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REVIEW ARTICLE

Biochemical Manifestation of HIV Lipodystrophy Syndrome

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ABSTRACT

Objectives

Highly active anti-retroviral therapy (HAART), including protease inhibitors (PI) have led to dramatic improvements in the quality and quantity of life in patients with acquired immunodeficiency syndrome (AIDS). However, a significant number of AIDS patients on HAART develop characteristic changes in body fat redistribution referred to as lipodystrophy syndrome (LDS). Features of LDS include hypertrophy in the neck fat pad (buffalo hump), increased fat in the abdominal region (protease paunch), gynecomastia and loss of fat in the mid-face and extremities.

Methods

The aim of this paper is to review the current knowledge regarding this syndrome. This article reviews the published investigations on biochemical manifestation of HIV lipodystrophy syndrome.

Results

It is estimated that approximately 64% of patients treated with PI will experience this syndrome. Biochemically, these patients have increased triglycerides (Trig), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and extremely low high-density lipoprotein-cholesterol (HDL-C).

Conclusions and Public Health Implications

It is hoped that awareness of this syndrome would aid in early diagnosis and better patient management, possibly leading to a lower incidence of cardiovascular complications among these patients.

Key Words

HIV Lipodystrophy Syndrome, Highly active anti-retroviral therapy, Nucleoside Reverse Transcriptase Inhibitors, buffalo hump.

Introduction

Lipodystrophy syndrome, a condition associated with metabolic abnormalities and distinct morphological changes has been increasingly reported in HIV-1 infected individuals[1]. HIV-LDS in infected patients is now considered a major adverse effect of antiretroviral therapy. Many descriptions of this syndrome are reported in the literature but there exists no universally agreed definition. In general, this condition is characterized by fat loss (lipo-atrophy) in the face, arms, legs, and buttocks; fat gain in the abdomen, over the back of the neck (dorso-cervical fat pad or "buffalo hump"), and in the breast and occasionally isolated lipomata may be present.

HIV-LDS has been associated with both protease inhibitor (PI) and nucleoside analogue therapy, particularly in combination therapy involving both classes of drugs[2, 3]. Current evidence suggests that HIV-LDS may affect up to half or even more HIV-infected patients receiving antiretroviral therapy[1, 4]. Thus as the survival rate of HIV positive individuals increases with the introduction of highly active anti-retroviral treatment (HAART), atherosclerotic vascular disease, severe premature coronary artery disease (CAD) and other metabolic diseases could become an important HIV–related complication. Indeed CAD and metabolic disorders have increasingly been reported in patients treated with these medications[5]. However, the mechanisms remain largely unknown.

The hallmark of HIV-LDS is a dyslipidemia, a biochemical abnormality of the blood lipid profile that frequently presents before distinctive clinical features of fat redistribution become apparent. To date, no consensus guidelines for treatment of LDS exist. A distinct feature of this condition, body fat changes, could be socially stigmatizing and pose serious problems in treatment compliance and antiretroviral therapy failure. Awareness of HAART complications therefore by all parties concerned, coupled with early diagnosis, could impact positively on HIV prognosis and management. This report aims at describing a typical HIV-LDS case including a review of diverse patho-physiological mechanisms thought to underlie development of this condition in HIV treated patients.

Methods

Studies were identified through a PubMed database search. Case-control and longitudinal studies into clinical and biochemical manifestation of HIV lipodystrophy were selected. Areas covered include data on lipid dysregulation, cytokines, adipokines, proteins, clinical manifestations and management strategies.

HIV-LDS: Clinical Features and Metabolic Changes

Body shape changes

A number of anecdotal reports of increased abdominal girth have been linked with the use of protease inhibitors[6, 7]. An ongoing Fat Redistribution and Metabolism (FRAM) study[8], a prospective, multi-center, cross-sectional investigation of HIV-infected subjects and controls aims to address some of the uncertainties concerning the prevalence, etiology, risk factors and clinical features of HIV-LDS. Preliminary findings to date, mainly from a subgroup of 1200 male subjects and 300 controls suggest a strong association between HIV and lipoatrophy (depletion of subcutaneous fat) but no association between HIV and visceral fat accumulation. It was therefore concluded that lipoatrophy develops independently of fat accumulation and therefore the term 'fat redistribution' may be a misnomer. Although HIV infection is well known to cause body wasting usually in advanced disease[9], it has not been shown to cause the fat accumulation, breast hypertrophy and buffalo hump of lipodystrophy. Generally

speaking, exposure to HAART (in particular PIs) appears to be relevant to the onset of HIV-LDS[10]. Thus the variability in clinical manifestations of this syndrome may reflect differences in the underlying pathogenesis.

Lipids

Changes in lipid profile have been the most remarkable biochemical abnormalities in HIV-LDS. The mechanisms predisposing to abnormal lipid profiles in HIV infected individuals are still a matter of debate because HIV infection itself is associated with several metabolic disturbances that may be part of host response to viral infection, decreased HDL-C and LDL-C have been demonstrated in HIV positive men[11]. However, these changes usually occur early in HIV infection. Very low density lipoprotein cholesterol (VLDL-C) also increases with immunosuppression as HIV infection becomes manifest. These changes are thought to lead to increased triglyceride levels[11, 12]. Furthermore, host response to viral infections also causes increases in Interferon-α which ultimately may cause both increased production and decreased clearance of triglyceride[13, 14].

Thus in a cross-sectional study, Carr *et al.*[15], reported that HIV positive patients on PI therapy had higher triglyceride levels (> 100%) and higher cholesterol levels (> 20%) than HIV positive patients not on PI therapy. Increased cholesterol and triglyceride levels have been reported in HIV negative healthy volunteers receiving ritonavir for 2 weeks[16], confirming a direct effect of PI treatment on lipid metabolism. Other studies which suggest increases in lipid levels include those of Periad *et al.*[17], which showed increases in mean plasma level of triglyceride (> 100%) and total cholesterol (> 40%) in patients treated with ritonavir compared with a PI naïve group matched for age and body mass index. Sergerer *et al.*[18] reported an average increase in plasma triglyceride by 25% and cholesterol by 15% at 3 months in 148 patients; there were no further significant increases after 3 months. A control group treated only with Nucleoside Reverse Transcriptase Inhibitors (NRTI) had no change in their lipid profiles. Taken together, it is now known that dyslipidemia associated with various stages of HIV/AIDS disease is cytokine mediated whereas dyslipidemias observed in HIV/AIDS treated patients on HAART is likely due to alteration in adipogenesis.

Insulin Resistance

Shikuma *et al.*,[19], reported increased fasting insulin and waist-hip ratios in non- wasting patients with AIDS suggesting that such body shape changes were related to HIV infection or to factors associated with immunological dysfunction. Hadigan *et al.*[20] compared metabolic parameters in 75 women with HIV, some of whom were not on PI therapy to 30 weight-matched but younger control women. They noted that fasting insulin was nearly double in HIV patients and independent of PI use. In line with this study, Behrens *et al.*[21] reported impaired glucose tolerance in 24 % of PI naïve patients. Collectively, these studies suggest that HIV itself may cause insulin resistance, which deteriorates with increasing duration of infection.

However, more recent studies suggest that insulin resistance in HIV positive patients is due to antiretroviral therapy and not to HIV infection. Prior to the introduction of HAART, HIV- infected patients were found to have normal or decreased glucose levels and no significant insulin resistance[22, 23]. While after therapy, hyperglycemia has been reported in several studies[15, 24] and the US Food and Drug administration have described 83 cases of new onset hyperglycemia or worsening pre-existing diabetes[25]. In one study, Carr *et al.*,[26], evaluated 116 HIV-infected, otherwise healthy patients receiving one or more PI, 32 HIV–infected PI-naïve patients, and 47 healthy male control subjects. Three recipients had worsening or new diabetes mellitus, and the 64% of PI recipients

who developed body composition changes had significantly higher insulin and C-peptide levels than PI naïve patients or controls. Other studies were those of Walli *et al.*[27] who performed intravenous glucose tolerance tests in 67 patients receiving PI- containing therapy, 13 PI-naïve patients and 18 HIV negative controls; 61 % of those receiving PI exhibited insulin resistance. In a 5–year cohort analysis in 221 HIV-infected patients, it was found that the incidence of new onset hyperglycemia was 5%. Thus protease inhibitors were independently associated with a five-fold increase in the incidence of hyperglycemia. Taken together, several of the studies cited above suggest that PI therapy may cause insulin resistance. Clinically it has been observed that PI therapy may predispose to glucose intolerance or indeed frank adult onset diabetes in some individuals. Such abnormalities may be more likely if lipodystrophy is present.

Pathogenesis of Lipodystrophy

It has been suggested that the pathogenesis of HIV-LDS may be multifactorial. Possible mechanistic abnormalities in HIV-LDS are described as below:

Inhibition of nuclear receptor complex (PPAR-gamma) and Retinoid X receptor (RXR)

The first attempt at defining the hypothesis for HIV–LDS pathogenesis was put forward by Carr *et al.*[26]. They postulated that protease inhibitors affect adipocyte differentiation by inhibiting the heterodimeric nuclear receptor complex composed of peroxisome proliferator activated receptor gamma (PPAR-gamma) and the retinoid X receptor (RXR). This complex enhances target gene transcription in pre-adipocytes. The catalytic region of HIV-1 protease (to which PI bind) has approximately 60 % homology to regions within cytoplasmic retinoic acid binding protein type I (CRABP-1), which enhances the production of cis-9-retinoic acid that is the sole ligand of RXR. Ligand binding to RXR, inhibit adipocyte apoptosis and up-regulate adipocyte differentiation and proliferation. Protease inhibitors may bind to and inhibit CRABP-1, cause decreased production of cis-9-retinoic acid, decreasing RXR-PPAR gamma activity and so reduce differentiation and increase apoptosis of adipocytes. PPAR-gamma is preferentially expressed in peripheral as against central fat so these changes are most marked in peripheral tissues. Although it is plausible from the discussion above that PIs may act as PPAR-gamma antagonists and predispose HIV-infected patients to develop HIV-LDS, this hypothesis has been disputed by Wentworth *et al.*[28], who studied the effects of PIs on human adipocytes *in vitro*. They found no evidence that PIs acted as PPAR-gamma antagonists suggesting that impaired adipogenesis does underlie PI-associated HIV-LDS but does not directly involve PPAR-gamma and RXR.

Inhibition of sterol regulatory binding element

The sterol regulatory element-binding proteins (SREBPs) are membrane bound transcription factors, which have been proposed to play central role in cellular lipid homeostasis[29]. They regulate the transcription of many genes including the LDL receptor gene. SREBPs have been found to be increased in the nuclei of hepatocytes of animals treated with ritonavir[30]. Furthermore, it has been suggested that PIs inhibit the protease that degrades SREBPs thereby leading to decreased degradation of apolipoprotein B-100, which will then cause increases in VLDL[31, 32].

Upregulation of Pro-inflammatory Cytokines

There is an association between HIV-LDS and levels of pro-inflammatory cytokines. Tumor necrosis factor-alpha (TNF-α) and its receptors are increased in HIV-infected patients[33] suggesting that increased concentrations of pro-inflammatory cytokines inhibit the production of acylation-stimulating protein (ASP), a protein which up-regulates the

pathways for glucose uptake and fat deposition in adipocytes; they demonstrated an association between lower limb lipoatrophy and subnormal ASP production.

Lipodystrophy and Glucose homeostasis

PI associated diabetes mellitus is similar to type 2 diabetes mellitus. Hyperglycemia is not associated with ketoacidosis and patients respond to oral hypoglycemia treatment[34], suggesting that the underlying mechanism is insulin resistance. In studies examining the effect of indinavir on adipocytes, dramatic inhibition of insulin-stimulated glucose uptake was reported[35]. Taken together, these results suggest that indinavir directly inhibit GLUT4 (a glucose transporter protein that mediates insulin-stimulated cellular uptake of glucose). Other studies have since supported these findings by demonstrating that indinavir induces muscle insulin resistance[36]. Furthermore, increased fasting glucose concentrations and increased secretory response of insulin, pro-insulin and C-peptide to glucose ingestion have been reported in patients treated with PIs[21].

Other Clinical signs include Familial combined hyperlipidemia (also called the atherogenic phenotype B) with a constellation of moderately elevated triglyceride (> 150 mg/dL), borderline or moderately decreased HDL-C. It may also manifest as normal or moderately elevated LDL, increased remnants composed of IDL, and small dense LDL[37] and increased apolipoprotein B[38]. Previously, this was thought to be a familial trait. More recently, it has become apparent that it can also be acquired and expressed as a result of obesity and insulin resistance. This phenotype has been shown to be linked to increases in heart disease[38]. The lipid profile in this lipidemia is very similar to that in the lipodystrophy syndrome. Although the exact mechanism leading to the atherogenic phenotype is unknown, it is known that insulin is an important regulator of fatty acid and lipid metabolism[39] and that the atherogenic phenotype is largely due to a net over production of VLDL by the liver causing increases in all beta-lipoproteins[38].

Mitochondrial toxicity

Madelung's disease or multiple symmetric lipomatosis (an inherited mitochondrial disease) has clinical features similar to HIV-LDS[40]. Thus certain lipodystrophy features are observed in patients' naïve to PI but treated with NRTIs (Definition) only[41, 42]. Brinkman *et al.*[43], had suggested that mitochondrial DNA polymerase (the sole enzyme responsible for mitochondrial DNA replication) may be inhibited by NRTIs causing mitochondrial dysfunction. Thus all toxic effects attributed to NTRIs such as peripheral neuropathy, myopathy, pancreatitis and lactic acidosis resemble the clinical syndrome seen in inherited mitochondrial diseases[44].

Steroid hormones and lipodystrophy

Changes in steroid hormone levels (particularly glucocorticoids and androgens) have been found in untreated HIV infected patients. Cortisol levels increase in HIV infected men in all stages of infection, whereas androgen levels are elevated early in HIV infection and decrease dramatically in AIDS[45, 46].

Management of Lipodystrophy

Treatment of metabolic dysfunction such as lipidemia and glycemia are required. Although, withdrawal of PI therapy for either NNRTI or ABC may improve the metabolic profile regression of lipodystrophy can occur and this may not be an option for all patients[47, 48]. Despite the lack of consensus treatment guidelines for HIV-LDS, management of lipid and glucose abnormalities should follow current treatment strategies or guidelines for HIV negative patient populations.

Lipid-lowering Agents

Statins and fibrates are commonly used for their lipid-lowering effects. Considerations for drug interactions should help guide the selection of the particular agent used from each class. Newer statins provide greater lipid reductions than the older pravastatin used in earlier studies[49, 50]. However, there may be greater risk for drug interactions with the newer statins. Fibrates which are more potent than statins in lowering triglyceride and raising HDL-C levels are often needed to reach current guideline targets[51].

Glycemia Control

The insulin sensitizing-agent, metformin is commonly used with consistent positive results (e.g. weight neutral or weight loss effects) in clinical trials[52]. The use of metformin with some HIV therapies can increase the potential for lactic acidosis[53]. Pioglitazone is the only thiazolidinedione that should be considered, however, the benefits are minimal[54]. Insulin-like growth factor (IGF), used in extreme insulin resistance syndromes, have demonstrated positive glycemic and cholesterol effects in HIV-LDS[55].

Lipoatrophy and fat accumulation

Plastic surgery and fat transplantation are options for HIV-LDS; however, they have no effect on lipid abnormalities or cardiovascular risk reduction and recurrence is common[56]. Tesamorelin, a synthetic analogue of human growth hormone-releasing factor, is indicated for the treatment of HIV-LDS. Reduction in visceral adipose tissue is significantly decreased and maintained at 26, and 52 weeks, respectively, with Tesamorelin[57, 58].

Conclusions and Public Health Implications

These findings suggest that the metabolic changes associated with the use of HIV PIs, including their adverse effects on triglyceride rich lipoproteins and their associated clinical features may be multi-factorial. Patients receiving HIV PIs should be screened for hyperlipidemias and may be candidates for lipid–lowering therapies that improve endothelial cell function and prevent adverse cardiovascular events. The potential for drug interactions between lipid lowering medications and HIV PIs should also be considered. Clinical decisions regarding initiation and intensification of drug therapies for patients with HIV infection should include their adverse effects on lipids, lipoproteins and cardiovascular function.

Conflicts of Interest: None.

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