Glucose disorders associated with antiretroviral therapy: An overview

S.K. MASTAN[1,3]*, G. CHAITANYA[2], K. RAGHUNANDAN REDDY[2,3] and K. ESWAR KUMAR[4]

[1]Department of Pharmacology, Vignan Institute of Pharmaceutical Technology, Duvvada, Gajuwaka, Visakhapatnam - 530 046 (India).
[2] Vikas College of Pharmacy, Jangaon–506 167, Warangal (India).
[3]Department of Pharmacology, Roland Institute of Pharmaceutical Sciences, Ambapua, Berhampur (GM) - 760 010 (India).
[4]Pharmacology Division, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530 003 (India).

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ABSTRACT

The availability of potent combination antiretroviral regimens has resulted in a dramatic reduction in HIV-1 associated morbidity and mortality in the developed world. However, the optimism generated by such treatment has been tempered by the recognition of an increasing array of adverse metabolic effects, which leads in to an increased risk of death from noninfectious causes like cardiovascular disease and diabetes etc. So it is crucial for patients with diabetes to manage their blood glucose levels in order to reduce the incidence of both microvascular and macrovascular diseases. This review briefly discuss with the various aspects of glucose disorders associated with antiretroviral therapy.

Key words: Glucose disorder, Antiretrovial therapy.

INTRODUCTION

Infection with HIV and consequent AIDS is a major public health problem affecting more than 40 million people world wide[1]. The availability of potent combination antiretroviral regimens has resulted in a dramatic reduction in HIV-1 associated morbidity and mortality in the developed world[2] and the lifespan of an HIV patient has steadily increased[3]. Because HAART has significantly reduced mortality, HIV infection is now considered a chronic, manageable illness. However, the optimism generated by such treatment has been tempered by the recognition of an increasing array of adverse metabolic effects. The HIV patients can have a normal lifespan, but with that comes an increased risk of death from noninfectious causes like cardiovascular disease and diabetes[4,5]. It is crucial for patients with diabetes to properly manage their blood glucose levels in order to reduce the incidence of both microvascular[6,7] and macrovascular diseases[8].

Since the advent of highly active antiretroviral therapy (HAART) in the mild-1990, abnormalities in glucose homeostasis have been reported with increasing frequency in persons with HIV[9-13]. The FDA issued a public health advisory warning regarding this adverse event in August 1997. By May 1997 it has received 83 reports of exacerbation of diabetes/hyperglycemia or new cases of diabetes in patients taking the drugs. Of these 83 patients, 27 required hospitalization (6 cases were life threatening)[11]. The number of cases rose to at least 230 by November 1997[14]. Insulin resistance has been described in 41 (61%) of 67 protease inhibitor-treated, HIV-infected patients[15], and impaired glucose tolerance was observed in 25 (35%) of 71 HIV-infected patients using HAART[16].

Subsequent studies have confirmed the association of hyperglycemia or diabetes mellitus (DM) with PI use[17-22]. More recently nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), but not nonnucleoside reverse transcriptase inhibitors (NNRTIs), were found to contribute to the disturbance of glucose metabolism[23-26]. Further more associations of hyperglycemia and DM with hepatitis C virus infection have been reported both in HIV-negative[27-29] and HIV-positive[30-32] populations.

Progression of insulin resistance to type-2 diabetes

Normal

- Normal insulin production and cell sensitivity to insulin.
- Characterized by normal blood glucose and insulin levels (Fasting glucose <100 mg/dL or glucose below 140 mg/dL after an oral glucose tolerance test).

Insulin resistance (IR)

- Loss of insulin sensitivity and compensation by increased insulin production.
- Characterized by high blood insulin levels (Fasting insulin over 15 units/mL).

Impaired fasting glucose (IFG)

- Progressive reduction in insulin sensitivity.
- Characterized by moderately elevated fasting blood glucose (fasting glucose: 100-125 mg/dL).

Impaired glucose tolerance (IGT)

- Continued lack of insulin sensitivity and reduced ability to produced insulin to compensate for food intake.
- Characterized by hyperglycemia after eating (glucose 140-199 mg/dL after an oral glucose tolerance test).

Diabetes mellitus (DM)

- Insufficient insulin production for proper cellular functioning.
- Characterized by persistent hyperglycemia both when fasting and after eating (fasting glucose over 125 mg/dL, or glucose over 200 mg/dL after an oral glucose tolerance test, or random non fasting glucose over 200 mg/dL if accompanied by diabetes symptoms)

Insulin resistance and abnormal glucose homeostasis

Insulin resistance, impaired glucose tolerance and frank diabetes mellitus were uncommon in HIV-infected individuals prior to the availability of potent antiretroviral therapy. Although fasting glucose levels remain normal in most patients receiving potent antiretroviral therapy, up to 40% of patients on a protease inhibitor-containing regimen will have impaired glucose tolerance[33] due to significant insulin resistance[20, 34]. The insulin resistance, glucose intolerance and diabetes are clinically significant because of its association with cardiovascular morbidity and mortality as well as therapeutic challenges of managing polypharmacy[35.]

Insulin resistance referrers to the reduced action of circulating insulin to induce uptake of glucose in to cells, where glucose then serves as a major substrate for cellular function. Insulin resistance is accepted as the underlying fundamental defect that predates and ultimately leads to the development of type 2 diabetes mellitus in the general non-HIV-infected population[36]. Insulin resistance is also a major component of the metabolic syndrome that-in association with other factors such as hypertension, hypercholesterolemia and central obesity defines pre-diabetic atherogenic state that leads to adverse cardiovascular events[36]. Insulin resistance is recognized as the core component of the metabolic syndrome, having been described by Reaven[37] as the 'Common Soil' from which all metabolic diseases develop. Insulin resistance is characterized by the reduced ability of insulin to inhibit hepatic gluconeogeneis and to increase muscle up take of glucose.

The pathophysiologic basis of insulin resistance in patients on potent antiretroviral therapy is unknown. Potential mechanisms include direct effects of antiretroviral drugs that impair cellular glucose uptake[38], or indirect mechanism related to body fat changes, including central obesity and/or peripheral lipoatrophy[34, 39, 40].

Insulin resistance is, however, difficult to quantify and there are no valid measured available for clinical practice [41, 42]. The gold standard measure is the hyperinsulinaemic euglycemic clamp, and invasive technique that is resource and time intensive, and suitable for research alone. Surrogate estimated such as fasting insulin and the homeostasis model assessment [43] are again only suitable for research and epidemiological settings.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Several NRTIs and drug combinations were related to the development of diabetes mellitus[44-46] in particular, these include lamivudine-stavudine, didanosine-stavudine and didanosine-tenofovir[47]. Only limited data are available on the association of diabetes mellitus or hyperglycemia with exposure of NRTIs. Regimens including stavudine[48], Didanosine plus tenofovir[25], lamivudine[24]. Among the currently used NRTIs, the strongest association with mitochondrial toxicity, measured as inhibition of the mitochondrial DNA polymerase-ã, is found for didanosine and stavudine[49]; notably these 2 drugs are strongly associated with diabetes mellitus[47]. Stavudine, zidovudine and didanosine were associated with significantly higher risk of diabetes mellitus during long term follow up then other NRTIs[50, 51].

Protease inhibitors (PIs)

As many as 80% of patients who receive PIs develop insulin resistance, and in genetically predisposed individuals, this can lead to overt diabetes[52, 53]. Up to 60% of HIV infected patients treated with protease inhibitors develop either impaired glucose tolerance (IGT) or type-2 diabetes[54-57]. Several researchers also documented varying rates of hyperglycemia and/or diabetes in HIV infected patients receiving protease inhibitor therapy[58]. This occurs through insulin resistance induced by this drug class[19,34]. Those patients who already have diabetes or who have traditional risk factors for type 2 diabetes mellitus should consider avoiding the use of a PI-based regimen as initial HIV therapy[59]. In vitro research indicating that PIs can directly impair insulin signaling in insulin responsive tissues at pharmacologic doses[60-61]. When PIs are discontinued or replaced with another class of medication, glucose values normalize and hyperglycemia reverses, further indicating that PIs have role in the pathogenesis of diabetes[62]. Indinavir appears to be the most problematic of the PIs and should not considered as a first-line choice [63].

The mechanism by which PIs induce insulin resistance is not clear. Studies with various cell lines, including 3T3-L1 adipocytes and L6-myotubes and in rats suggest, however, that PIs acutely inhibits the cellular glucose-transport system[64-68.] The hypothesis is that PIs inhibit CRABP-1-modified and cytochrome P450-3A-mediated synthesis of cis-9-retinoic acid and peroxisome proliferator-activated receptor type-g (PPAR-g) heterodimer. The inhibition increases the rate of apoptosis of adipocytes and reduces the rate at which pre-adipocytes differentiate into adipocytes, with the final effect of reducing triglyceride storage and increasing lipid release. PIs-binding to LRP would impair hepatic chylomicron uptake and endothelial triglyceride clearance, resulting in hyperlipidemia and insulin resistance[69,70]. PIs also affect insulin signaling at the level of insulin-receptor substrate (IRS)-1 phosphorylation[71,72], association of the P85 subunit of phosphatidylinositol 3-kinase (PI3-kinase)[72] and/or Thr 308/Ser 473-Akt phosphorylation[67, 72] in HepG2 hepatoma cells[72] or 3T3-L1 cells[67] respectively.

Mechanisms for the PI-induced effects may differ between short-and long-term exposure. These short-term exposure appears to predominantly affect the glucose-transport system[38, 60, 66, 67] whereas effects on insulin signaling at the level of IRS-1[72], PI3-kinase[73] and/or AKT[72] are observed any after a larger exposure.

Long-term exposure to PIs not only induces peripheral insulin resistance but also impairs glucose stimulated insulin secretion from beta cells and this effect will appear to be differing between PIs[73]. Clinical studies have shows that treatment including indinavir, lopinavir/ritonavir and amprenavir cause IR and decreased glucose tolerance both in healthy HIV-seronegative and seropositive subjects[74-78]. These in vivo observations are supported by in vitro studies showing that protease inhibitors dose-dependently inhibit GLUT-4-mediated glucose up take in 3T3-L1 adipocytes[79]. One proposed mechanism is that HIV PIs induce development of central/visceral obesity, which in turn causes insulin resistance[18]. In rat model of insulin resistance, PIs cause acute and reversible changes in peripheral insulin sensitivity[66] and in healthy human volunteers[76]. PIs are capable of acutely inducing impaired β-cell glucose sensitivity in rodents, both in vitro and in vivo. Further clinical studies will be required to determine whether the effects of PIs on rodent β-cells function can be transferred to human patients[80].

Recommendations for assessment and monitoring[59]

Initiation of protease inhibitor therapy may induce new or accelerate preexisting abnormalities in glucose tolerance. Fasting glucose should be assessed before and during treatment (3–6 months after starting and annually thereafter) with potent antiretroviral therapy that includes a protease inhibitor. Oral administration of 75 g of glucose may help to identify patients with impaired glucose tolerance, particularly those with risk factors for type 2 diabetes mellitus and/or severe body fat changes. Diabetes mellitus (fasting blood glucose ≥126 mg/dL [7.0 mmol/L] or a glucose level ≥200 mg/dL [11.1 mmol/L] 2 hours after oral administration of glucose) and impaired glucose tolerance (glucose level e”140 mg/dL [7.8 mmol/L] 2 hours after oral glucose) are defined as for HIV-1 uninfected individuals.

Treatment

The emergence of the insulin resistance, glucose intolerance and diabetes produce

Table 1: FDA approved drugs used in the treatment of hiv infection

Generic Name(s)	Brand Name	Approval Date	Manufacturer Name
Nucleoside Reverse Transcriptase Inhibitors (NRTIs):			
Zidovudine, Azidothymidine, AZT, ZDV	Retrovir	19-Mar-87	GlaxoSmithKline
Didanosine, Dideoxyinosine, ddI	Videx	9-Oct-91	Bristol Myers-Squibb
Zalcitabine, Dideoxycytidine, ddC	Hivid	19-Jun-92	Hoffmann-La Roche
Stavudine, d4T	Zerit	24-Jun-94	Bristol Myers-Squibb
Lamivudine, 3TC	Epivir	17-Nov-95	GlaxoSmithKline
Abacavir sulfate, ABC	Ziagen	17-Dec-98	GlaxoSmithKline
Enteric coated Didanosine, ddI EC	Videx EC	31-Oct-00	Bristol Myers-Squibb
Abacavir, Zidovudine, and Lamivudine	Trizivir	14-Nov-00	GlaxoSmithKline
Tenofovir disoproxil fumarate, TDF	Viread	26-Oct-01	Gilead Sciences, Inc.
Emtricitabine, FTC	Emtriva	02-Jul-03	Gilead Sciences
Abacavir and Lamivudine	Epzicom	02-Aug-04	GlaxoSmithKline
Tenofovir disoproxil fumarate and Emtricitabine	Truvada	02-Aug-04	Gilead Sciences, Inc.
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs):			
Nevirapine, NVP	Viramune	21-Jun-96	Boehringer Ingelheim
Delavirdine, DLV	Rescriptor	4-Apr-97	Pfizer
Efavirenz, EFV	Sustiva	17-Sep-98	Bristol Myers-Squibb
Etravirine	Intelence	18-Jan-08	Tibotec Therapeutics
Protease Inhibitors (PIs):			
Saquinavir mesylate, SQV	Invirase	6-Dec-95	Hoffmann-La Roche
Ritonavir, RTV	Norvir	1-Mar-96	Abbott Laboratories
Indinavir, IDV	Crixivan	13-Mar-96	Merck
Nelfinavir mesylate, NFV	Viracept	14-Mar-97	Agouron Pharmaceuticals
Saquinavir (No longer marketed)	Fortovase	7-Nov-97	Hoffmann-La Roche
Amprenavir, APV	Agenerase	15-Apr-99	GlaxoSmithKline
Lopinavir and Ritonavir, LPV/RTV	Kaletra	15-Sep-00	Abbott Laboratories
Fosamprenavir Calcium, FOS-APV	Lexiva	20-Oct-03	GlaxoSmithKline
Atazanavir sulfate, ATV	Reyataz	20-Jun-03	Bristol-Myers Squibb
Tipranavir, TPV	Aptivus	15-Apr-99	GlaxoSmithKline
Darunavir	Prezista	23-Jun-06	Tibotec, Inc.
Fusion Inhibitors:			
Enfuvirtide, T-20	Fuzeon	13-Mar-03	Hoffmann-La Roche & Trimeris
Entry Inhibitors-CCR5 co-receptor antagonist:			
Maraviroc	Selzentry	06-August-07	Pfizer
HIV integrase strand transfer inhibitors:			
Raltegravir	Isentress	12—Oct-07	Merck & Co., Inc.

pharmacological challenge because of the potential for significant drug-drug interaction associated with the treatment for the diabetes and for HIV infection. The glucose metabolism abnormalities are formidable problem, not only because of the potential for serious drug-drug interactions but also because their treatment adds to the completing of already challenging HIV treatment regimens. In order to avoid undue toxicity with resultant decrease in drug adherence, it is important to understand and avert drug-drug interactions associated with antiretroviral therapy and treatment of emerging glucose disorders associated with HIV infection.

Patients with diabetes and HIV need to follow the clinical recommendations given by 12-member panel of International AIDS Society-USA[59]. Type 2 diabetes will respond to life style modifications including regular physical activity, caloric restriction and modest weight (waist) reduction. Because diabetes related to PI use has been associated with impairment of glucose up take by the muscle and hepatic glucose distribution, drug selection for treating hyperglycemia should address these deficits [59]. Metformin has been found to improve insulin sensitivity and reduce abdominal fat in HIV infected HAART recipients[81, 82]. The thiazolidinediones class of insulin sensitizers in several studies reduced insulin resistance in HIV-associated lipodystrophy[81, 82] and may be considered in those patients with type 2 diabetes and impaired glucose tolerance.

A possible solution to improving goal achievement could be to have a pharmacy-run clinic whose staff would meet with HIV patients with diabetes to discuss glucose monitoring, medication regimens and work to attain the American Diabetes Association goals of therapy. Pharmacist-run diabetes clinics have proven effective in a variety of settings[83-85].

CONCLUSION

HIV and diabetes are both chronic diseases that significantly affect life style. When they intersect, the treatment regimens required for both diseases can be overwhelming for patients. Understanding the glucose disturbances that are possible with antiretroviral therapy/HAART, performing appropriate screening for glucose intolerance and diabetes and making prudent changes in the HIV therapy when necessary, and treating patients for alterations in glucose metabolism are the key components of care for at risk patients.

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