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Diabetes Associated with Antiretroviral Therapy in HIV Patients - An Overview

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ABSTRACT

Diabetes is more common among HIV-positive individuals. People with HIV can expect to live longer and have better quality of life thanks to antiretroviral therapy. Although the condition itself raises the risk of high blood sugar, some HIV treatments are also thought to raise the risk of insulin resistance and diabetes. Numerous antiretroviral medications for the treatment of HIV infection have been licensed in India. These medications include protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, and integrase strand transfer inhibitors (INSTIs). Protease inhibitors are among those in this classified that have been linked to insulin resistance, and there are only a few published studies that link the usage of integrase strand transfer inhibitors (INSTIs) to abnormal glucose metabolism. HIV infection and diabetes co-infection complicate medical standards of care. To inform the treating physician about the diagnosis and treatment of diabetes in HIV-infected patients, this article describes the medicines that raise the risk of Diabetes Mellitus associated with antiretroviral drugs.

Keywords: Antiretroviral drugs, Protease inhibitors, Diabetes

INTRODUCTION

Antiretroviral therapy (ART) rebuilds immune function and lowers HIV-related adverse outcomes. Compared to the general population, HIV-positive individuals have a four times greater incidence of diabetes [1]. Antiretroviral therapies prolong life expectancy and improve the quality of life of HIV-infected patients. India has granted permission for many antiretroviral drugs for the treatment of HIV. The initial class of antiretroviral medications to be developed was the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) authorized by the FDA. Ex. Zidovudine, Lamivudine, Abacavir and Tenofovir disoproxil fumarate [2]. The HIV-1 reverse transcriptase (RT) is directly inhibited by the non-nucleoside reverse transcriptase inhibitors (NNRTIs), which bind to the enzyme in a reversible and non-competitive way. Nevirapine and efavirenz are the medications that are now on the market. Protease inhibitors make up the third category of medications. The maturation of the HIV virus depends on protease during its life cycle. These medications stop HIV from replicating by attaching to proteolytic enzymes, called proteases. Ritonavir, Lopinavir, and Atazanavir are the medications [2]. Integrase strand transfer inhibitors (INSTIs), which include elvitegravir and dolutegravir, are oral medications used to treat HIV infection. Antiretroviral medications offer numerous known advantages, but there are also several negative effects that have been observed [3]. It has been observed that protease inhibitors (PIs), and to a lesser extent nucleoside/tide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), can alter lipid and glucose metabolism, resulting in hyperglycemia, dyslipidemia, and insulin resistance [4,5]. In addition, immunological activation and ongoing inflammation brought on by HIV infection may make insulin resistance worse.

DRUG-INDUCED DIABETES

Drug-induced diabetes is defined as diabetes brought on by taking drugs. Different methods can lead to drug-induced diabetes [6]. They include glucose intolerance, insulin resistance and increased hepatic glucose synthesis, decreased

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insulin secretion and autoimmune beta cell destruction. It is imperative to remember that prolonged use of antisocial drugs at increasing doses typically results in drug-induced hyperglycemia [6]. Numerous mechanisms have been proposed to explain how the toxicity of antiviral medications can result in insulin resistance and diabetes mellitus. Indinavir reduces insulin sensitivity with a single dose, while protease inhibitors and NRTIs have distinct effects on mitochondria and the glucose transporter GLUT4 [7,8]. The nucleoside / tide reverse transcriptase inhibitor stavudine has the highest correlation with mitochondrial toxicity, as determined by inhibition of the mitochondrial DNA polymerase-g.

Iatrogenic causes are assumed to be the main cause of hyperglycemia in HIV/AIDS patients. Protease inhibitors are one class of antiretroviral that has been linked to an increased risk of diabetes in HIV-infected individuals. They hinder the rate-limiting stage in glucose uptake into muscle and adipose tissue, GLUT-4-facilitated glucose transport, which raises insulin resistance [9]. Positive family history of diabetes, lipodystrophy, weight increase, advanced age, and hepatitis C infection are risk factors for diabetes progression when receiving protease inhibitor medication. Different protease inhibitors have different metabolic effects. For instance, lopinavir and ritonavir increase fasting triglycerides and free fatty acids while without worsening insulin sensitivity, but indinavir promotes insulin resistance without affecting lipid metabolism. Ritonavir and indinavir both inhibit GLUT-4; however drugs like amprenavir and atazanavir haven't been shown to have the same impact.

The nucleoside analogues drug class is another one that is utilized. Although nucleoside/nucleotide reverse transcriptase inhibitors have been demonstrated to raise the incidence of diabetes, it was first believed that they were less likely to produce metabolic abnormalities. Stavudine poses the highest risk, however zidovudine also carries a substantial amount of it. Lipodystrophy, insulin resistance, and mitochondrial dysfunction are some of the hypothesized mechanisms. Only HIV-infected individuals receiving long-term treatment with nucleotide reverse transcriptase inhibitors may experience these mechanisms [10].

Although there is a link between highly active antiretroviral therapy (HAART) and the onset of diabetes, this does not imply that people with HIV and diabetes should not be offered HAART. In order to choose the appropriate anti-diabetic therapy, treating physicians need be aware of the main mechanism of diabetes associated to each medication. There is currently no proof that NNRTIs, integrase inhibitors, or CCR5 antagonists enhance the risk of diabetes in HIV-positive individuals.

HIV weakens the immune system by destroying CD4 T lymphocyte cells, which defend against infection and illness. Through alterations in pancreatic beta-cells, inflammation, and elevated insulin resistance, the viral illness increases the risk of higher blood glucose levels [11]. Although the condition itself raises the risk of high blood sugar, some HIV treatments are also known to raise the risk of diabetes and insulin resistance. They consist of nucleoside reverse transcriptase inhibitors and older protease inhibitors [6,11]. Protease inhibitors work by inhibiting the protease enzyme and preventing the post-translational cleavage of polyproteins into active proteins.

Consequently, mature HIV is not put together. Inhibitors of nucleoside/tide reverse transcriptase attach to the expanding HIV DNA and prevent reverse transcriptase, which affects chain termination [12]. The percentage of HIV patients receiving highly active antiretroviral medication who have hyperglycemia with or without diabetes ranges from 3% to 17% [6]. Antiretroviral therapy should not be stopped because of drug-induced diabetes. However, there are options that can lower the chance of these negative consequences. When necessary, individuals on zidovudine, an older nucleoside/tide reverse transcriptase inhibitor, can be switched to abacavir, tenofovir, or tenofovir disoproxil fumarate, a first-line nucleoside/tide reverse transcriptase inhibitor because there is a lower chance of metabolic disorders like hyperglycemia with these drugs.

Additionally, individuals who are on a protease inhibitor may benefit from a first-line treatment based on an integrase strand transfer inhibitor (INSTI) [13]. However, it is permissible to continue with close monitoring of glucose readings if a patient is stable on a PI-based regimen, has recognized resistance to the advised first-line drugs, and has documented intolerance to the advised medications.

Any HIV patient who has diabetes or insulin resistance has to be sent for advice to an endocrinologist. Clinical pharmacists can also be very helpful in deciding which agents are indicated by guidelines to start using while maintaining proper dosage and evaluating drug-drug interactions.

Additional Monitor fasting blood glucose every 6 to 12 months in those at risk for diabetes who have not yet received a diagnosis to determine whether diabetes mellitus has progressed. Since there may be higher RBC turnover and potential for artificially lower A1C, this approach is recommended and more accurate than HBA1c monitoring in HIV patients [14] All HIV patients receiving antiretroviral therapy should receive lifestyle counseling, which includes implementing a diet reduced in cholesterol, saturated fat, and trans fat. The promotion of increased physical exercise is also necessary [14].

MONITORING AND MANAGEMENT

Patients should get information on the warning signs and symptoms of hyperglycemia when they begin taking drugs that have the potential to induce diabetes or cause hyperglycemia. Polydipsia, polyuria, and polyphagia are

important indicators of hyperglycemia. Patients should follow up with a medical expert if symptoms appear.

DISCUSSION

Antiretroviral (ARV) medication combinations can be used in treatment plans to control HIV illness. Antiretroviral therapy (ART) as it stands now prevents viral replication, aids in immune system recovery, and restores a person's ability to fight off opportunistic infections but does not cure HIV infection. HIV-related morbidity and mortality have significantly decreased because to antiretroviral medications. HIV is now a chronic, treatable condition rather than an ailment that would ultimately result in death. To obtain the greatest level of viral suppression, antiretroviral medication combinations are necessary.

Actually, it's assumed that iatrogenic causes of hyperglycemia in HIV/AIDS patients are the main factor. Protease inhibitors are one class of antiretroviral that has been proven to increase the risk of developing diabetes in HIV-infected individuals (PIs). The rate-limiting stage in glucose uptake into muscle and adipose tissue, GLUT- 4-mediated glucose transport, is interfered with by PIs, increasing insulin resistance [15]. Positive family history of diabetes, weight increase, lipodystrophy, advanced age, and hepatitis C infection are all risk factors for developing diabetes while receiving PI therapy. Different PIs have various metabolic effects. While lopinavir and ritonavir raise fasting triglycerides and free fatty acids without affecting insulin sensitivity, indinavir causes insulin resistance without affecting lipid metabolism. Ritonavir and indinavir both inhibit GLUT-4, whereas amprenavir and atazanavir have no such effect.

Due to their great efficacy, excellent tolerability, low toxicity, and high genetic barrier to resistance, second-generation INSTIs are presently the preferred class in ART regimens [16].

Deranged glucose metabolism is a result of INSTIs. [17]. Diabetic ketoacidosis or a hyperosmolar hyperglycemia condition, which are both life-threatening acute consequences of severe hyperglycemia (Plasma glucose level >250 mg/dl), were recognized. The DTG-based ART regimen has been associated with the potential adverse effect of hyperglycemia. In ART regimens involving dolutegravir, baseline and ongoing plasma glucose monitoring may be necessary.

CONCLUSION

The risk of acquiring DM was shown to be four times higher in HIV-positive patients receiving HAART than in HIV-negative patients. From a molecular standpoint, prolonged use of antiretroviral medications may cause insulin resistance, a typical disease in the follow-up of PLH, which may eventually result in T2DM. By interfering with insulin signaling at the cellular level, these medications may directly cause insulin resistance, or they may do so inadvertently as a result of cART's effects on lipid metabolism. It becomes difficult to assert that one specific drug is responsible for the onset of T2DM, nevertheless, because PLH are treated with combined antiretroviral regimens that contain medications that may differ in their propensity to promote insulin resistance.

The risk of acquiring diabetes mellitus (DM) was shown to be four times higher in HIV-positive patients using HAART. It was frequently linked to severe adverse effects, related to both acute and chronic toxicities, resulting in peripheral neuropathy, lactic acidosis, hyperlactatemia, lipoatrophy, dyslipidemia, and T2DM, even though it was thought to be effective at inhibiting HIV replication when used in combination with other medications [18]. Due to these unfavorable results, the World Health Organization suggested substituting tenofovir or zidovudine for stavudine in early HIV treatment regimens in 2010 [19]. All HIV patients receiving antiretroviral therapy should receive lifestyle counseling, which includes implementing a diet reduced in cholesterol, saturated fat, and trans fat. The promotion of increased physical exercise is also necessary.

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