TREATMENT OF HIV- INFECTED DIABETIC PATIENTS

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Summary

It is estimated that over 39 million people worldwide are infected with the human immunodeficiency virus (HIV). The introduction of protease inhibitors as part of the anti-HIV therapy has contributed to a huge reduction in the number of people who die from the acquired immunodeficiency syndrome (AIDS). However, the use of these drugs has been associated with new-onset diabetes, recent studies have confirmed a higher rate of diabetes among people with HIV, compared with the general population. This implies that a significant number of people may eventually be at risk of disabling or life threatening diabetes complications, such as kidney failure or heart disease along with the complication of AIDS. This article correlates different contributing factors of HIV infected patients to the development of diabetes mellitus.

Key Words: HIV; AIDS; Diabetes; Insulin Resistance

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Introduction

HIV is a retrovirus that infects a key component of the body's immune system i.e. CD4 positive T cells, which leads to 'immune deficiency' and leaves them vulnerable to various infections.

Since the emergence of the HIV pandemic, over 25 years, there has been great advance in the care and treatment of people who are diagnosed with the virus. The use of highly active antiretroviral treatment (HAART), such as the use of protease inhibitors in a potent combination regimen (mainly with nucleoside reverse transcriptase inhibitors NRTIs), has prolonged the life of many people. Protease inhibitors when used with other drugs form a 'cocktail' of antiretroviral therapy, prevent the development of HIV by blocking the ability of the virus to replicate itself, increases CD4 lymphocyte numbers, and reduces the incidence of opportunistic infections.

Nowadays, treatment enables people infected with HIV to live longer than was previously possible. As a result, various complications develop in people, including insensitivity to insulin and diabetes. The incidence of new onset diabetes in people with HIV is significantly higher than that was seen in the general population (1).

Epidemiology

Diabetes is four times more common in HIV patients receiving antiretroviral treatment than without the antiretroviral treatment. Protease inhibitors have a direct role in the development of insensitivity to insulin and diabetes. Insensitivity to insulin is a critical early step towards the development of type 2 diabetes. Of the various types of diabetes, protease-induced diabetes mostly resembles type 2 diabetes. It is estimated that up to 40% of the people with HIV who are on a regimen of protease inhibitors have impaired glucose tolerance (IGT) and has 2-7% prevalence of diabetes (2, 3).

Age-specific relative risk for diabetes in persons with HIV compared with those without was indeed higher in all age groups, highest among 18 to 24 years of age (4). Clinical and invitro data support a direct causative role of

certain PIs in the pathogenesis of insulin resistance and DM in patients with HIV infection (5). Other data have linked insulin resistance and diabetes to the lipodystrophy syndrome that is prevalent in HIV infected patients and whose pathogenesis poorly understood (6, 7). The risk factors for DM established in the general population such as family history, obesity, race/ethnicity, age, and dyslipidemia (8) are poorly correlated in HIV infected patients.

However reports exist on the potential relation between DM and liver disease in HIV infected patients, which may be of importance in associating DM with hepatitis C virus (HCV) infection in the general population (9, 10). Drugs such as Megestrol acetate and Corticosteroids produce severe hyperglycemia in HIV-infected persons (11).

To identify potential risk factors for diabetes in HIV-infected persons, a retrospective case-control study of patients attending an urban HIV clinic was carried out. The development of overt hyperglycemia was a result of complex metabolic cascade beginning with insulin resistance. Patients with obesity, lipodystrophy, HCV co infection, hepatic steatosis, family history of diabetes and hypertriglyceridemia, independently or in combination, needs close monitoring for the development of DM. Ideally; patients with these conditions should avoid PI based therapy or PIs should be used in a more favorable metabolic profile. The oral glucose tolerance test is useful tool to screen for sub clinical DM in patients at risk. Risk factors can be reduced by taking care of HIV infected persons.

Multivariate Analysis of Covariates Associated with DM in HIV Infected cases versus matched controls found a family history of DM, elevated body mass index (BMI), and serum alanine transaminase (ALT) levels are associated with the development of DM in HIV infected patients. This study suggested complex interrelation among genetic host factors, treatment-related metabolic changes, and liver injury in the pathogenesis of DM. Larger prospective studies are needed to delineate the relative contribution of other factors to the development of diabetes, such as specific PIs, liver disease, lipodystrophy, and other metabolic disorders.

In another cohort study carried by women's interagency HIV study (WIHS), HIV-positive women taking protease inhibitors develop diabetes three times more than HIV positive women on non-protease inhibitors combinations or HIV negative women.

Etiology

Diabetes in HIV patients is caused by the protease inhibitors, the HIV infection itself and other treatments against the virus, such as 'nucleoside analogue therapy', is associated with insensitivity to insulin. Furthermore, other medications used by people with HIV predisposes to diabetes. These include Megestrol, Pentamidine, and Prednisone. In addition, other risk factors such as a family history of the diabetes, smoking, obesity, co-infection with hepatitis-C contribute to the high rates of diabetes among people in this group.

Pathophysiology

Effect of Protease Inhibitor Therapy

A preponderance of evidence implicates several PIs in the pathogenesis of insulin resistance. This process may involve different insulin target organs.

General Evidence Implicating PIs in Insulin Resistance:

Indinavir, Saquinavir, or Ritonavir in HIV infected patients increased fasting glucose level to 11% and fasting insulin level to 96% within a few months of initiation of therapy (12). Indinavir was shown to increase fasting insulin and glucose levels while decreasing insulin-mediated glucose disposal in HIV negative patients (13). In one study, Amprenavir did not induce insulin resistance at 24 weeks, but a trend toward development of insulin resistance emerged by 48 weeks (14). Use of Nelfinavir for 6 to 12 months was associated with a non significant trend toward insulin resistance, although blood glucose levels remained normal (15).

Site-Specific Evidence Implicating PIs in Insulin Resistance:

Adipose tissue

Indinavir, Amprenavir, and Ritonavir in invitro inhibited insulin-stimulated, GLUT4-mediated glucose uptake by adipocytes (16, 17). The inhibition appears to have a very rapid onset and was reversible. Ritonavir, Nelfinavir, and Saquinavir induced peripheral insulin resistance and impaired glucose-stimulated insulin secretion from beta cells (18). Adipocytes exposed to Nelfinavir showed decreased insulin-mediated recruitment of serine/threonine kinase Akt (also known as protein kinase B) and protein kinase C-zeta to plasma membrane (19). This indirectly interferes with GLUT4-mediated glucose transportation in adipocytes. Some PIs inhibit clearance of triglycerides from the circulation, which led to increased circulating free fatty acid levels; this was positively correlated with insulin resistance (20). Inhibition of lipolysis and reduction in circulating free fatty acid levels improved insulin sensitivity in some PI-treated patients (21).

Skeletal muscle and Liver

Indinavir inhibited glucose transport in skeletal muscle (22). Indinavir reduced insulin-stimulated glycogen synthesis in HepG2 hepatoma cells (23). PI-treated HIV-infected patients with diabetes had higher levels of alanine transaminase than do those without diabetes. An elevated liver enzyme level predicted insulin resistance in lipodystrophic patients (24).

Pancreas

Intravenous infusion of Indinavir impaired glucose sensing by beta cells, and inhibited glucose stimulated insulin release (25). Nelfinavir impaired the compensatory increase in insulin production in insulin resistant HIV infected patients (26). Indinavir increased insulin concentrations and the insulin-to-glucose ratio in healthy HIV seronegative males (27). Although it was hypothesized that inhibition of aspartate endopeptidase, the enzyme responsible for conversion of proinsulin to insulin, is one of the pathways through which PIs induce insulin resistance, (28) this is uncertain because PI exposure was shown to decrease the proinsulin-to-insulin ratio (25).

Other Potential Causes

Insulin resistance was described in patients receiving single-class antiretroviral therapy with nucleoside reverse transcriptase inhibitors (NRTIs), suggesting that NRTIs are potential culprits, although to a much lesser extent (29). Production of adiponectin is reduced by lipoatrophy, a known adverse effect of NRTIs. Adiponectin improves insulin sensitivity by increasing transportation/oxidation of free fatty acids and inhibition of hepatic glucose output, hypoadiponectinemia due to direct or indirect effects of NRTIs is thought to be a pathway for insulin resistance (30). Serum adiponectin level was shown to inversely correlate with fasting insulin concentration and with hepatic fat content (31).

Insulin resistance is a component of the lipodystrophy syndrome, and fasting insulin levels appear to correlate with waist and thigh circumferences. Multivariate modelling was used to estimate an approximate 1% increase in fasting insulin level for every 1% increase in visceral fat or every 1% decrease in abdominal subcutaneous fat (29). Insulin levels and resistance are higher in patients with both peripheral lipoatrophy and visceral adiposity than in those who have either alone (32).

Signs And Symptoms

The physical symptoms include fatigue, frequent urination, due to the need to get rid of excess glucose, constant thirst due to loss of fluid, blurred vision and weight loss

Complications

There is no systematic evaluation of comparison between prevalence of the complications in HIV and non-HIV diabetic populations. However, the HIV diabetic population tends to have more chance for development of complications. For example, diabetic foot can easily occur in HIV infected patients. There are many underlying opportunistic infections in HIV that have common dermatologic manifestation on the foot such as fungal nail infections that can increase the chance of diabetic foot (33). The underlying opportunistic infections in retina such as cytomegalovirus retinitis increase the chance of developing diabetic retinopathy in HIV infected patients (34). Control of opportunistic infections reduces these diabetic complications in HIV cases. With increasing importance of non-HIV-associated diseases, especially for

DM, attention should be focused on prevention and control of those disorders in HIV-positive individuals (35). Interventions targeting modifiable risk factors, including overweight and physical inactivity, are warranted (36).

Primary care for HIV-infected patients with Diabetic complications

Diabetic foot

Quarterly foot examinations are recommended for HIV-infected patients with DM (37). Due to the immune impairment, severe infection as consequence of diabetic foot can be expected. The early recognition of infection, particularly osteomyelitis, is paramount in the management of diabetic foot disease. Careful clinical appraisal remains the cornerstone of the assessment. Hematologic, biochemical, and radiological investigations are important aids in assessing the severity of infection. Microbiological assessment, particularly in more severe infection, requires good quality samples, combined with rapid transport in an appropriate medium and effective communication with the laboratory (38).

Diabetic retinopathy

In a series of 200 AIDS patients evaluated clinically, AIDS retinopathy was present in 66.5% with 64% having cotton-wool spots, and 12% having intraretinal hemorrhages (34). Increased risk for diabetic retinopathy is reported in HIV infected patients with DM (39, 40). Regular opthamalic examination is therefore mandatory for all HIV-infected patients with DM.

Nephropathy

HIV-associated nephropathy (HIVAN) is now the third leading cause of end stage renal disease in African Americans between the ages of 20 and 64 years (41). Atta et al. (42) proposed that HIV patients with nephrotic range proteinuria warranted a kidney biopsy because the presence of nephrotic range proteinuria, even in the presence a low CD4 count, did not establish the diagnosis of HIVAN. The Association of the Infectious Diseases Society of America recommends screening for chronic kidney disease in HIV infected patients; screening tests should be similar to those for patients with DM to detect early renal involvement (41). In seropositive patients with renal disease, renal biopsies should be performed to confirm the diagnosis and determine

the true incidence. Special attention should be directed toward understanding the underlying cause of HIVAN (43).

Insulin resistance (IR) caused by fat accumulation (lipodystrophy) is common in PI-treated patients, Diabetes is less common, but still 2-4 times higher than in general population. In general population (and presumably in HIV-positive patients), IR increases risk for coronary artery disease. Risk factors for IR/DM is abdominal fat accumulation, peripheral fat wasting, family history of DM, obesity, age, HCV, low CD4 count, black/Hispanic race. Corticosteroids, growth hormone, Megestrol acetate, immunosuppressants, and atypical antipsychotics contribute to the development of DM. The following is the potency of PIs on IR, Indinavir >>nelfinavir, ritonavir, lopinavir > saquinavir, amprenavir>> atazanavir.

Diagnosis

American Diabetes Association (ADA) defines confirmed DM if fasting glucose >126 mg/dL with a repeat test and a random plasma glucose >200 mg/dL and assigned as Impaired fasting glucose (IFG) when plasma glucose levels are 100-125 mg/dL, glucose tolerance test (OGTT) is considered with 75g oral glucose, more sensitive than fasting glucose. Assigned as impaired glucose tolerance (IGT) if the rage is 140-199 mg/dL and DM if the level is equal to or more than 200 mg/dl. IGT or IFG is considered as pre-DM. Fasting glucose at baseline should be checked, prior to and 3 & 6 months after antiretroviral therapy (ART) initiation, then yearly if normal. Urinary micro albumin levels have been correlated with CD4 T-cell and white blood cell counts, tumor necrosis factor α and β2-microglobulin levels, suggesting an association between AIDS progression and microalbuminuria. By monitoring urinary micro albumin levels, patients susceptible to the development of nephrotic syndrome could be identified and prophylactic measures can be initiated (44). No accepted role for clinical use of insulin levels to assess IR.

Diagnostic tests to detect diabetes mellitus and Insulin resistance

Fasting glucose Test

Detects impaired fasting glucose or overt diabetes that may be caused by insulin resistance, confirmed fasting glucose

level of > 126 mg/dl is diagnostic of diabetes, fasting glucose level of 110 to 126 mg/dl indicates impaired fasting glucose, limited clinical utility and detects fasting hyperglycemia, which may be a manifestation of insulin resistance. The HIV Medicine Association of the Infectious Diseases Society of America recommends that fasting glucose levels be monitored before and during antiretroviral therapy.

Glycosylated hemoglobin

Estimates blood glucose control in the preceding 3 months, used to monitor glycemic control in patients known to be diabetic, clinically not useful in diagnosing routine DM.

Glucose tolerance

Measures insulin output in response to oral glucose load, normal fasting insulin is approximately 5 to 20µU/mL, post glucose tolerance test level is usually < 150 µU/mL, some experts consider fasting insulin levels of > 15 µU/mL suggestive of insulin resistance, severely insulin-resistant persons often have fasting insulin levels of > 50 – 70 µU/mL and post glucose tolerance test levels of >350 µU/mL (45).

C-peptide

Often elevated in insulin-resistant patients, clinically not useful in diagnosing routine DM.

Proinsulin

Insulin precursor made up of insulin and C-peptide, releases insulin after cleavage by pancreatic endopeptidases, clinically not useful in diagnosing routine DM.

Homeostatis model for the assessment of insulin resistance

Calculated as fasting glucose × insulin ÷ 22.5, used in research, clinically not useful in diagnosing routine DM.

Hyperinsulinemic euglycemic clamp Technique

Considered the gold standard, but application is limited to research.

Treatment

Diet, Exercise, Risk Factors Modification

Balanced diet and regular exercise are crucial. American Diabetes **A**ssociation (ADA) recommends diet consisting of 50% carbohydrates (higher-fiber, unrefined preferred), 30% fat (unsaturated preferred), and 20% protein.

Dietary changes recommended for people with diabetes include, fiber rich foods like whole grains, beans, and fresh fruits and vegetables and reducing consumption of saturated fats (i.e. animal fats such as butter, lard, cream). Reducing consumption of trans fatty acids (margarine) and hydrogenated fats (found in prepared foods, e.g. cakes, biscuits, pizza) and increasing consumption of polyunsaturated fats (oils from corn, sunflower, safflower, and soybeans). Consultation with a specialist HIV dietitian is recommended before commencing a diet targeting diabetes, to ensure it will not worsen wasting, levels of blood fats, or the absorption of anti-HIV drugs. Modest weight loss (10%) in those with BMI >25 reduces glucose intolerance and can prevent onset of DM in non-HIV infected population at risk. Life style modification has shown to improve metabolic parameters in HIV-infected patients. Aggressive risk factor modification for coronary disease include maintenance of dylipidaemia, hypertension (HTN) maintenance (generally with angiotensin- converting enzyme inhibitors ACE-I, e.g. Captopril, Enalapril), cessation of smoking, cocaine avoidance, aspirin therapy (44).

Medications (oral)

First line treatment for DM, is with Metformin or Thiazolidinediones (TZDs) such as Pioglitazone. Metformin reduces hepatic IR associated with reduced visceral fat, BP, triglycerides (TG) (10-20%) in HIV positive subjects. Some studies have shown decreased limb fat with Metformin and contraindicated in patients with lipoatrophy and Serum Creatinine >1.5 mg/dL, an absolute contraindication due to lactic acidosis risk. NRTIs have enhanced theoretical risk of, liver disease, and coronary heart failure. More common complications are gastrointestinal abnormalities like nausea, vomiting and anorexia. Dose should be started at 500 mg q.i.d, titrated up to 2 g b.i.d (max dose 850 t.i.d). Thiazolidinediones (Pioglitazone) reduces peripheral IR as peroxisome proliferator-activated receptor (PPAR) gamma agonists. Pioglitazone should be started at 15 mg, titrated up to 45 mg/d, maximum effect seen after several weeks.

Fluid retention is common, contraindicated in coronary heart failure, liver disease. Combination of Metformin and TZDs is not established in HIV-positive patients, but synergy is expected. Sulfonylureas, Meglitinides, Exenatide, Sitagliptin or Acarbose are used as 2nd line therapies. Till today there is no accepted role for pharmacological interventions in IR or pre-diabetes, though data are emerging (44).

Insulin

Low dose of glargine (10-15 units) at bedtime or NPH insulin in combination with oral anti-diabetic agents are used in patients who do not respond to oral hypoglycemic agents. Insulin effectively controls glucose with individualized regimen (44).

Modification of Antiretroviral therapy

Switching from protease inhibitors to an alternative medication controls the diabetes. Some PIs, especially Atazanavir (ATV) is preferred because it causes less insulin resistance (45).

Follow up and monitoring

HIV-patients on regimen with protease inhibitors should monitor blood glucose levels monthly once. Patients with pre-DM should be screened for blood glucose levels at 3-6 months intervals. HIV-patients with diabetes should monitor for complications, opthamalic examination, spot urine for micro albumin and foot examination at 6-12 months intervals.

Conclusions

HIV and diabetes are both chronic diseases that significantly affect lifestyle. When they intersect, the treatment regimens required for both diseases can be overwhelming for patients. A screening for glucose intolerance and diabetes in HIV therapy are necessary for treating patients with alterations in glucose metabolism, are the key components of care for at-risk patients. The other metabolic disturbances associated with HIV medications, such as lipoprotein and fat distribution abnormalities, increases risk for cardiac disease. Glucose metabolism alterations in HIV patients are similar to those of type 2

diabetes. Therefore, the best clinical care regimen will reduce the risk factors like cardiac disorders, insulin resistance/diabetes, lipid abnormalities, and body fat abnormalities.

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