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Insulin Resistance and Glucose Dysregulation In HIV Treated Patients

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Abstract
The emergence of a new HIV infected elderly population as a result of chronic use of highly active antiretroviral therapy (HAART) has attributed to the increase of metabolic disorders particularly insulin resistance(IR) and diabetes, dyslipidemia and lipodystrophy.The pathogenesis of these metabolic derangements is complex and multifactorial and could be a consequence of an interplay between traditional age-related risk factors, HIV infection, antiretroviral therapy effects, the inflammatory effect and immune activation in this population. IR in HIV infection has numerous causes which include not only the direct effects of antiretroviral drugs but also factors such as aging and restoration to health accompanied by fat accumulation. Studies have shown that insulin levels increase over time with antiretroviral therapy, likely the result of improved health, fat accumulation, and aging, and that increases in visceral fat and upper trunk fat are associated with a higher risk of IR in HIV infected and uninfected individuals. Since metabolic and cardiovascular disease (CVD) increase with aging, knowledge of the optimal management of these conditions is essential for practitioners caring for HIV infected patients including endocrine subspecialists. This review aims to synthesize the current knowledge on insulin resistance and dysregulation of glucose on treated HIV population.

Keywords: HIV; Highly active antiretroviral therapy(HAART); Insulin resistance; diabetes; dyslipidemia and lipodystrophy

1. Introduction

As the number of HIV infected patients are increasing living beyond the age of 50 years , the history of the disease has changed from opportunistic infections and immune dysfunction to chronic disease [1]–[3]with a range of metabolic complications including IR, impaired glucose tolerance(IGT),type 2 diabetes mellitus(T2DM), dyslipidemia and changes in body fat distribution (lipodystrophy) [4]–[8]. Metabolic disorders in HIV infected patients are connected with the side effect of HAART, but may also be linked to the lipogenic, pro-inflammatory or immunostimulatory nature of HIV infection[9], host genetic risk, other medication side effects, and lifestyle/behavioral habits (diet, exercise, smoking)[10].The link between HIV therapy and IR was broadly established in 1990, and the US Food and Drug Administration issued a report that described the onset of DM and hyperglycemia in HIV infected patients who were on protease inhibitors(PIs)[11]. Abnormalities in glucose metabolism occur commonly in HIV infected patients and some cohorts have shown a higher than expected risk of IR and DM compared with that for HIV-negative control populations[12], [13].IR is one of the WHO criteria for metabolic syndrome(MS), it is considered to be the link between the clustering of metabolic disturbances within the metabolic syndrome, including abdominal obesity, diabetes, hypertension and dyslipidemia [14]. IR and DM are associated with age, so increased life expectancy with the use of HAART is likely to increase the prevalence of diabetes and thus increases the risk of a future coronary heart disease (CHD) event by almost 2.5 times in HIV population[15].

IR is strongly linked with CHD and debate exists over whether it is the prime causal factor or a risk marker[16].Factors known to cause IR outside HIV infection include obesity, physical inactivity, the use of

some drugs (e.g glucocorticoids and niacin), and acute bacterial infection.In HIV infected individuals the development of IR is multifactorial with causes including restoration of health, direct drug effects of PIs and nucleoside reverse transcriptase inhibitors(NRTIs)[10], [17], increased visceral adipose tissue, age, and inactivity[16].IR and IGT as well as dyslipidemia seem to have a complex pathogenesis and are related to HIV itself, ARV drugs as well as genetic predisposition[18]–[21].Disorders of glucose metabolism have been reported at 23% after only 2 years of PI therapy[22]. The Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D) study has shown a significant association between new onset of DM and exposure to HAART and effect driven mainly by exposure to thymidine analogues[23]. Brown et al reported that there was an increased risk of DM in HIV infected patients(11.5%) vs non-HIV patients (6.5%).While older ART regimens contributed substantially to insulin resistance and body composition changes, current regimens have more subtle effects on glucose and fat metabolism.

2. Mechanism of Insulin Resistance And Glucose Dysregulation

IR refers to the reduced action of circulating insulin to induce uptake of glucose into the cells resulting in hyperinsulinemia and impaired insulin secretion. Insulin plays a major role in the induction of postprandial glucose uptake by stimulating insulin receptors on the cell surface resulting in glucose phosphorylation and translocation of glucose transporter 4(GLUT4) from the cell cytosol to the cell surface where glucose is taken into the cell [5].Interaction of this pathway in several points may result to IR[14], [24].Insulin normally suppresses hepatic glucose production and promotes hepatic glycogen and lipid synthesis.IR underlies many metabolic conditions, it is a core feature of T2DM and accompanied abdominal obesity, present in atherothrombotic cardiovascular disease(CVD) and underlies dyslipidemia characterized by hypertriglyceridemia and low HDL cholesterol.IR precedes the development of overt diabetes mellitus in many human and animal models[25]–[27] and is associated with elevated hepatic lipid contents in multiple disease models in non-HIV infected and HIV infected patients[28], [29]. The additional risk factors in HIV infected individuals are the proinflammatory effect of the HIV itself, the direct effect of HAART(especially PIs) and the indirect consequences of treatment through lipodystrophy [11], [30], [31],HCV-co-infection, low CD4 count and hepatic steatosis[32]–[34]. Guillen et al reported that age, diastolic blood pressure, weight, BMI, abdominal circumference and fasting blood glucose (FBG) was associated with IR among HIV patients as they were in general population[35].Early descriptions of IR in HIV infected HAART recipients were in the context of drug-induced lipodystrophy, a known insulin resistance state[14], [36], [37]. The early studies indicating an increased prevalence of disorders of glucose metabolism were derived from cohorts of patients with lipodystrophy, in these studies, the prevalence of diabetes was 2% among protease inhibitor recipients with lipodystrophy[36] rising to 7% over 14 months of observation[14].The prevalence of hepatic steatosis in HIV infected patients is high, especially in patients on NRTIs[38].

IR is mainly mediated in three organs; the liver, skeletal muscle and adipose tissue. Reaven et al described IR as the common soil from which all metabolic diseases develop[39]. Prior to the availability of HAART type 2 DM was relatively uncommon in HIV infection[14], [40], [41].Clamp studies before the HAART era showed normal insulin action[5] but ART, in particular, PIs have been shown to induce IR in HIV patients, a single dose of the PI indinavir-induced a 30% reduction in insulin sensitivity(by hyperinsulinemic euglycemic clamp) in healthy HIV negative subjects[5]. Some of the NRTIs and PIs are associated with diabetes mellitus as a result of inducing lipodystrophy, mitochondrial toxicity or direct effects on glucose metabolism[42]–[44].PIs are the main ART drugs associated with IR but some studies have shown that cumulative exposure of NRTIs has an increased risk of diabetes in HIV infected individual.[42]. In a study of HIV patients who commenced PIs with NRTI at the same time, the measured insulin secretion and beta cell function reduced by 25%-50%[43].In Another large multicentre AIDS cohort study, the incidence of T2DM was more than four times greater among patients on ART than in HIV seronegative controls[44]. The development of IR and DM with HAART is time-dependent.This has been shown in a study that 4.3% HAART experienced participants developed type 2 DM between 6-18months on therapy and 6.1% between 19-31months of therapy (44).In this study, the HAART experienced group with a family history of type

2DM were 7 times more likely to develop T2DM than HAART-naive[45].

2.1 Dyslipidemia

It has been observed that the presence of dyslipidemia (i.e. hypertriglyceridemia and low plasma HDL concentration) is highly indicative of underlying IR in patients with HIV despite fasting normoglycemia [13].Dyslipidemia occurs in up to 70%-80% of HIV infected patients receiving HAART and can be associated with all the available PIs, although hypertriglyceridemia appears to be more frequent in patients treated with ritonavir [7]. Hypertriglyceridemia and low plasma HDL cholesterol concentrations are the most common lipid abnormalities associated with T2DM and IR syndrome[46].Thus lipid-lowering therapy is often required with statins and fibrates in HIV patients with IR associated with dyslipidemia. Dube et al observed that use of PIs has been associated with hyperlipidemia that is more common and more severe than what was observed before the advent of HAART,62 patients(47%) of 133 PI recipients at one clinic had lipid abnormalities that met the 1994 NCEP intervention criteria[47]. In another study, it was found that in IR HIV subjects there is increased in intramyocellular lipid content related to impaired mitochondrial activity [31].These studies showed that in HIV infected patients on ART there are derangements of lipid profile which has a strong association with IR and diabetes.

2.2 Lipodystrophy

Hyperinsulinemia may be accompanied by truncal adiposity, loss of limb fat, an increased waist to hip ratio and a buffalo hump [48], a condition known as lipodystrophy. Insulin resistance is also a component of the lipodystrophy syndrome, and fasting insulin levels appear to correlate with waist to hip ratio. Presence lipodystrophy appears to accelerate the failure of insulin secretion, with early observational studies showing a sevenfold rise in diabetes prevalence in the relatively short term.[49]. Multivariate modeling was used to estimate an approximate 1% increase in fasting insulin level for every 1% increase in visceral fat or every 1% increase in abdominal subcutaneous fat [13]. PIs were the first class of ARV drugs associated with lipodystrophy when the initial patients identified as having HIV associated lipodystrophy were reported in 1997 [50], [51].In one study it has been shown that Lipodystrophy (lipoatrophy with abdominal lipohypertrophy)is associated with disturbed glucose metabolism, reduced insulin action, intramyocellular triglyceride accumulation [37].It is known that high circulating fatty acids, through a mechanism termed lipotoxicity, interfere with post-insulin receptor signaling pathways and this is one of the mechanism postulated to occur in the common form of obesity-induced IR and T2DM[14].Indeed increased visceral fat has been shown to be associated with the development of T2DM while peripheral and subcutaneous fat levels inversely correlate to the development of T2DM.[45], [52].In Willing and Overton study found that the treated HIV participants increased upper trunk subcutaneous adipose tissue (SAT) with decreased leg SAT which was associated with higher 2-hour postprandial glucose [10].In contrast to white adipose tissue measured in these studies, brown and beige adipose tissue(BAT) increase metabolic rate and improve insulin sensitivity but are reduced in HIV individuals[11], [53], [54]. Koethe et al found that greater adipose tissue stores contribute to IR and circulating cytokines in HIV infected patients on ART [55]. In a multi-country study of 33,000 subjects in the Data Collection on Adverse Events of Anti HIV Drugs(D.A.D) cohort, a BMI>30kg/m2 was associated with a 4.5 fold higher risk of incident exposure to stavudine, zidovudine, didanosine and other ART agents known to cause alterations in fat partitioning and adipocyte energy metabolism[55].Carpentier et al showed that insulin-mediated suppression of plasma free fatty acid concentrations was impaired both prior to and following the introduction of HAART compared to healthy matched controls [56]. There is sufficient evidence that lipodystrophy is linked to hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, peripheral insulin resistance and even to overt diabetes [36], [57]. Jasik et al proved that ARV therapy leads to an increase of fasting, as well as postprandial free fatty acids(FFAs). The study showed that even without significant lipodystrophy HIV infected individuals experienced increase lipolysis as well as can have adipocyte FFA trapping and these can be the triggered event in other metabolic complications as hypertriglyceridemia and IR [32]. Lipodystrophy may also result in B-cell dysfunction and is associated with impaired feedback of insulin on B-cells. In contrast to other studies, Sutin et al suggested that IR in HIV patients is related more closely to fat accumulation in the liver than the intra-abdominal fat[28].The above observations indicate that therapeutic interventions with increased FFA's levels can be beneficial in HIV infected ARV treated patients.

2.3 Inflammation

The inflammatory profile in HIV treated patients is equivalent to that found in IR obesity despite lower body fat. TNF-alpha, a proinflammatory cytokine produced by multiple cell types including macrophages, lymphocytes and endothelial cells that contributes to the inflammatory cascade is highly expressed in treated HIV patients[58]. The Grunfeld lab found that interferon alpha levels were higher in patients with AIDS compared with those with uncomplicated HIV infection and matched healthy controls[59].It is also produced in adipose tissue and interacts with insulin receptors to attenuate the effect of insulin binding to its receptor, as a result, increasing IR[17]. Brown and associates study suggest that despite the decrease in most inflammatory markers with ART initiation, markers of TNF-alpha activation 48 weeks after treatment contributes to the pathogenesis of diabetes[17], [60]. In HIV patients on HAART lipodystrophic adipose tissue manifests as an altered profile of secreted cytokines with increased TNF-alfa and IL-6.These cytokines are responsible for IR at the adipocyte level resulting in increased lipolysis and FFA fluxes which in turn induce IR at the level of muscle and liver[53]. Beyond the effect of ART on IR and development of DM, chronic inflammation during HIV infection may accelerate the development of comorbid conditions such as DM[17], [34].This inflammatory state may explain the development of DM among HIV infected adults at a younger age and among the nonobese. In the Multicenter AIDS Cohort Study IR markers were higher in all groups of HIV infected men compared with HIV uninfected control subjects even among those who were not receiving ART[61].Evidence of HIV mediated inflammatory IR was noted in a number of insulin-regulated pathways prior to the HAART era.In another crossectional study found that TNF-alpha levels were higher in HAART naive HIV patients than their HAART treated counterparts, levels of insulin-sensitizing hormone adiponectin were decreased in both groups compared to healthy controls and were correlated inversely with IR as measured by HOMA-IR [62]. Low adiponectin is associated with visceral obesity and predicts CVD [11], [53], [63] and T2DM [22]. The fatty acid binding protein 4(FABP4) has been suggested to be another adipokine produced in adipocytes as well as macrophages and endothelial cells involved in body weight control, glucose, lipid metabolism and pancreatic beta cell function [64]–[66].In HIV infected treated patients, FABP4 positively correlated with glucose, insulin and triglyceride concentration [67].FABP4 could be used as a marker of metabolic disturbances in HIV infected patients.

3. Insulin Resistance And Antiretroviral Drugs

Since the introduction of ART,26 drug compounds have been approved by the US Food and Drug Administration(FDA)[68]. The aim of using ART is to inhibit HIV replication to decrease viral burden, thereby increasing CD4 counts and decreasing the risk of opportunistic infections and to prevent transmission[69]. There are six major groups of ART according to their mechanism of action. (Fig of ART article 5).Entry inhibitors, integrase inhibitors, reverse transcriptase inhibitors(RTIs)including nucleoside/nucleotide reverse transcriptase inhibitors(NRTIs) and nonnucleoside reverse transcriptase inhibitors(NNRTI), PIs and multiclass drug combinations[69]. The combination therapy of HIV protease inhibitors, reverse transcriptase inhibitors, and/or integrase inhibitors referred to as highly active antiretroviral therapy(HAART) and is currently the most effective therapy.The preferred initial management is the combination of two nucleoside reverse transcriptase inhibitors with a nonnucleoside reverse transcriptase inhibitors or with PIs. After initiation of ART, an HIV infected individual first starts by regaining weight and well being this comes as a result of the improve in appetite and caloric intake, second the effect of specific ART on various metabolism as glucose regulations[3].

The mechanism by which ARV causes metabolic complications are entirely not clear but the hypothesis on which the old ARVs; NRTIs AND PIs have been associated with mitochondrial dysfunction and oxidative stress, altered adipogenesis and differentiation, impaired glucose transport, altered expression of lipid metabolism genes and impaired lipolysis[69]. Some studies suggest that the duration of using the ART is a consistent factor in association with the increased rate of diabetic risk. From the limited data from previous

studies on newer ARVs, it is suggested that they have a more favorable profile on metabolic changes compared to the older ARTs. For example, second generation PIs even with ritonavir boosting also seem to have favorable metabolic profiles[69]. In willing and Overton study showed that the integrase strand transfer inhibitor(ISTI) class of ART has similarly demonstrated a favorable profile in terms of lipids and glucose metabolism[10]. A recent AIDS Clinical Trial Group(ACTG) study evaluated the metabolic effects of an ISTI(raltegravir),and two boosted PI regimens(darunavir and atazanavir) paired with tenofovir/emtricitabine, the investigators reported significant gains in all fat depots assessed(limb fat, subcutaneous fat, visceral fat, trunk fat) and in lean body mass[70]. Individuals on newer, more lipid friendly HAART are not completely spared from dyslipidemia and diabetes mellitus as longer life spans allow a restoration of health and development of these age-related metabolic diseases.

3.1 Protease Inhibitors(PIs)

Soon after the introduction of first-generation HIV PIs in 1996, HIV infected patients were found to have a higher incidence of metabolic disorders including DM[71], [72]. The major metabolic side effects associated with HIV PIs are lipodystrophy syndrome and IR (18), some authors suggested that the use of this class of drugs accounts for over 60% of metabolic changes in HIV patients[46], [73]–[75]. The explanation on the mechanism involved in the induction of IR by PIs includes inhibition of the activity of glucose transporters (GLUT1 and GLUT4) in the plasma membrane[44], inhibition of preadipocyte/adipocyte differentiation and induction of apoptosis in mature adipocytes[76]–[78].Hruz et al and Murat et al suggested that one of the main mechanisms responsible for the induction of IR by PIs is the inhibition of transporter GLUT4[79]. Some research findings suggest that PIs containing regimens impair glucose tolerance by two mechanisms; first by the induction of peripheral insulin resistance in skeletal muscle and adipose tissue, and second by impairing the ability of the beta cells to compensate of these changes[11]. Many PIs including ritonavir(RTV) and lopinavir(LPV) also impair adipocyte differentiation[80]–[82] likely by preventing maturation and nuclear localization of sterol regulatory element binding protein 1(SREBP) and inhibition of peroxisome proliferator-activated receptor gamma (PPAR-GAMA) leading to IR[46], [83].SREBP and PPR-GAMA are involved in IR by regulating the production and release from adipocytes, adipokines such as adiponectin and leptin which mediate the insulin action in peripheral tissues and glucose metabolism[5].Thiazolidinediones(TZD) has been shown to improve IR in an individual with HIV induced lipodystrophy by acting as direct PPAR-GAMA agonist[4].

GLT4, the principal glucose transporter found mainly in adipocytes and skeletal muscles, was the first molecule identified to be a direct target of PIs in the pathogenesis of IR [84].This effect was first demonstrated when indinavir, by inhibiting GLUT4, was found to impair insulin-mediated uptake of glucose into adipocytes in vitro[68]. In another study insulin, IR developed rapidly after a single dose of the PI indinavir in a healthy HIV negative subjects with a reduction in insulin sensitivity(by hyperinsulinaemic euglycaemic clamp) by 30% [14].GLUT4 inhibition occurs in a dose-dependent manner and is evident within the range of the therapeutic concentrations achieved in HIV infection [85].Both ritonavir(RTV) and lopinavir(LPV) are among the more potent inhibitors of GLUT4 [86], [87]. PIs could inhibit the proteases responsible for the conversion of proinsulin into insulin as well as protease regulating insulin catabolism generating a state of hyperinsulinemia and hyperglycemia[30]. The newer PIs, atazanavir(ATV) and darunavir appear to have minimal impact on glucose metabolism in either HIV infected or HIV uninfected persons and rarely cause IR [88]–[90](21, a fact that could explain the improvement of IR in pretreated patients switching to these drugs. Stanley et al concluded that insulin-mediated glucose uptake into anterior thigh muscle increased significantly in subjects who switched to ritonavir-boosted ATV compared to those who remained on ritonavir-boosted LPV($p=0.0035$), decreased fasting glucose($p=0.002$), decreased triglyceride and total cholesterol and significantly reduced visceral fat over 6 months [85].

3.2 Nucleoside reverse transcriptase inhibitors (NRTI)

This is another class of ART which increases the risk of developing IR and DM in HIV infected patients[3].This was first raised by Brinkman et al in 1999.The nucleoside analogues work by inhibiting HIV reverse transcriptase and DNA polymerase gamma.This lead to mitochondrial toxicity depending on the type of cells, for example, mitochondrial dysfunction in muscle cause IR and in adipose tissue promotes lipoatrophy[91].A study of >1200 patients enrolled in the Multicenter AIDS Cohort Study(MACS) found an 8% increase in the incidence of developing hyperinsulinemia each year the patient is exposed to NRTIs[3]. In another study concluded that cumulative exposure to NRTI is associated with IR and incidence of diabetes or hyperglycemia 4-fold higher in HIV infected men than in uninfected men[12]. There is no direct association between NRTIs with IR and DM. Stavudine(d4T) is the NRTI most strongly associated with a reduction of subcutaneous fats (lipoatrophy) mainly peripheral[92].In one study it was observed that effect of discontinuing chronic use of stavudine in HIV positive patients who have developed marked fat loss in the limbs, the metabolic and clinical abnormalities was partially reversible after 6 months[93]. Another thymidine analogue, zidovudine(AZT) has also been associated with lipodystrophy although the effect is less severe compared to stavudine[11]. Abacavir is an effective alternative replacement for d4T or PIs or NNRTIs, this may lead to the gradual recovery of peripheral fat loss [94].

3.3 Nonnucleoside reverse transcriptase inhibitors (NNRTIs)

The NNRTIs cause alterations in the lipid profiles, although generally to a lesser degree than has been observed with PIs.NNRTI use is associated with a substantial increase in HDL-cholesterol levels to a degree not generally seen with PIs [7] which make them superior to PIs in preventing CVD. One study showed that nevirapine had a tendency to increase HDL-cholesterol, which is an advantage for cardiovascular risk [11].NNRTI efavirenz(EFV) has been associated with only very modest changes in glucose metabolism up to 48 weeks[95]. In contrast to other studies, Erlandson et al demonstrated a significantly larger increase in glucose with an assignment to EFV compared to ritonavir-boosted ATV even after adjusting for changes in body composition in multivariate analyses [96]. In a study of Almeida SEM et al also suggested that both PI and NNRTI containing HAART increased total cholesterol, triglyceride and glucose level compared to baseline, regardless of PI-containing HAART [97].

4. Prevalence of Insulin Resistance And Diabetes Mellitus In Treated Hiv Patients

Before the introduction of ARTs, the disorders of glucose metabolism were uncommon in HIV infected people. Studies report that diabetes rate of 2.0-2.6% in treatment-naive HIV patients [3], but this changed after the advent of HAART especially the PIs AND NRTIs. Certain factors add in predisposing these patients to increase risks of diabetes such as the presence of lipodystrophy, obesity and ethnic predisposition [3]. The Data Collection on Adverse Events of Anti-HIV Drugs(DAD) study has shown a significant association between new onset of DM and exposure to HAART an effect driven mainly by exposure to thymidine analogues [98].Most new DM diagnoses occurred in an era when HIV infected patients were exposed to first generation ART agents with significant metabolic toxicities [99].This is consistent with previous studies and might be related to the use of older NRTIs and PIs which have a role in the development IR[99].Among HIV infected patients, the risk for progression to diabetes is significantly greater among patients with baseline IR estimated to be five times higher for those with considerably elevated HOMA-IR levels at baseline [4]. In one recent study reported that 1 in 10 HIV infected adults receiving medical care had DM and in comparison with general adult population suggest that DM among HIV infected persons may develop at earlier age and in the absence of obesity [34],this study also suggested that increasing age, obesity, longer duration of HIV infection and the mean CD4 were independently associated with a higher DM prevalance and compared with the general population HIV infected individuals had a 3.8% higher prevalence of DM after adjusting for age, sex, race/ethnicity, education, poverty level, obesity and HCV infection [34]. In a study that examined HIV negative(n=710)and untreated HIV infected

patients(n=157) found that fasting glucose was similar between treatment-naive HIV infected patients and those which are HIV negative [5]. Another prospective study shows that 10% of ART recipient HIV individual developed DM within 4 years followed period compared to 3% HIV seronegative men [12] after adjustment of age and BMI the difference represented a greater than 4-fold increase in relative risk of developing DM. In a study done by Guillen et al using the HOMA method reported that prevalence of insulin resistance among patients on HAART was ranging from 13% to 45.7% and the factors associated with IR were age and BMI [35], also reported a high prevalence of hyperglycemia(47%) [35]. In a longitudinal study of IR on HIV individuals on newer ART regimens, identified IR in 21% of participants which represents a significant decrease from estimates of 35-63% prevalence IR with older ART regimens [5], [30], [100] ,however the decrease in IR occurred alongside an increase in diabetes diagnoses and obesity prevalence. Jemsek JG et al found that alteration of insulin sensitivity in the early stages of antiretroviral therapy tends to normalize over time [88]. In another study it was also reported that the prevalence of IR was not significantly higher among patients who were more than one year on HAART compared to those who were less time on treatment[35], suggesting that IR is more pronounced early during treatment.This is inconsistent with other studies in which IR increased with the chronic use of ART especially the older ones.

5. Diagnosis Of Insulin Resistance And Diabetes In Hiv Patients.

There are various methods for measuring IR in HIV patients which are similar to in general population and mostly used in clinical investigations. The euglycemic insulin clamp is considered the gold standard, intravenous glucose tolerance test, homeostasis model assessment(HOMA), quantitative insulin sensitivity check index(QUICKI), the insulin-glucose ratio(FGIR) and the Bennett Index. Insulin sensitivity measurement by the euglycemic clamp technique is used only for research purposes. There is a close correlation between the HOMA-IR index and insulin sensitivity determined by the clamp technique [101]. The HOMA mathematical model is a clinical and epidemiological tool used to estimate IR based on the plasma levels of fasting glucose and insulin. It is calculated by insulin concentration(micro/ml) multiplied by the result of glucose concentration(mmol/l) divided by 22.5; a score of higher than 4 indicates insulin resistance which is useful in epidemiologic studies. Elevations in fasting insulin above 15mcIU/ml(fasting) and/or 50mcIU/ml(postprandial) signify increased insulin secretion secondary to IR. The interlaboratory variability should be noted. Several other variables such as family history of diabetes, BMI, blood pressure, waist and hip circumference, fasting triglycerides, HDL, glucose, insulin and hepatic enzymes all correlate with insulin resistance.

Screening of DM in HIV infected patients is currently recommended before HAART initiation, from 3-6 months after initiation and annually thereafter [102].In general population HbA1c has been recommended for screening of DM however in HIV infected patients HbA1c may underestimate glucose exposure which can lead to underdiagnosis(145 in 35).Factors associated with discordance between actual and predicted HbA1c include higher mean corpuscular value use of HAART [60]. In some studies, it has been observed high HbA1c–glucose discordance with current NRTIs [44] this may be because of the high turn over of the red blood cells in these patients. In another study, HbA1c underestimated average blood glucose by approximately 1.7mmol/l [103].Because of the potential inaccuracy of HbA1c, fasting plasma glucose test or 2-h plasma glucose value after an oral glucose challenge should continue to be used(2018 ADA). The Infectious Diseases Society of America (IDSA) recommends the assessment of fasting glucose and fasting lipids prior to and within 4-6 weeks after starting HAART [104].Additionally, the International Association of AIDS-USA recommends repeating these measurements at the time of switching therapy, 3 to 6 months after switching therapy and at least annually thereafter while on stable therapy [33].

6. Management of Insulin Resistance and Diabetes In Treated Hiv Patients.

Patients with IR tend to remain euglycemic as long as there is an adequate compensatory increase in insulin secretion from the pancreas. IGT and diabetes insure when the level of IR exceeds the compensatory increase in pancreatic insulin output [105]. There is no clear rationale for the treatment of IR per se and there is no drug licensed for this purpose alone. The management of IR focuses on prevention. The key to effective prevention of IR is an assessment of the risk factors including obesity, lifestyle factors (diet and physical activity), genetic predisposition, and the HIV related factors such as lipodystrophy, ARV drugs especially PIs and hepatitis C co-infection. Fitch and colleagues found that both lifestyle modifications (exercise and diet) and metformin improved symptoms of metabolic abnormalities in HIV patients [106]. A reduction in body weight and increase in physical activity have been shown to increase insulin sensitivity and also delay the onset of overt diabetes. HIV infected patients require aggressive treatment including low-fat diets, avoidance of simple sugars, and elimination of alcohol intake [45]. Since the pathogenesis of IR results in abnormal glucose metabolism and finally DM, the pharmacological approach will start with insulin-sensitizing agents such as metformin and thiazolidinediones(TZDs) [91].

6.1 Metformin

Metformin is a biguanide and is the first choice in management of abnormal glycemic control and insulin resistance, it also reduces the hepatic glucose toxicity but the concomitant use with NRTIs may increase the risk of lactic acidosis [42], [91] .if the patient is using NRTIs should be stopped when lactate level has reached 15mmol/l(7). it is suggested that metformin reduces fasting plasma glucose, visceral fat(VAT) and IR and also reduces serum markers of endothelial dysfunction(PAI-1 and tPA) which may be increased in this group of patients [110].Reduction of high insulin levels and level of PAI-1-tPA complex minimizes endothelial injury and thrombus formation. Metformin has been demonstrated to reduce VAT in HIV patients but with the accelerated subcutaneous fat loss as well [113]. In a study of double-blind placebo-controlled trial metformin 500mg twice a day was given to a lipodystrophic HIV positive patient with impaired glucose tolerance or hyperinsulinemia for 12 weeks, results was a significant reduction of insulin area under the curve 120 min after an oral glucose tolerance test in the metformin arm compared with placebo [113]. In another study of Driscoll et al demonstrated that metformin in combination with exercise in HIV infected patients with fat redistribution and hyperinsulinemia was more effective in reducing waist-to-hip ratio, blood pressure, and insulin levels when compared to metformin alone. Several metabolic parameters have improved in HIV infected patients who were given metformin, including insulin sensitivity, surrogate measures of CVD, and lipid parameters [10]. .Metformin is contraindicated in co-morbid conditions such as TB, cachexia, lipoatrophy.(article 4). Metformin is also contraindicated in renal impairment (serum creatinine >150umol/l or eDFR<60ml/min), pregnant and breastfeeding

6.2 Thiazolidinediones(TZD)

TZD is another class of insulin sensitizer which increases insulin sensitivity, increases glucose metabolism in muscle and promote adipogenesis. Among the TZD approved in the management of DM are rosiglitazone and pioglitazone. Rosiglitazone and pioglitazone act by enhancing the peripheral insulin sensitivity, they stimulate peroxisome proliferator-activated receptor gamma and studies have shown an increase subcutaneous fat in diabetic patients and HIV seronegative patients with lipid distribution disorders after given TZD[114]. Hadigan et al reported that rosiglitazone improved IR, increased adiponectin levels, reduced lipoatrophy and decreased hyperinsulinemia and free fatty acids despite the ongoing ART [11]. The FDA recommends a regular check-up of liver function test for the patients using TZD for the first 12 months of usage. The possibility of slight increases in subcutaneous fat makes them the preferred drug class in patients with lipodystrophy, however, they are contraindicated in hepatic dysfunction and heart failure.

Other approaches include recombinant leptin, this has been investigated as an approach to improve metabolic abnormalities among HIV infected patients [107], [108], its administration in HIV patients with lipoatrophy and hypoleptinemia has been associated with increased insulin sensitivity and reduced triglyceride levels in two small pilot studies [108]. The treatment of ART-associated dyslipidemia falls into three categories which include a change of ARV scheme, changes of lifestyle, and prescription of lipid-lowering agents [109].All HIV infected patients require an annual assessment of their lipid profile before the beginning of the ART and at every three months after the initiation of the treatment or after any change in their therapeutic regimen [110].The pharmacological treatment of dyslipidemia in patients with HIV follows the same criteria of the national cholesterol education program(NCEP) as for the general population including statins, fibrate, and niacin [47]. Statins have been demonstrated not only to effectively reduce LDL cholesterol in HIV infected patients but also to reduce markers of T cell and monocyte activation and reduce inflammatory cytokines that contribute to lipid and glucose disorders[10].However in one study, a sharp increase in HOMA-IR was observed as early as 48 weeks after statin therapy, indicating a concern for the possible increase in diabetes risk after long-term statin use in HIV patients [111], [112], this is an area which needs further studies. While growth hormone(GH) failed as a therapy in HIV patients due to induction of severe IR and frank diabetes, Tesamorelin, a GH releasing analog, has been FDA approved to reduce visceral fat deposition in HIV patients.

7. Conclusion

Since WHO recommendations changed to a test and treat policy meaning that ART should be started immediately in all individuals diagnosed with HIV regardless of age or CD4 cell count, this means, the number of patients exposed to ART will increase and therefore awareness of metabolic complications in this group of patients should be increased especially in health care providers of HIV infected patients. Opening special metabolic clinics in centers caring for HIV infected individual so that to facilitate the screening and managing of the increased number of metabolic complications in these patients. The development of IR can be minimized by choosing the HAART regimens that have the least effects on metabolism, by supporting lifestyle changes in those with a high risk of developing IR or cardiac disease and careful routine monitoring to enable early treatment of the risks. Newer ART regimens are less toxic to cellular function and metabolism but have failed to completely eliminate metabolic dysfunction with HIV infection. Currently there are limited studies on the response to diabetic medications in HIV infected patients with T2DM, whether these patients respond to diabetic medical therapy similarly to the HIV uninfected population is an area to be further explored.

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