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Lipodystrophy Syndrome in HIV Infection

What is it, What Causes it and How Can it Be Managed?

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Contents

Abstract

Since the introduction of HIV-1 protease inhibitors as components of antiretroviral drug combination regimens, the clinical course of HIV disease and opportunistic infections has changed dramatically. Besides the favourable virological, immunological and clinical impact of highly active antiretroviral therapy (HAART), several adverse drug reactions have been observed in patients with HIV receiving therapy. Particularly, peripheral lipodystrophy, central adiposity, dyslipidaemia and insulin resistance have been described with a prevalence of up to 80% in patients infected with HIV, and attributed to almost all components of HAART. Hyperlipidaemia is characterised by an increase of low and very low density lipoprotein-cholesterol as well as apolipoproteins B and E. Several studies

strongly suggest that there are either multiple syndromes or a variety of factors inducing different changes that influence the ultimate phenotype. Similarities between HIV-associated fat redistribution and metabolic abnormalities with both inherited lipodystrophies and benign symmetric lipomatosis suggest the pathophysiological involvement of, for example, nuclear factors like lamin A/C and drug-induced mitochondrial dysfunction. Moreover, there is some evidence that cytokines and hormones impair fat and glucose homeostasis in patients with HIV receiving HAART. Three years after the first description of HIV therapy–associated abnormal fat redistribution, there is still an ongoing discussion about the case definition, diagnostic procedure and treatment options for both body shape changes and metabolic disturbances. Regarding therapy, there is a major concern about possible complex pharmacological interactions and overlapping adverse effects between HAART and, for example, lipid-lowering therapy. In addition, the likely contribution of both nucleoside analogue reverse transcriptase inhibitors and protease inhibitors to the development of abnormal fat redistribution in patients with HIV limits options of changing to alternative effective antiretroviral drug combinations. Thus, the occurrence of hyperlipidaemia, maturity onset diabetes mellitus, and marked changes in body habitus resulted in important social and clinical consequences such as an increased risk of atherosclerosis. It also sheds new light on the use of protease inhibitors regarding risk factors for the initial treatment decision. In this article, we discuss the features, pathogenesis and treatment options for body fat redistribution and metabolic disturbances associated with HAART in HIV-1 infection.

1 Lipodystrophy under Highly Active Atiretroviral Therapy (HAART)

1.1 Background

The use of HIV-1 protease inhibitors in antiretroviral combination regimens has led to reduced morbidity and mortality in patients with advanced HIV disease.[1,2] Currently, 5 protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir and amprenavir) are used in HIV therapy, usually in combination with other antiretroviral drugs (table I). Protease inhibitors interfere with the post-translational processing of HIV precursor proteins and thereby prevent the formation of new infectious virus particles.[3] However, a variety of unfavourable effects have been documented in patients treated with highly active antiretroviral therapy (HAART).[3-6] Only a few of these are drug specific, such as indinavir-associated crystalluria; others have been initially proposed as class-specific adverse drug reactions. Indeed, a wide range of body habitus abnormalities have been observed over the past 3 years in patients receiving protease inhibitors.[7-9] However, similar changes in body composition have also been observed in individuals receiving protease inhibitor–sparing regimens. The most obvious clinical feature of those observations consists of unusual distribution of body fat. Most of these patients also have complex metabolic alterations, e.g. changes in lipid profile, development of diabetes mellitus in some patients.

Based on an extended search of English language medical literature (using Medline and PUBMED up to March 2000 and the search terms HIV, lipodystrophy, abnormal fat distribution, metabolic, diabetes mellitus, highly active antiretroviral therapy and protease inhibitor) and our own experiences, this article will discuss the features, pathogenesis and treatment options of body changes and lipid disturbances associated with HAART in HIV infection.

1.2 What is it?

In the past, 'lipodystrophy' has been frequently used as a general term for diverse body shape changes observed in association with HAART,[8] although the term properly describes fat loss only. Therefore, we would suggest the term 'fat redistribution syn-

Table I. Characteristics of HIV-1 protease inhibitors

Characteristic	Indinavir	Ritonavir	Saquinavir	Nelfinavir
Dosage forms	200, 400 and 333mg capsules	100mg capsule 80 mg/ml oral solution	200mg capsule	250mg tablet 50 mg/g oral powder
Dosage[a]	800mg tid	600mg bid	600mg tid	750mg tid
Serum half-life	1.5-2h	3-5h	1-2h	3.5-5h
Metabolism	CYP3A4	CYP3A4>2D6	CYP3A4	CYP3A4
Drug interaction	Inhibitor of CYP3A4	Inhibitor of CYP3A4	Inhibitor of CYP3A4	Inhibitor of CYP3A4
Adverse effects[b]	Nephrolithiasis GI-intolerance Nausea Diarrhoea Hyperbilirubinaemia Headache Dizziness Rash Thrombocytopenia Hyperglycaemia Fat redistribution Lipid abnormalities	GI-intolerance Nausea Diarrhoea Paraesthesia Hepatitis Transaminase level elevation Hyperglycaemia Fat redistribution Lipid abnormalities	GI-intolerance Nausea Diarrhoea Hyperglycaemia Fat redistribution Lipid abnormalities	GI-intolerance Nausea Diarrhoea Headache Transaminase level elevation Hyperglycaemia Fat redistribution Lipid abnormalities

a Other doses may be recommended, especially in combination regimens with 2 protease inhibitors.

b Main adverse effects.

bid = twice daily; **CYP** = cytochrome P450 enzyme; **GI** = gastrointestinal; **tid** = 3 times daily.

drome' to characterise the variety of observed changes in body shape. In our opinion it is reasonable to distinguish different components of this syndrome as lipohypertrophy, lipodystrophy (or lipoatrophy), and a mixed form composed of both alterations. Several studies strongly suggest that there are either multiple syndromes or a variety of factors inducing different changes that influence the ultimate phenotype.[10-12]

The first individuals with HIV infection with lipodystrophy were recognised and described because of an increase in waist size with truncal obesity (called 'crixy belly') and/or the development of atypical fat pads,[13-18] commonly at the back of the neck (called 'buffalo humps'). The presence of vastly increased visceral fat deposits may lead to problems related to pressure upon the organs, with symptoms of bloating, pain and abdominal discomfort.[11] Other common manifestations of body fat redistribution in the literature include loss of subcutaneous fat which leads to thinning of the skin on arms and legs and a resulting increase in prominence of subcutaneous veins.[7,8,19] In the face, increased wrinkling, especially in the nasolabial folds, has been described. Additionally, women may experience breast enlargement,[20-23] although the noted prevalence differs between studies depending on the estimation of changes and the variable association with the use of protease inhibitors.[12] More rarely, men also have reported breast growth.[24,25] Interestingly, 1 case of early onset lipodystrophy has been observed during postexposure prophylaxis[26] and similar body alterations have been observed in children receiving HAART.[27]

In general, changes are more related to the regional distribution of fat rather than to the absolute amounts of fat or lean tissue. All currently used protease inhibitors (except amprenavir because of its short duration of marketing) have been reported to be involved in abnormal fat redistribution. Importantly, several studies observed improvement in quality of life along with gain of both fat mass and lean mass in patients with HIV infection treated with protease inhibitors.[28-31] These changes, which reflect beneficial effects on body composition, probably result from a reduction in viral load and suppression of viral and CD4+ cell turnover.[32] However, the impact of HAART on resting energy

expenditure is unclear, since several studies revealed unchanged, increased, or even decreased expenditure, possibly attributable to differences in study design, study population and follow-up period.[32,33]

1.3 Fat Accumulation

1.3.1 Dorsocervical Fat Pad

The so called 'buffalo hump' in patients infected with the HIV virus receiving antiretroviral therapy represents an accumulation of fat under the skin in the dorsocervical region.[16,34-37] Very similar buffalo humps have been classically observed as reversible phenomena in Cushing's syndrome. Lo et al.[16] first described dorsocervical fat pads in 8 individuals with HIV infection while they were receiving a stable antiretroviral regimen, but only 4 of the 8 were taking protease inhibitors. When compared with controls with HIV infection, the 8 men with buffalo humps also had a significantly higher proportion of abdominal fat. However, lipid patterns, fasting glucose and cortisol levels were similar in the 2 groups. Thus, buffalo humps were not related to hypercortisolism, nor were they unique to individuals receiving protease inhibitor therapy. The prevalence of dorsocervical fat pads is much lower than that of abdominal obesity or fat loss in the face or the extremities.

1.3.2 Increased Abdominal Girth

In the first report of truncal obesity ('protease paunch') in patients with HIV infection, later confirmed by others,[7,8,20,38] Miller et al.[14] analysed abdominal computed tomography (CT) scans. Of 20 men receiving indinavir, 10 had experienced increased abdominal girth about 3 months after starting the protease inhibitor therapy. CT scans were used to measure total and visceral adipose tissue in the group with increased abdominal girth and in those without truncal obesity. Analysis of fat distribution and comparison of the visceral to total fat ratio revealed that in some patients with HIV infection taking indinavir, treatment-accumulated intra-abdominal fat may cause abdominal symptoms and gastrointestinal discomfort. In addition, asymptomatic men taking indinavir also had a higher mean visceral to total adipose tissue ratio than those not taking the drug.[14,38] Increased abdominal girth has been reported also in protease inhibitor–naive individuals.[38] Often, increases in visceral fat are observed along with decreases in subcutaneous fat elsewhere.[8,19,20] As increased abdominal girth and visceral fat are normal components of aging in the general population and all components of HAART have been shown to contribute to visceral fat accumulation, there may be several factors involved in the development of increased abdominal girth.

1.3.3 Benign Symmetric Lipomatosis

Another distinct fat distribution pattern less frequently reported in association with HIV treatment has clinical similarities to the benign or multiple symmetric lipomatosis, also called Madelungs disease or Launois-Bensaude adenolipomatosis.[39,40] It is characterised by a symmetric accumulation of fat, usually in the head (face), neck, and shoulders, but sometimes occurring in the chest, abdomen, and upper thighs. Benign symmetric lipomatosis without a background of HIV infection occurs most frequently in men who are alcoholics and is associated with glucose intolerance and hyperlipidaemia. The possible association with altered mitochondrial function has important implications for HAART-associated fat redistribution. Hengel et al.[40] published a case report concerning a 34-year-old man with HIV infection who had benign symmetric lipomatosis. The man developed abnormal fat distribution in the supraclavicular area and a buffalo hump while taking zidovudine, lamivudine and indinavir. The patient presented with minimally elevated blood glucose, but normal cholesterol and cortisol levels. A normal dexamethasone suppression test ruled out Cushing's syndrome.

1.4 Fat Loss

1.4.1 Lipodystrophy without HIV Infection

Lipodystrophy denotes regional or generalised lack or loss of subcutaneous fat and this syndrome is rare in individuals without HIV infection. The various syndromes that have been reported may be either familial or acquired and are classified as localised, partial or generalised. Inherited lipodystrophies include congenital lipodystrophy[41,42]

(Berardinelli-Seip-Syndrome) and familial partial lipodystrophy[43-45] (Dunnigan variety, Köbberling variety). Congenital lipodystrophy is an autosomal recessive disorder with very low prevalence and is associated with an almost complete absence of metabolically active adipose tissue.[46] In addition, it is characterised by the presence of acanthosis nigrans, muscle hypertrophy, hypertriglyceridaemia, pancreatitis and diabetes mellitus with severe insulin resistance.[41,42]

Familial partial lipodystrophies were extensively reviewed by Köbberling and Dunnigan[45] who suggested a classification into 2 types. In type 1 lipodystrophy, onset of disease starts in childhood and affects the limbs with sparing of face and trunk. In type 2 lipodystrophy of adulthood, the trunk is also affected and only face and vulva are spared. The mode of inheritance was shown to be autosomal dominant, with females being worse affected than males. Metabolic abnormalities in these patients show variable degrees of severity. However, a high incidence of abnormal glucose tolerance and insulin-resistant diabetes mellitus, hyperlipoproteinaemia with predominant elevation of triglycerides, acanthosis nigrans, and hepatomegaly have been described. Linkage analysis of 5 independent affected families succeeded in mapping a candidate gene to chromosome 1q21–q22. Recently, 5 different missense mutations in LMNA, encoding lamin A/C have been identified among patients with familial partial lipodystrophy and their kindreds.[47] Although we excluded germline mutations of LMNA in exon 8 in HIV-infected patients with lipodystrophy, we suggest that lamin A/C and its related proteins represent important candidate pathways to be involved in HAART-induced lipodystrophy.

Acquired lipodystrophy syndromes can be generalised[48] (Lawrence syndrome), partial[49] (Barraquer-Simons) or localised.[50] Generalised acquired lipodystrophy has been described in only about 50 cases in the literature so far. The onset is in childhood or adolescence and characterised by hepatomegaly and metabolic alterations (insulin resistance and hyperlipidaemia). Acquired partial lipodystrophy is more common and is accompanied by less severe metabolic alterations. Clinical features present with progressive fat loss from the face, neck, trunk or arms and normal or excess fat in the hips and legs. The onset often follows a febrile illness and may be associated with collagen vascular disease, mesangiocapillary glomerulonephritis and C3 deficiency.[51]

1.4.2 Lipodystrophy with HIV Infection

Lipodystrophy in individuals with HIV infection receiving protease inhibitor–containing combination regimens is commonly characterised by the loss of subzygomatic fat in the face leading to increased wrinkling in the nasolabial folds, and fat wasting in the arms, legs, buttocks and rarely in the subcutaneous abdominal area (fig. 1). When severe, facial wasting occurs at the temples and in the eye sockets. Additionally, prominence of subcutaneous veins, particularly in the extremities, has been observed with lipodystrophy.[7,8,19-21,52]

The possible association of lipodystrophy accompanied by metabolic disturbances with protease inhibitor therapy in HIV was first reported by Carr et al.[8] Depending on the definition and severity of lipodystrophy, the reported prevalence of this condition in individuals taking protease inhibitors ranges widely from 5 to 80%. One of the best follow up descriptions of HIV-related lipodystrophy assessed 113 patients who were receiving HIV-1 protease inhibitors for a mean of 21 months.[53] Diagnosis and severity of lipodystrophy was highly (98%) concordant between the patient's self report (questionnaire) and physical examination. Among the protease inhibitor recipients, 83% were reported to have lipodystrophy, which was usually mild according to a score system concerning severity and body region. Only 1 patient (4%) in the protease inhibitor–naive control group reported signs of lipodystrophy.

There is limited information on the natural course of lipodystrophic alterations because almost all studies with cross-sectional design are based on single measurements. The study by Carr et al.[53] indicated that more protease inhibitor recipients reported worsening (58%) of lipodystrophy than improvement (28%) during an follow up of 13.6 months

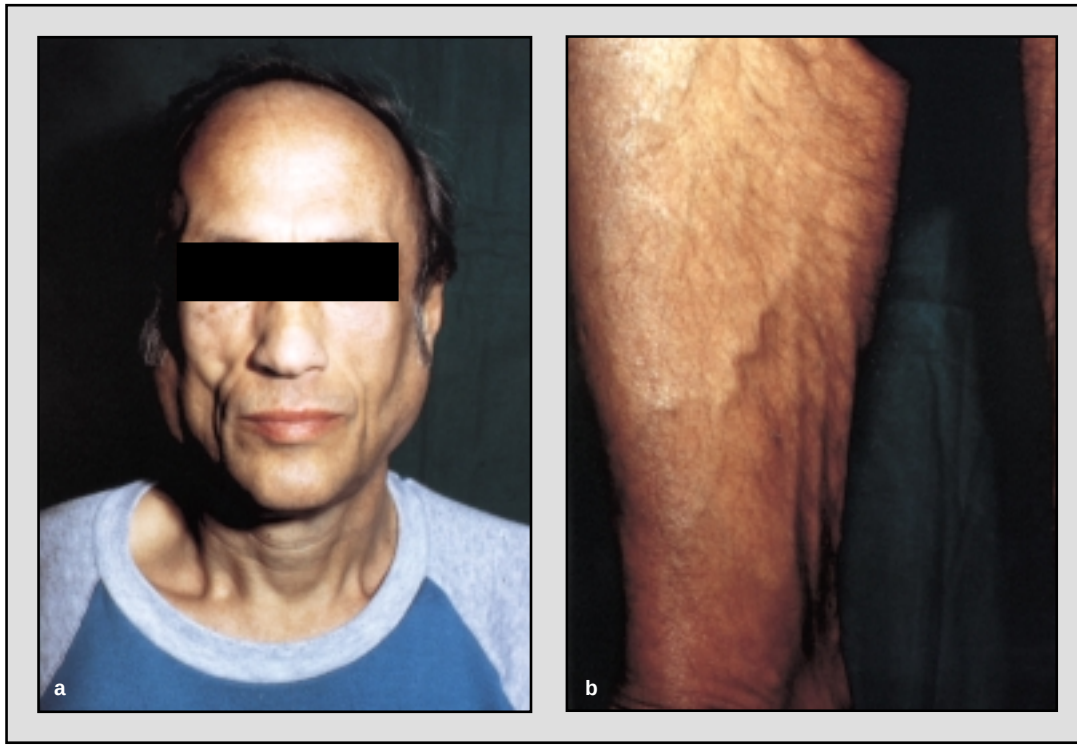

Fig. 1. Peripheral fat wasting in a patient receiving antiretroviral therapy including a protease inhibitor. (**a**) 18 months following the initiation of a triple drug regimen this patient presented with characteristic loss of subzygomatic fat in the face, leading to increased wrinkling in the nasolabial folds, temple hollowness, sunken eyes, and prominent zygomatic arch. (**b**) In addition, he developed marked wasting of peripheral fat leading to prominence of subcutaneous veins mimicking varicosis. Body shape alterations were accompanied by marked hyperlipidaemia and subsequent development of type 2 diabetes mellitus.

independent of cessation or switching of therapy. Notably, several studies indicate the occurrence of increased visceral fat distribution preceded the era of HAART or developed in patients never been treated with protease inhibitors but with nucleoside-analogue reverse transcriptase inhibitors (NRTIs), especially with stavudine.[11,38,54-61] Thus, the alterations in body fat distribution may be caused by the HIV infection itself or may additionally be related to other drug combination components.

1.5 Case Definition

In order to establish a case definition for the syndrome to standardise patients reporting and explicitly to improve clinical research, several criteria for the fat redistribution syndrome were proposed at the 1st International Workshop on Lipodystrophy and Adverse Drug Reactions held on 26 to 28 June 1999 in San Diego, CA, USA. Clinical criteria for fat wasting of different body areas have been described as sunken cheeks, temple hollowness, sunken eyes, prominent zygomatic arch (face), skinny, prominent nonvaricose veins (arms and legs), loss of skin folds, loss of contour and fat (buttocks). Similarly, fat accumulation was categorised into 5 areas: increased abdominal girth, breast enlargement, dorsocervical fat pads, facial fat accumulation, and lipomas. Methods of assessing fat accumulation and its monitoring (table II) include self reports, clinician assessment, and anthropometric measurements (skinfold thickness) and imaging (dual energy x-ray

absorptiometry, magnetic resonance tomography or CT).

Anthropometry is based on the assumption that the fat depots in the subcutaneous fat are highly correlated with visceral fat. In infancy and childhood, subcutaneous fat represents a major portion of total fat, but with increasing age this depot may be reduced to less than 10% of the total, rendering anthropometry of decreasing accuracy with increasing age. Peripheral fat loss together with abdominal fat accumulation would further impair calculations of total body fat. However, the equipment for this procedure is economic and can be easily used in clinical settings. Only minimal cooperation from the patient is required and it is a reasonable tool for intraindividual longitudinal studies on pure lipodystrophy.

Dual energy x-ray absorptiometry, originally used for measuring bone density, quantifies bone, muscle and fat by their varying densities. However, this technique does not reliably distinguish between subcutaneous and intra-abdominal fat and differences between machine calibrations make comparison of the data from different centres challenging. CT has the disadvantage of radiation exposure, and magnetic resonance tomography is hampered by the lengthy scanning times. Moreover, all these techniques are very expensive to be added to routine clinical practice, and the analysis of results is not well standardised between groups. We suggest sonography as a potential method for objective measurement of abnormal fat deposits and lipodystrophy as already shown in other studies.[62,63] Finally, it has to be considered that in contrast to metabolic parameters, there are no values of normality for regional fat distribution and its change with increasing age in the general population. Therefore, in the absence of those data, each patient must act as her or his own control to assess the evolution of body fat changes.

Table II. Recommended clinical and laboratory tests in patients with abnormal fat redistribution

Clinical tests and data
Body composition analysis [DEXA and/or CT-scan (VAT:TAT ratio)]
Bodyweight and BMI
CVD risk factors
Blood pressure
Family history for CVD and diabetes mellitus
Liver steatosis
Signs of avascular necrosis
Laboratory tests
Total cholesterol including
LDL-C
VLDL-C
HDL-C
Triglycerides
Fasting C-peptide[a]
Fasting insulin[a]
Fasting glucose[a]
Leptin
Lactate
Liver function tests
Pancreatic enzymes

a If possible, basal (after an overnight fast) and 120min value of oral glucose tolerance test.

BMI = body mass index; **CT** = computed tomography; **CVD** = cardiovascular disease; **DEXA** = dual x-ray absorptiometry; **HDL-C** = high density lipoprotein-cholesterol; **LDL-C** = low density lipoprotein-cholesterol; **VAT:TAT** = total to visceral adipose tissue ratio; **VLDL-C** = very low density lipoprotein-cholesterol.

1.6 Metabolic Abnormalities

1.6.1 Changes in Lipids

Along with the first description of body fat changes, several studies have documented hypertriglyceridaemia and hypercholesteraemia in addition to insulin resistance as a common feature of protease inhibitor therapy.[8,20,64-73] The relationship between changes in body fat and lipid levels, glucose levels and insulin is not yet understood because alterations in the lipid profile do not clearly correlate with body fat changes. There is some evidence that metabolic disturbances develop more rapidly following the initiation of HAART or the addition of protease inhibitors to double/triple drug combination regimens.

We[64,66] and others[8,53,69,71] have characterised the lipid profiles of protease inhibitor recipients in comparison with protease inhibitor–naive patients. Our analysis of the lipid pattern revealed that 57 to 71% of protease inhibitor recipients had detectable hyperlipidaemia, defined as fasting cholesterol >5.2 mmol/L and/or triglycerides >2.3 mmol/L.

Table III. Serum lipid alterations associated with HIV infection and protease inhibitor therapy

	HIV infection	Protease inhibitor therapy
Triglycerides	↑	↑↑
Total cholesterol	↓	↑
VLDL-C	↓	↑
LDL-C	↓	↑
HDL-C	↓	↓

HDL-C = high density lipoprotein-cholesterol; **LDL-C** = low density lipoprotein-cholesterol; **VLDL-C** = very low density lipoprotein-cholesterol; ↑ = increase; ↑↑ = marked increase; ↓ = decrease.

HAART was associated with significantly higher fasting cholesterol, triglycerides, low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol levels, as confirmed by other studies.[8,20,53,69,71] All protease inhibitors used (saquinavir, indinavir, nelfinavir and ritonavir) were associated with variable forms of hyperlipidaemia according to the Fredrickson classification.[66]

Assessment of apolipoproteins (apo) revealed a highly significant proportion of patients with elevated mean fasting serum values of apoB and apoE in patients receiving protease inhibitor treatment, compared with protease inhibitor–naive patients ($p < 0.005$), possibly attributable to increased synthesis.[74] According to follow-up studies, the prevalence and extent of hyperlipidaemia remained stable over time.[53,70] It is of note that the genetic apoE2 and E4 background is involved in manifestation of hyperlipidaemia. apoE genotyping may be a useful tool to evaluate individuals at risk for protease inhibitor–associated hyperlipoproteinaemia.[66,75]

Acute pancreatitis, the most important complication due to hypertriglyceridaemia (especially postprandial), has been reported in some cases.[76,77] Some authors have indicated the likely involvement of reduced hepatic lipoprotein lipase activity in patients with elevated triglycerides,[66,78,79] others have failed to demonstrate altered enzyme activity *in vitro* and *in vivo* after short term administration of ritonavir to volunteers.[80] Interestingly, HAART had no significant influence on high density lipoprotein-cholesterol (HDL-C) levels.[64,66] As found among protease inhibitor recipients, low plasma levels of HDL-C are known to occur early in the course of HIV disease (table III).[81]

Metabolic alterations such as hypertriglyceridaemia have been reported in individuals infected with the HIV virus since the early 1980s, particularly in the late phase of the disease in patients with marked immunodeficiency and, to a lesser extent, as described with protease inhibitor therapy.[82-85] According to the studies by Grunfeld et al.[85] and Hellerstein et al[86], major causes of hypertriglyceridaemia were shown to be elevated rates of *de novo* lipogenesis and delayed clearance of triglycerides in the postprandial period.[85,86] These abnormalities, particularly low cholesterol and increased triglyceride levels have been shown to be associated with immune dysfunction.[82,87] Interestingly, we and others[66,69,80] found elevated values of lipoprotein(a), an important atherogenic risk factor, in association with protease inhibitor therapy. This observation, probably resulting from increased synthesis,[69] was unexpected as plasma lipoprotein(a) levels are highly genetically determined. There is some evidence that lipid disturbances occur more rapidly following administration of protease inhibitors than abnormalities in glucose metabolism and fat redistribution. Protease inhibitors, in particular, have been strongly implicated in lipid disturbances because of the frequently described improvement of hyperlipidaemia following discontinuation of therapy, together with observations that combinations of different protease inhibitors lead to synergistic effects on lipid metabolism.

In summary, protease inhibitor therapy is accompanied by lipid abnormalities which are significant risk factors for coronary heart disease (table III, fig. 2). Abnormalities observed are high total- and LDL-C and low HDL-C levels which occur in a considerable proportion of patients receiving protease inhibitors.[88,89] Recent data indicate an increasing rate of myocardial infarction in patients with HIV and HAART-associated hyperlipoproteinaemia.[4,90-97] Moreover, avascular necrosis of the bone may also be related to metabolic complica-

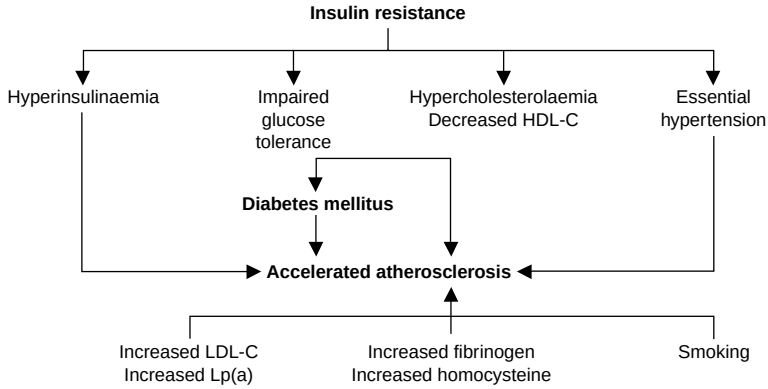

Fig. 2. Frequent risk factors for accelerated atherosclerosis in HIV therapy.
HDL-C = high density lipoprotein-cholesterol; **LDL** = low density lipoprotein-cholesterol; **LP(a)** = lipoprotein(a).

tions observed under HAART, as hyperlipidaemia and HIV infection are known risk factors for osteonecrosis of the femoral head. (fig. 3).[98-100] Although the prevalence of this pathology is much lower than that of metabolic abnormalities, the number of reports is increasing.

1.6.2 Glucose Homeostasis

Impaired Glucose Tolerance

Insulin resistance, impaired glucose tolerance[8,71,101-103] and diabetes mellitus[103-109] (sometimes leading to ketoacidosis[110]) have been documented in several studies as features of protease inhibitor therapy. Carr et al.[53] reported impaired glucose tolerance (according to the 1998 American Diabetes Association guidelines) in 16% of protease inhibitor recipients.[53] An additional study[71] reported that 54% of patients treated with protease inhibitors had impaired glucose tolerance determined by an oral glucose tolerance test according to the 1985 WHO definition. Additionally, Walli et al.[71] found insulin resistance in 61% of 67 patients treated with protease inhibitors using a careful intravenous insulin tolerance test. Both studies found that patients with impaired glucose tolerance had greater insulin resistance. By analysing the oral glucose tolerance tests in more detail, we found significantly increased and delayed insulin and C-peptide release in the protease inhibitor-treated group compared with protease inhibitor-naive patients.[64] Protease inhibitor therapy was associated with increase of fasting insulin, C-peptide and proinsulin. 46% of patients taking protease inhibitors presented with impaired glucose tolerance according to the WHO definition. More importantly, an excess in proinsulin secretion was a characteristic feature of the protease inhibitor recipients suggesting impaired β-cell function of the pancreas in these patients.

β-cell dysfunction and hyperproinsulinaemia may have several explanations as secondary reactions to external factors, β-cell distress, increased β-cell secretory demand due to insulin resistance, impaired maturation of proinsulin to insulin or compromised insulin secretion. Interestingly, direct inhibition of prohormone processing as a result of inhibition of prohormone convertase-1 and –2 by protease inhibitors has recently been excluded *in vitro*[111].

Alterations in glucose metabolism were not necessarily linked to lipid disturbances.[64] Despite the fact that HIV infection itself has been suggested to increase peripheral insulin sensitivity,[112] impaired glucose tolerance has even been noticed oc-

casionally among protease inhibitor–naive patients and in nonwasting individuals with AIDS.[113] The situation in women is less clear and may be different, since a study in women with HIV infection found an increased insulin to glucose ratio and elevated insulin levels even among women with HIV infection who had significant wasting, in addition to among patients not receiving protease inhibitor therapy.[114] However, only 17 protease inhibitor-treated (mean duration 6 months) women were included in the comparison. A further study[21] in a large cohort of 306 women found normal glucose and C-peptide levels in patients with and without signs of lipodystrophy.

Diabetes Mellitus

In contrast to glucose intolerance, the incidence of diabetes mellitus in patients receiving protease inhibitors seems to be low (7 to 14%),[8,64,71] although protease inhibitor-associated diabetes may be severe and associated with ketoacidosis. Pre-existing factors such as a family history of diabetes increase the risk and insulin and oral hypoglycaemic agents may be required for control of blood glucose homeostasis.[107] Some reports describe improvement of diabetes by discontinuation of protease inhibitor therapy.[64,109]

As suggested in patients not infected with the HIV virus, manifestation of diabetes may depend on stepwise development. We propose for protease inhibitor-associated diabetes that the first step, the transition from normal to impaired glucose tolerance, would depend mainly on the presence of insulin resistance. The second step, worsening from impaired glucose tolerance to diabetes, although accompanied by some further deterioration of insulin resistance, is assumed to be primarily dependent on the development of β-cell dysfunction.[64]

2. Lipodystrophy under HAART: Hypothesis for Pathogenesis

Little is known about the pathogenesis of protease inhibitor–associated body fat changes or metabolic alterations. It has been postulated that HIV infection and disease progression themselves probably plays a role in fat redistribution, because of the

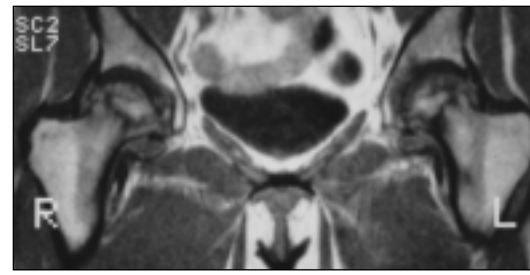

Fig. 3. Avascular osteonecrosis of both femoral heads (magnetic resonance tomography). Clinical occurrence of avascular necrosis was associated with combined hypercholesterolaemia and triglyceridaemia in this patient with HIV infection who was treated with highly active antiretroviral therapy for 16 months.

observation that fat abnormalities are also seen in other chronic disease states.[54,55] Introduction of antiretroviral combination regimens has shown to favourably affect nutritional status in HIV-infected patients by promoting bodyweight gain, albeit with a variable response.[28-31] Thus, suppression of viral replication and improvement of immune function by HAART has been assumed as underlying mechanism for these new fat abnormalities.

Additionally, endocrine dysfunction (e.g. hypercortisolism) has been suggested to be involved in the development of lipodystrophy and metabolic abnormalities.[115-117] However, we and others found no correlation of hyperlipidaemia with decline in viral load or improvement of immune function, nor with free urine cortisol levels in patients treated with protease inhibitors.[8,16,20,64] A recent study[116] reported increased serum corticotropin levels along with elevated urine 17-hydroxycorticosteroid levels and decreased free cortisol in patients with HIV infection and lipodystrophy. Urinary cortisol disposition seems to be altered in patients with HIV infection treated with multidrug regimens including protease inhibitors. However, the authors concluded to a distinct pathogenesis from any known hypercortisolism. Another study[117] provided evidence that decreased dehydroepiandrosterone and increased cortisol in patients with lipodystrophy may contribute to the reduction in peripheral lipogenesis. Thus, the definitive role of steroid hormone perturbations in HAART-associated fat redistribution re-

mains to be determined as cross-sectional studies reveal conflicting results and are limited in explaining pathogenetic relationships.

Studies in AIDS-related wasting have demonstrated the important role of proinflammatory cytokines in body shape changes.[118-120] Increased levels of interferon-α, tumour necrosis factor, interleukin-1, and interleukin-6 were correlated with the development of AIDS, elevated triglyceride levels and lipogenesis.[4,120,121] In contrast, a critical role of cytokine activities in protease inhibitor–associated fat redistribution and abnormal lipid profiles has been assumed but not yet been established.

Besides the implication that changes are already present and are deteriorated by some effect of antiretroviral treatment and particularly protease inhibitors, there are several hypotheses regarding direct pathogenic effects of protease inhibitors and other components of antiretroviral therapy. These include protease inhibitor-induced inhibition of insulin degrading enzymes leading to hyperinsulinaemia, increased hepatic lipogenesis and insulin resistance.[122] However, we found no impaired hepatic insulin clearance in protease inhibitor recipients.[64]

Australian researchers[123] have offered an explanation of the pathogenesis of lipodystrophy based on homologies in the amino acid sequences of the catalytic site of HIV-1 protease and 2 proteins critically involved in the regulation of lipid metabolism, low density lipoprotein receptor-related protein (LPR) and cytoplasmic retinoic acid binding protein type 1 (CRABP-1). Thus, drug-induced inhibition of HIV-1 protease has been proposed to inhibit the host cell-derived proteins involved in lipid and carbohydrate metabolism. However, neither LPR nor CRABP-1 have been well studied to date. The latter, together with cytochrome P450 (CYP) 3A, is involved in the production of cis-9-retinoic acid. According to the hypothesis,[123] inhibition of the CRABP-1-mediated cis-9-retinoic acid stimulation of the retinoid-x receptor and peroxisome-proliferator-activated receptor type gamma (PPAR-γ) may result in reduced differentiation and increased apoptosis, followed by impaired fat storage and release of lipids into the circulation. This hyperlipidaemia would be exacerbated by protease inhibitor blocking of CYP 3A and binding to hepatic and endothelial LPR. In fact, there is some evidence for increased peripheral adipocyte apoptosis in protease inhibitor-associated lipodystrophy.[124]

To test this hypothesis, a recent study[125] using three-dimensional crystallographic analysis of HIV-1 protease and CRABP-1 did not reveal structural similarities between the 2 proteins. Additional experiments showed that the isomerisation of cis-retinoic acid was not catalysed by CYP 3A, which does not provide support for the hypothesised effect of protease inhibitors. However, the authors were able to demonstrate that protease inhibitors are potent inhibitors of adipocyte differentiation.[125] This is in marked contrast to experiments demonstrating enhanced adipogenesis following incubation of a different preadipocyte cell line with indinavir and ritonavir.[126]

Further arguments against the sequence homology hypothesis arose from a recent study[127] in which inactivation of the LPR gene in mice had no effect on the general health of the animals. While knockout of the LPR gene resulted in accumulation of cholesterol rich lipoproteins, an accompanying upregulation of LDL in the liver compensated for the dysregulation and achieved balance in lipid homeostasis. However, *in vitro* data from other studies[128-130] using mesenchymal stem cells are consistent with altered retinoid signalling by indinavir (dependant on the concentration of retinoid acid in the assay). In addition, it has been suggested by the same group that several but not all protease inhibitors block both adipogenesis and lipoprotein lipase expression and stimulate fat turnover *in vitro*.[129,130] Inhibition of adipocyte differentiation by HIV protease inhibitors *in vitro* has been confirmed by others in addition to excluding the interaction of protease inhibitors with PPAR-γ.[124,131] Taken together, interpretation of these preliminary *in vitro* studies is limited by artificial conditions using immature cell culture systems with high, and perhaps intracellular accumulation of, drug concentrations.

Very recently, a new mechanism of mitochondrial toxicity has been hypothesised to be involved in the development of lipodystrophy.[132,133] Since DNA polymerase-γ is the only DNA polymerase involved in mitochondrial DNA replication, the observed inhibitory action of NRTIs on this enzyme *in vitro* and *in vivo*[134] may interfere with mitochondrial replication and function (fig. 4). Thus, resulting apoptosis or complement (C3) deficiency, as found in benign or multiple symmetrical lipomatosis, may result in abnormal fat distribution. This model takes into consideration the accumulating reports of fat redistribution, often with absence of hyperlipidaemia[59,135,136] in protease inhibitor–naive patients.

Several studies indicated higher relative risk for development of lipodystrophy with a history or current use of stavudine or lamivudine.[57-61] More recently, a study[137] evaluated the role of different NRTI regimens in combination with protease inhibitors in the development of lipodystrophy. Diagnosis was based on a combination of body composition and metabolic changes. The group receiving the combination of stavudine + didanosine had a higher prevalence of lipodystrophy (89%) than the group receiving zidovudine + lamivudine (52%). Switching therapy in a small group of 10 patients from stavudine + didanosine to zidovudine + lamivudine, while maintaining the protease inhibitor resulted in significant improvement of triglyceride levels and anthropometric measurements.

Mitochondrial toxicity with delayed onset, as a common pathway for adverse effects of NRTIs, may be related to various other clinical manifestations including polyneuropathy, myopathy, steatosis, lactic acidosis, pancreatitis and pancytopenia.[132,133] The tissue selectivity may be related to differential phosphorylation of NRTIs or specificity of cellular kinases for NRTI phosphorylation, variable penetration into cells, the intrinsic importance of oxidative phosphorylation in specific cell function and the proliferation rate of the tissue. The relationship of mitochondrial toxicity to lipodystrophy has not yet been proven because of the lack of simple test systems. Interestingly, some authors observed increased serum lactate levels along with abnormal liver function in patients with lipodystrophy who have never received protease inhibitors.[61] In a cohort of more than 150 patients with HIV infection, we observed a significant association between lactate levels and the use of didanosine, stavudine and lamivudine, similar to the observations of the *in vitro* studies. Serum lactate was also closely correlated to serum triglycerides, indicating that mitochondrial toxicity has a profound effect on lipid metabolism (unpublished data). Potential ways to detect early lactate acidosis as the lactate to pyruvate ratio in response to an oral glucose tolerance test should be attempted in future clinical investigations analysing drug-related lipid abnormalities.

In summary, the causes of body fat redistribution and metabolic abnormalities in HIV infection and its treatment are likely to be multifactorial. The heterogeneous phenotypes with lipodystrophy and abnormal fat accumulation in the same individual, and their sometimes independent occurrence from lipid and glucose disturbances, are unlikely to be caused by the same pathophysiological basis. Accumulating evidence indicates that fat redistribution is not restricted to use of protease inhibitors, while hyperlipidaemia seems to be closely related and nucleoside analogues are usually associated with fat loss changes. Whether or not glucose abnormalities are direct or independent manifestations of lipid disturbances, or even their cause, is as yet not clear.

3. Lipodystrophy under HAART: Treatment Options

3.1 Switch from Protease Inhibitors to Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

Since the mechanisms and pathophysiology involving body fat redistribution are poorly understood, little is known about treating or preventing them. One experimental approach to the management of lipodystrophy and metabolic abnormalities, predicted on the assumption that protease inhibitors are the primary culprit, has been the switch from protease inhibitors to non-nucleoside analogue reverse

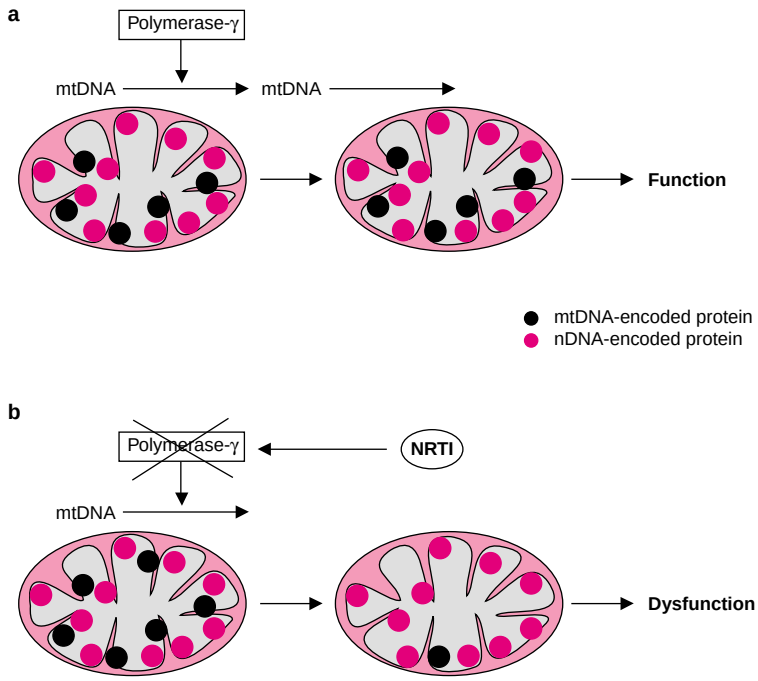

Fig. 4. Proposed mechanism of mitochondrial dysfunction induced by nucleoside analogue reverse transcriptase inhibitors (NRTIs). Proteins of the respiratory chain are encoded by mitochondrial DNA (mtDNA). Most respiratory enzymes are encoded by nuclear DNA (nDNA). DNA polymerase-γ is the only enzyme responsible for the replication of mtDNA. (**a**) Mitochondrial function depends on the balance expression of both mtDNA and nDNA. (**b**) Inhibition of DNA polymerase-γ by NRTIs is suggested to induce depletion of mtDNA and dependent proteins, therefore leading to mitochondrial dysfunction (reproduced from Brinkman et al.,[133] with permission)

transcriptase inhibitors (NNRTIs) such as nevirapine.[138,139] One study reported significant improvements in cholesterol, triglycerides, glucose and a fasting insulin resistance index 6 months after withdrawal of protease inhibitors and replacement by nevirapine.[138] Partial improvement of body shape, particularly in peripheral fat wasting, was subjectively reported in 91% of patients, although none regained their body shape as prior to the changes. Another study also failed to demonstrate complete reversal of body composition changes, despite improvement of metabolic alterations, 6 months after substituting nevirapine for the protease inhibitor.[139] Since maintenance of virological control after switching ranged from 90 to 100% and several authors reported benefits in terms of adherence, switching to nevirapine may be a promising approach to manage metabolic abnormalities and fat redistribution, despite the occurrence of adverse events such as hepatitis.[140] Changes in body composition or improvement of metabolic measurements were not observed 3 months after switching from protease inhibitor treatment to another NNRTI (efavirenz) in 2 small studies.[141,142]

Two uncontrolled studies have reported beneficial effects on lipodystrophy with significant decreases in triglyceride levels and increases in subcutaneous fat fold thickness after the switch from

stavudine + didanosine to zidovudine + lamivudine.[143,144] These data should be confirmed in larger trials but further support the likely involvement of NRTIs in both fat distribution and lipid disturbances. Although the switching of antiretroviral drugs can not be generalised at present for treatment of lipodystrophy and lipid disturbances, it should be considered in selected patients with, for example, accumulating cardiovascular risk factors.

3.2 Recombinant Human Growth Hormone

Recombinant human growth hormone has previously been shown to induce nitrogen retention in various catabolic conditions. In addition, recombinant human growth hormone has been successfully used to improve body composition during AIDS wasting[145,146] and opportunistic infections. Moreover, growth hormone is known to restore lean body mass in people with AIDS-related wasting.[147] It promotes increases in lean tissue and destruction of fat, both subcutaneous and visceral. However, growth hormone does not appear to reduce lipid levels. Several small studies[147-149] and case reports[150] indicate that subcutaneous treatment with 6mg recombinant human growth hormone may lead to an improvement in altered in fat distribution, particularly a decrease (59%) in visceral adipose tissue and an increase in lean body mass. Results were obtained by anthropometric measurements in addition to whole body magnetic resonance tomography. However, therapy with recombinant human growth hormone may be associated with adverse effects including oedema, arthralgia, elevated pancreatic enzymes and, most importantly, hyperglycaemia. Since people with fat redistribution taking antiretroviral therapy may be already be at risk for developing diabetes, growth hormones should be used with caution. Growth hormone is unlikely to be appropriate therapy, particularly for those patients experiencing severe metabolic disturbances.

3.3 Lipid-Lowering Therapy

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are drugs with structural similarity to HMG-CoA, a precursor of cholesterol, and are competitive inhibitors of HMG-CoA reductase, the last regulated step in cholesterol synthesis.[151] These drugs lower serum LDL-C levels by upregulating LDL-C receptor activity in addition to reducing the entry of LDL-C into the circulation. Therapy with HMG-CoA reductase inhibitors reduces the incidence of coronary artery disease, and the risk of angina pectoris and cerebrovascular events. The maximum reduction in serum LDL-C levels induced by treatment with statins ranges from 24 to 60%. Moreover, all HMG-CoA reductase inhibitors lower serum triglyceride levels.[151] With the exceptions of fluvastatin and pravastatin which are metabolised by CYP 2C9 and sulfation (and possibly other mechanisms), respectively, most of the HMG-CoA reductase inhibitors are metabolised by the CYP 3A4 system.

Little information is available on the safety and efficacy of HMG-CoA reductase inhibitors in individuals with HIV infection with hyperlipidaemia. Drugs inhibiting CYP 3A4 retard the metabolism of HMG-CoA reductase inhibitors and these include antibacterials, antifungal drugs and HIV protease inhibitors.[151] Since HMG-CoA reductase inhibitors, protease inhibitors, and NNRTIs are metabolised by the same CYP 3A isoenzyme in the liver, there are concerns as to how HMG-CoA reductase inhibitors may interact with HAART. The mutual influence of HMG-CoA reductase inhibitors and protease inhibitors may lead to altered serum drug concentrations and may increase the risk for viral rebound, toxicity, and other adverse effects.[77] A recent study[152] examined the pharmacokinetics of 3 HMG-CoA reductase inhibitors administered in combination with 2 protease inhibitors (ritonavir plus saquinavir). The authors observed a modest decline in pravastatin concentrations (median of 0.5-fold) in the presence of the 2 protease inhibitors. However, substantial increases in simvastatin (31.6-fold) and atorvastatin (4.5-fold) concentrations occurred during coadministration of ritonavir and saquinavir. These findings provide reasons to be cautious when using atorvastatin or pravastatin and to avoid simvastatin in patients with HIV infection receiving protease inhibitors. Since the influence of HMG-CoA re-

ductase inhibitors on protease inhibitor concentrations are still unknown, larger studies are necessary to evaluate the safety and drug interactions of lipid-lowering therapy.

Fibrates are the most effective triglyceride-lowering drugs. Their primary indication for therapy is a serum triglyceride level of >11.5 mmol/L. The fibrates increase fatty acid oxidation in the liver and thereby reduce secretion of triglyceride rich lipoproteins. The drugs act by activating the nuclear transcription factor peroxisome proliferator-activated receptor-α (PPARα), upregulating the expression of LDL-cholesterol and apolipoprotein A-I and downregulating the expression of the apolipoprotein CII gene.[151]

One study[153] reports treatment of patients with HIV infection with protease inhibitor–associated hyperlipidaemia (according to the criteria of the US National Education Program) with gemfibrozil and atorvastatin. The latter agent is thought to lower triglyceride levels more than other HMG-CoA reductase inhibitors. Of 25 patients treated with gemfibrozil alone, 19 had a suboptimal response when atorvastatin was added to their regimen. Patients who received both medications showed reductions in their lipid levels, with triglyceride levels falling by 60% over 6 months and mean cholesterol levels declining by 30%. Additionally, another study concluded that gemfibrozil was an effective treatment for hypertriglyceridaemia.[154] Eight HIV-infected men taking HAART added gemfibrozil to their treatment regimen and triglyceride levels fell on average from a high of 20.5 mmol/L almost to the level reported before initiation of protease inhibitor therapy (3.4 mmol/L; median value). The majority of patients had high cholesterol levels that did not appreciably decline. The authors noted that men switching from indinavir to nelfinavir experienced rebounds in triglyceride levels, despite continuing to use gemfibrozil. Thus, as most patients with extremely high levels may experience only a modest decline in triglycerides, further studies are necessary to evaluate the clinical benefit of fibrate therapy in patients undergoing HAART.

Based on recent studies demonstrating favourable effects of exercise training on both triglycerides, trunk fat and lean body mass in HIV-infected patients with metabolic disturbances,[155-157] we would recommend intensified physical exercise as an effective therapeutic approach to improve the lipid profile and body composition.

3.4 Antidiabetic Agents

Troglitazone, a drug acting as an insulin sensitiser via PPARγ activation to increase muscle and liver insulin responses,[158] has been successfully used to improve insulin resistance in a small number of patients with impaired glucose tolerance or diabetes mellitus.[159] However, response to treatment may be transient or insufficient to normalise glucose homeostasis and adverse events overlapping with those of antiretoviral therapies may increase liver toxicity.

Metformin is a biguanide antidiabetic drug that increases the sensitivity of peripheral tissues to insulin. A small study[160] analysed HIV-infected patients with central adiposity after starting protease inhibitor therapy. Of a total of 27 patients, 14 receiving metformin 850mg 3 times daily for 2 months were compared with 13 patients in control group. Metformin was shown to significantly decrease the plasma insulin response to oral glucose administration. Patients given metformin had a marked decrease in both the visceral adipose tissue and the visceral to total adipose tissue ratio, and an associated decrease in serum triglyceride levels.

3.5 Liposuction

Anecdotal reports[161] have described successful liposuction in patients with fat redistribution, particularly a buffalo hump.[162] This procedure should be considered only in rare cases with marked abnormal cervical fat pads, as the fat deposits may reappear and there is a lack of controlled research studies to evaluate the safety and utility of liposuction as a treatment for fat abnormalities.

4. Conclusions

Clinical features of abnormal fat redistribution and metabolic alterations associated with antiretroviral therapy are variable. The pathogenetic development of lipid disturbances and altered body shape appears to be multifactorial. Risks and benefits of treatment (excess benefit of viral suppression over the risk of adverse effects) with protease inhibitors in an individual patient should be weighted. The safety and efficacy of protease inhibitor–containing and –sparing regimens and their involvement in lipid and glucose homeostasis are currently being studied in prospective clinical trials (e.g. ATLANTIC-Study with FATLANTIC-Substudy).

Currently, we recommend the assessment of glucose and lipid parameters before initiating and during antiretroviral therapy. In the future, we expect that pre-existing individual risk factors for metabolic disturbances (e.g. dyslipidaemia, impaired glucose tolerance, apoE genotype, increased fibrinogen and homocysteine) may influence treatment decisions in HAART. Management of metabolic abnormalities must be individualised for each patient. Diabetes should be treated as in patients without HIV infection; insulin resistance and hypertriglyceridaemia may benefit from exercise training.[155-157] In patients with manifestations of coronary artery disease, thromboembolic events, and particularly in those with clustered cardiovascular risk factors,[163] lipid-lowering medication (fluvastatin, pravastatin) and control of additional risks of accelerated cardiovascular disease (e.g. smoking) are recommended. At present, there is no general indication for discontinuation or change of antiretroviral therapy simply on the basis of the development of abnormal fat redistribution, although it may be useful for selected patients.

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