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Incidence of Diabetes and its Control Measures in AIDS Patients

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Abstract

HIV and diabetes are both chronic diseases that significantly affect the human lifestyle and their quality of living. When these two diseases coexist, their treatment would be overwhelming for patients. Highly active antiretroviral therapy (HAART) became the standard of care in HIV infection. As the treatment for HIV has been developed and the access to therapy has been improved, the incidence of HIV-associated diabetes began to grow. Diabetes can be an important consequence of HAART. This review describes various metabolic complications such as AIDS-related insulin resistance, Glucose Intolerance and Hyperglycemia after HAART and also gives a brief account on the control measures.

Keywords: Acquired immunodeficiency syndrome; Human Immunodeficiency Virus; Antiretroviral therapy; highly active antiretroviral therapy; Combination antiretroviral therapy; Diabetes Mellitus; Hypoglycemia; Insulin Resistance; Glucose Intolerance; Hyperglycemia

Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; HIV: Human Immunodeficiency Virus; ART: Antiretroviral Therapy; HAART: Highly Active Anti-Retroviral Therapy; cART: Combination Anti-Retroviral Therapy; NRTIs: Nucleotide Reverse Transcriptase Inhibitors; NNRTIs: Non-Nucleotide Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; DM: Diabetes Mellitus; MetS: Metabolic Syndrome; CVD: Cardiovascular disease; IGT: Impaired Glucose Tolerance; OADs: Oral Anti Diabetic Drugs

Introduction

Acquired immunodeficiency syndrome (AIDS) is a caused by the human immunodeficiency virus (HIV) that belongs to a subset of retroviruses called lentiviruses [1]. HIV/AIDS is the fourth leading cause of mortality and remains the greatest public health crisis in today's world [2]. The main reason is not only a major public health issue, but also a socio-economic and developmental crisis that affects all sectors of the population [3]. Continuous efforts are being made to identify novel effective therapies that can assist in controlling the spread of HIV [1].

Chronic human immunodeficiency virus (HIV) infection is characterized by defects in the immune system including depletion of CD^{4+} T-cells and impaired T-cell function. The immune suppression in AIDS patients is the major cause of various opportunistic diseases [4]. HIV/AIDS patients are prone to the development of not only opportunistic infections [5] such as various bacterial, fungal, protozoal and viral diseases, but also endocrine disorders such as diabetes mellitus (DM) [6].

Human immunodeficiency virus and host cell protein interaction network has provided an opportunity for development of novel antiviral therapeutics targeted to host proteins required for virus infection [7]. Successful antiretroviral therapy (ART) suppresses viral replication [8]. The introduction of the highly active antiretroviral therapy (HAART) also called as combination antiretroviral therapy (cART) in 1996 has drastically reduced the morbidity and mortality associated with the HIV infection. The potent combination of antiretroviral (ARV) therapy has changed the course of HIV disease from an invariably fatal illness to a chronic but manageable one [9]. There are currently 20 antiretroviral drugs that have been approved for the treatment of HIV. They were divided into six classes of ART which inhibit HIV replication [10]. Each of these classes of drugs inhibits HIV replication at different stages in HIV life cycle. The decision of ART depends upon the CD^{4+} count of each individual [11].

Highly active antiretroviral therapy (HAART) became the standard of care in HIV infection [12] and includes the combination of three different types of highly effective anti-HIV-1 drugs, including nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs) and non-peptidic viral protease inhibitors (PIs) [1,13]. This therapy helped in substantially reducing viral load, slowing HIV replication, increasing CD^{4} lymphocyte numbers, and reducing the incidence of opportunistic infections [14].

NRTIs are currently an essential part of highly active antiretroviral therapy (HAART) for the treatment of HIV. However, the use of some dideoxynucleotide analogues may be limited by mitochondrial toxicity [15]. *NNRTIs* based antiretroviral therapy (ART) regimens have been recommended and widely used because of their reliable efficacy, low pill burden, and low cost [16]. The *PIs* have come into use as the human immunodeficiency virus (HIV) encodes within its genome an aspartyl protease that is required to process viral precursor polyproteins and is essential for the proper formation of infectious HIV virions.

With the advent of antiretroviral therapy (ART), the incidence of perinatal HIV-1 transmission has decreased from 20-25% to less than 2%. However, recent studies suggest that exposure to antiretroviral medications may have marked adverse effects, independent of HIV status [17]. Adverse events are common in patients receiving ARV therapy [18]. Current highly active antiretroviral therapy (HAART) for the treatment of HIV infection is associated with long term side effects

[15]. The effect of HAART can be assessed by classifying the individuals into three groups - (1) HIV seronegative, (2) HIV infected not using HAART, and (3) HIV infected using HAART [19].

Highly active antiretroviral therapy (HAART) is generally associated with disturbance of lipid metabolism, fat mass distribution and insulin resistance [20]. HIV-related opportunistic infectious diseases and autoimmune disorders have also been observed [21]. It has also been found out that protease inhibitor use is associated with metabolic abnormalities [22]. Patients who receive protease inhibitors (PIs)-based antiretroviral therapy (ART) show a higher Hepatitis C viremia than those treated with nonnucleoside reverse transcriptase inhibitors (NNRTI) [23]. Even with combination antiretroviral therapy (cART), the durability of HIV control is limited by many factors such as adherence to treatment, drug toxicity, bioavailability etc [24].

HIV Treatment – Diabetes

HIV and diabetes are both chronic diseases that significantly affect the human lifestyle and their quality of living. When these two diseases coexist, their treatment would be overwhelming for patients. HIV disease being an important global problem, increasing prevalence of Diabetes Mellitus (DM) is observed among these patients [25]. HIV infection is characterized by an immunodeficient state caused by active replication of the virus. In order to achieve maximum suppression of viral replication, the use of combination therapy served as an important consideration [14].

Glucose is the prime fuel as the source of energy for humans. However, the glucose levels in circulation have to be very tightly maintained. Alterations in the normal glucose levels in blood will lead to abnormal physiological states causing either hypoglycemia (low glucose levels) or hyperglycemia (high glucose levels) [26]. Diabetes mellitus is a disease of abnormal glucose metabolism resulting in hyperglycemia due to either a deficiency of insulin secretion or insulin resistance or both [27]. Diabetes is one of the most frequent metabolic diseases and is widely distributed in various populations; its prevalence appears to be increasing rapidly [28]. People with diabetes have problems converting food in to energy. It is also defined as chronic disorders of carbohydrate metabolism due to the lack of insulin result in the hyperglycemia [29]. The current estimated prevalence of diabetes worldwide is 285 million people [30].

The prevalence of diabetes mellitus is rising at an alarming rate. Epidemiological studies of diabetes mellitus have shown that gender, age, and ethnic background are important factors when considering the development of diabetes mellitus and its complications [31]. Various other factors like metabolic syndrome (MetS) [32], Obesity have shown a profound effect. Increased obesity in the population has lead to increased number of diabetic patients [33]. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production [34]. Classic signs and symptoms of diabetes include polyuria, polydipsia, polyphagia, weight loss, headache, tachycardia, palpitations, and blurred vision. The primary pathophysiological defects include excessive hepatic glucose production, impaired peripheral glucose uptake by insulin-sensitive tissues, and insufficient insulin secretion/increased β-cell apoptosis [35].

The prevalence of diabetic complications was high [36]. Type 2 diabetes mellitus is a chronic disease [37] with severe late complications and high mortality [38]. Diabetes mellitus (DM) long-term complications are progressive and almost resulting by chronic exposure to high blood levels of glucose resulting from defects in insulin metabolism and dysfunction in carbohydrate, lipid and protein metabolism [39]. It is also associated with long-term complications of peripheral nervous system and the central nervous system [40], has a profound effect on the skeleton and can lead to osteoporosis [41]. Cardiovascular disease (CVD) is a major complication and a leading cause of early death among persons with diabetes [42]. Diabetes affects patients' physical, emotional and psychological status, leading to many diseases and complications which burden patients, family and community [43].

The risk factors for diabetes, such as family history of the disease, obesity, and sedentary lifestyle, are important in people with HIV [44]. The traditional risk factors for DM are responsible for most of the increased risk in the HIV infected population [45]. As the treatment for HIV has been developed and the access to therapy has been improved, the incidence of HIV-associated diabetes began to grow. The incidence of new-onset diabetes in HIV-infected persons was found to be significantly high. Three subgroups of patients with diabetes and HIV have been identified

- Patients with preexisting diabetes who contract HIV

- Those who are diagnosed to have diabetes at onset of HIV infection

- Those who develop hyperglycemia after start of therapy

The recent development of highly active antiretroviral therapy (HAART) has drastically improved the life expectancy of AIDS patients but the long-term use of novel, potent antiviral agents has lead to new problems and complications [46]. Increasing numbers of AIDS patients are receiving protease inhibitors (PIs) for the treatment of their HIV infection [47]. The prevalence of AIDS-related insulin resistance, Glucose Intolerance and Diabetes increased dramatically after HAART [25].

Insulin resistance

Insulin is needed to help control the amount of sugar in the body. Insulin is one of the most extensively studied proteins in many fields [48]. Insulin resistance is a condition in which the body cannot use insulin effectively and higher concentrations of insulin are required to exert normal effects. Fasting insulin levels may be high because of compensatory insulin secretion by the pancreas [49]. As a result, blood sugar and fat levels rise. High glucose levels can be a side effect of HIV drugs. Specifically, the protease inhibitors (PIs) can make it difficult for insulin to get glucose into the cells. This is called insulin resistance. It can lead to pre-diabetes and diabetes. Insulin resistance may result from antiviral medication directly impairing glucose uptake in the muscle. Insulin resistance may also increase the risk of coronary heart disease [50].

When people are insulin resistant, their muscle, fat, and liver cells do not respond properly to insulin. As a result, their bodies need more insulin to help glucose enter cells. The pancreas tries to keep up with this increased demand for insulin by producing more. Eventually, the pancreas fails to keep up with the body's need for insulin. Excess glucose builds up in the bloodstream, setting the stage for diabetes. Many people with insulin resistance have high levels of both glucose and insulin circulating in their blood at the same time [51]. Insulin Resistance occurs as a result of disturbances in lipid metabolism and increased levels of circulating fatty acids that accumulate within the insulin sensitive muscle, liver and adipose tissues [52].

Reports of insulin resistance and the development of overt diabetes increased with the routine clinical use of PIs [14]. The various mechanisms that contribute to insulin resistance include chronic inflammatory changes caused by HIV, and side effects of antiretroviral medication, such as the interference of protease inhibitors (PIs) in the activity of glucose transporters, the damage to mitochondria caused by NRTIs etc [44].

Insulin resistance among treated HIV-infected patients is multifactorial. It includes common contributors to insulin resistance such as obesity, genetic influences, and physical inactivity; antiretroviral drugs and lipodystrophy [53]. The coexistence of obesity, glucose intolerance, dyslipidemia, and hypertension, is termed as insulin resistance syndrome [54]. Insulin resistance is manifested early in the natural history of the disease but glucose tolerance remains normal because of a compensatory increase in insulin secretion and hyperinsulinemia [55].

Glucose intolerance

Impaired glucose tolerance (IGT) is a pre-diabetic state of dysglycemia that is associated with insulin resistance and increased risk of cardiovascular pathology [56]. Impaired glucose tolerance and diabetes mellitus can occur in HIV patients receiving HAART [57]. Protease inhibitors do not increase risk of glucose intolerance or insulin resistance among pregnant women [58].

Hyperglycemia

Diabetes is a chronic disorder characterized by high levels of glucose in the blood and is a common disorder affecting individuals of all ages [59]. Hyperglycemia is a symptom of Diabetes [60]. Increased risk of diabetes mellitus is observed in people taking HAART, specifically protease inhibitors (PIs). Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis has been reported in HIV-infected patients taking PIs. Diabetes mellitus, one of the most prevalent diseases in developing world, is a metabolic disorder characterized by hyperglycemia and other metabolic alterations due to relative or absolute insulin deficiency [61]. Treatment with HIV protease inhibitors (PIs) and infection with hepatitis C virus increase the risk of hyperglycemia and diabetes in people with HIV. The risk of developing hyperglycemia is the same with all PIs. People who are older, obese [62], family history with diabetes are also at greater risk for developing hyperglycemia [60]. Hyperglycemia is also associated with excessive free radical generation and oxidant stress [63].

Control Measures

Current therapies require lifelong treatment which can be associated with significant toxicity and economic cost. In some instances, the use of cART may be restricted by contraindications, drug resistance, or limited access. There is a need for simple treatment options which provide sustained potency, limited toxicity, and a high genetic barrier to development of resistance [64]. Patients with HIV should be screened for diabetes at diagnosis, at onset of HAART therapy, and three to six months after HAART [65].

Understanding the glucose disturbances that are possible with PI therapy, performing appropriate screening for glucose intolerance and diabetes and making prudent changes in HIV therapy when necessary, and treating patients for alterations in glucose metabolism are the key components of care for at-risk patients [14]. Maintaining a healthy weight and increasing physical activity, Diabetes treatment, with oral agents or insulin may be useful [44]. Counseling will be an important requirement for Anti Retroviral treatment [3]. Research suggests that physical activity is inversely related to numerous metabolic disorders in people who are living with HIV [66].

Despite all the advances in diabetes treatment, education remains the cornerstone of diabetes management. Diabetes education is important in improving diabetes self-management and providing effective diabetes treatment. Differences in diet, exercise levels, stress and other factors may all affect blood glucose levels, so people should be educated about how these factors affect them and the various control measures [67].

Psychosocial support is an integral part of effective diabetes management; it is of utmost importance in patients who have to handle the double stress of diabetes and HIV. Diet, physical activity/exercise and cessation of smoking are the important measures. Oral Anti Diabetic Drugs (OADs) should be used in patients with Diabetes and HIV with great care. Insulin is the drug of choice for management of diabetes with HIV. HIV-infected patients should be taught how to dispose of lancets, glucose strips, insulin syringes, pens and needles, to prevent HIV transmission [65].

PI-based regimes should be avoided in patients at high risk of developing diabetes. Patients should be counselled about the potential risks, discomforts and benefits of HAART, and encouraged to follow a healthy lifestyle while monitoring glycemia regularly. The effective management of diabetes in HIV infected patients requires a thorough understanding of pathophysiology and pharmacology [65].

Conclusion

The recent development of highly active antiretroviral therapy (HAART) has drastically improved the life expectancy of AIDS patients but the long-term use of novel, potent antiviral agents has lead to new problems and complications. Current therapies require lifelong treatment which can be associated with significant toxicity and economic cost. Hence there is a need for simple treatment options which provide sustained potency, limited toxicity, and a high genetic barrier to development of resistance. The effective management of diabetes in HIV infected patients is therefore required to avoid undesirable consequences.

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