, and atherosclerosis. It is an independent risk factor for cardiovascular disease,[9,10] and with HIV is an issue of global public health importance. The objective of this review is to discuss the aetiopathogenesis and treatment of insulin resistance in HIV and AIDS.

Aetiopathogenesis

Protease inhibitors

Many studies have shown that protease inhibitors do cause some metabolic effects such as insulin resistance and hyperglycaemia. Some of these drugs directly bind to and block the insulin-sensitive glucose transporter (GLUT 4) thus inhibiting glucose transport.[11,12] This effect, which has been demonstrated in both adipocytes and myocytes, induces peripheral insulin resistance in skeletal muscle and adipose tissue and impairs the ability of beta cells to compensate.[13] However, there are other mechanisms by which protease inhibitors cause insulin resistance in HIV disease. These include the antiretroviral treatment-related effects such as restoration of health, improved immune function, and changes in the body composition.[14,15] Lipdystrophy is often a long-term sequelae of protease inhibitors has been associated with insulin resistance. Both indinavir and lopinavir/ritonavir have also been shown to cause insulin resistance in HIV-negative individuals.[16] However, not all these drugs cause insulin resistance, or at least, to the same severity. The new generation protease inhibitors appear to have a milder insulin resistant effect and the prevalence of resulting diabetes is lower than that described in the early 2000s.[17] Nelfinavir and atazanavir do not seem to cause insulin resistance.[18]

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The role of inflammation and lipotoxicity

Although the exact mechanism is unknown, HIV itself has been linked to insulin resistance.[19] Although there is debate on the role of HIV in adipose tissue inflammation, the ability of the virus to modify adipocyte phenotype has been revealed in some studies.[20,21] Moreover, macrophages in lipodystrophic adipose tissue may become infected with modified characteristics. These cells when activated can secrete proinflammatory cytokines such as TNF-alpha and IL-6 which control adipocyte metabolism, decrease adiponectin production and induce insulin resistance and lipolysis.[22,23] This concept, called lipotoxicity, may explain why in the absence of antiretroviral drugs, chronic HIV disease is associated with abnormal metabolic changes including insulin resistance and dyslipidaemia.[24,25]

Nucleoside and non-nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors (nRTIs) may contribute to insulin resistance, usually indirectly through metabolic changes and fat redistribution.[26,27] But unlike protease inhibitors, there is no direct association with insulin resistance. The lipid changes include increased truncal fat, lipoatrophy, and elevated serum insulin concentrations.[28] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are not associated with the development of insulin resistance.

Treatment

Prevention should be the focus in the management of

insulin resistance in HIV infection. This is by assessment of risk factors for insulin resistance in each patient at the onset of treatment and at regular intervals. The evaluation of the risk profile affects the choice of antiretroviral treatment. Patients with high risk of developing insulin resistance should begin lifestyle modification that has been found to delay or prevent the onset of diabetes.[29] There can also be a switch to a more metabolically friendly HAART regime before insulin resistance occurs. Lifestyle modification, however, is the treatment of choice for insulin resistance in HIV infection, and the use of pharmacologic interventions for is generally not recommended, partly because of problems of safety and the uncertainty of their long-term benefits. However, if glucose tolerance is significantly altered, metformin or thiazolidinediones can be used.[30] Recent small studies of metformin and rosiglitazone in HIV infected patients with insulin resistance have shown statistically significant decreases in the insulin area-under-the-curve with both drugs.[31,32] If the patient is overtly diabetic, the treatment follows the same strategies as used in the general diabetic population, with priority given to insulin sensitisers.

Conclusion

Insulin resistance is common in HIV infection and its cause is multifactorial, though it is a well-established complication of HAART. Adequate evaluation of individual patients for risk factors for insulin resistance as well as the choice of HAART regime is crucial and critical. More worrisome is the fact that the diagnosis of insulin resistance in clinic settings is very difficult and thus it is usually inferred. It is important to understand appropriate ways to prevent and treat insulin resistance to reduce morbidity and mortality in the era of HAART.

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