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# Lipodystrophy: The Metabolic Link of HIV Infection with Insulin-Resistance Syndrome

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Additional information is available at the end of the chapter

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## 1. Introduction

Human lipodystrophies are a heterogeneous group of diseases characterized by generalized or partial fat loss. If localized, they are often associated with fat hypertrophy in other depots, varying according to the type of lipodystrophy. Lipodystrophies can be genetic, which is usually uncommon, or acquired. Genetic lipodystrophy is generally related to severe metabolic alterations including insulin resistance (IR) and its associated complications, such as glucose intolerance and diabetes, dyslipidemia, hepatic steatosis, polycystic ovaries, acanthosis nigricans and early cardiovascular (CV) complications [1, 2]. The autosomal recessive congenital generalized lipodystrophy (CGL) and autosomal dominant familial partial lipodystrophy (FPL) are the two most common types of genetic lipodystrophy [2]. Lipodystrophies have been reported in the medical literature for more than 100 years [2, 3]. However, only 13 years ago, new lipodystrophy syndromes were recognized, being associated with viral infection, specifically with the human immunodeficiency virus, in patients treated with combined antiretroviral therapy (cART) [4]. This has become the most frequent form of lipodystrophy [2]. Some first-generation antiretroviral drugs used in HIV patients are strongly related with peripheral lipoatrophy and metabolic alterations [1].

Human lipodystrophies leads to severe metabolic alterations resulting in premature CV complications. On the other hand, high adiposity, such as seen in obesity, also increases metabolic alterations and leads to increased CV risk. So, it seems that the two extremes, the absence or the excess of fat mass, are associated with the same metabolic and CV complications. The consequences of increased fat depots are markedly dependent upon their localization. Adipose tissue in the lower part of the body is able to expand and can therefore accumulate excessive energy from diet, store triglycerides, and it appears to be protective at the metabolic level [5].

By contrast, accumulation of fat in the upper part of the body is deleterious. Therefore, decreased peripheral subcutaneous adipose tissue (SAT), and even more increased visceral adipose tissue (VAT), are strongly associated with metabolic alterations and IR [1].

With regards to the HIV-associated lipodystrophy, the available data suggest that this condition is caused by a complex interaction involving side effects of cART, disease related inflammation, and individual characteristics [6]. At present, HIV-infected patients are exposed to an increased metabolic risk like the general population, resulting from ageing, increased weight and fat gain, high fat and energy food and marked sedentariness. Moreover, a number of additional factors could worsen their metabolic profile, such as the ongoing HIV infection, the presence of lipodystrophy and the continuous use of antiretroviral drugs [7]. HIV-associated lipodystrophy is also associated with premature aging [8] resembling metabolic laminopathies and progeria [1]. Premature aging of HIV-infected patients affects bone, brain, vascular wall, muscles, kidney and liver, and results of the combined effects of long-term HIV-1 infection, depleted immune responses, the toxicity of some antiretrovirals and lipodystrophy. Cellular senescence seems to result from prelamin-A accumulation induced by some antiretroviral drugs, mitochondrial dysfunction and oxidative stress. In addition, increased cytokine release in lipodystrophy further contributes to premature aging and therefore, to early CV and hepatic disease risks [9].

We focus on adipocytes dysregulation in genetic and acquired lipodystrophy, with emphasis on the most common form, HIV-lipodystrophy, from the etiology to its complications.

## 2. Adipose tissue biology – Three different adipose tissue compartments

Adipocytes are a dynamic and highly regulated population of cells. Adipose tissue is characterized by a marked cellular heterogeneity among its cellular components: adipocytes, preadipocytes, fibroblasts, macrophages, lymphocytes, endothelial cells and multipotent stem cells, able to differentiate into several cell types. Adipose tissue can release regulatory factors (adipokines, cytokines, or chemokines) or metabolites (FFAs) capable of influencing other surrounding cells, thus establishing active cross-talk among cells within adipose tissue. [9]. Overall, fat tissue consists of approximately one third mature adipocytes. The remaining two thirds are a combination of small blood vessels, nerve tissue, fibroblasts and preadipocytes in various stages of development. Preadipocytes have the ability to proliferate and differentiate into mature adipocytes, conferring a constant functional plasticity on adipose tissue [10]. Preadipocytes mature in two steps: differentiation and then hypertrophy. During the early maturation stage, an increased number of mitochondria are required [11, 12], resulting in small adipocytes, which are highly sensitive to insulin and that secrete high levels of adiponectin [12]. By contrast, older adipocytes increase in size (hypertrophy), their functional activities are lost and they become resistant to insulin. These adipocytes also exhibit decreased numbers of mitochondria with impaired mitochondrial reactive oxygen species (ROS) generated by the respiratory chain, which could have dual effects on adipocyte differentiation. New adipocytes form constantly to replace lost adipocytes, to the extent

that 50 % of adipocytes in the human subcutaneous fat mass are replaced approximately every eight years. Preadipocytes are recruited to become lipid-filled mature adipocytes at the same rate that adipocytes die, and in this way the fat mass is in constant flux, and adipocyte number is kept constant. Cellular death of fat cells in white adipose tissue occurs primarily by necrosis-like cell death, which involves macrophage recruitment and a subsequent inflammatory response. This has been implicated in the metabolic complications of obesity. Increased visceral fat mass leads to IR and a low-grade inflammation status in which many adipokines and other adipocyte and macrophage factors are involved [13].

Adipose tissue is not homogeneous but rather a tissue with specific regional compartments with varying roles and metabolic functions [14]. Individually considered, adipose tissue compartments have stronger associations with physiological and pathological processes than does total adipose tissue mass [15-17]. The upper-body adipose tissue, including visceral fat, is involved in fat storage after meals and the release of free fatty acids (FFA) between meals to feed the liver, muscles and other organs, therefore sparing glucose for the brain. Visceral fat has a more lipolytic profile than subcutaneous fat. Peripheral lower-body fat, in the femoro-gluteal region, is mainly used for its storage capacity, thereby buffering excess fat [7]. The femoro-gluteal fat depot is relatively insensitive to lipolytic stimuli and highly sensitive to anti-lipolytic stimuli, and may play a protective role by acting as a “sink” for circulating FFA [18]. This uptake of FFA prevents ectopic fat storage in the liver, skeletal muscle, and pancreas, which causes IR and beta-cell dysfunction [19]. The excessive lipolytic capacity of visceral fat (and probably subcutaneous upper-body depots as well) results in a condition referred as lipotoxicity (see section below on lipotoxicity) [7]. The reasons for the lower degree of expansibility of visceral adipocytes remain unknown. Visceral adipose tissue (VAT) differs histologically from subcutaneous adipose tissue (SAT): it has smaller adipocytes and a larger supply of nerves and vessels; VAT has many of the characteristics of brown adipose tissue turned into white adipose tissue [20].

### 3. Lipohypertrophy and lipoatrophy

Adipose tissue can be subject of different influences and undergo different transformations. SAT has a lower mitochondria content and this contributes to adipocyte apoptosis and therefore, to more lipoatrophy. VAT, with a higher number of resident macrophages [21] and more 11 $\beta$ hydroxysteroid dehydrogenase activity than SAT [22], is predisposed to hypertrophy. Hypertrophied VAT from HIV-infected patients demonstrates mitochondrial dysfunction but not impairment of adipogenic gene expression in comparison with SAT [23]. cART can differentially alter fat development depending on the environment and physiology of the different compartments. In the case of lipoatrophy, because peripheral subcutaneous adipocytes cannot store triglycerides, non-lipoatrophic fat depots such as VAT, probably buffers the increase in FFA, which worsens lipohypertrophy [8].

Subcutaneous adipocytes seem to be more susceptible to the deleterious effects of protease inhibitors (PIs) than visceral adipocytes [24]. Accordingly, studies performed on control human SAT explants reveal that some PIs increase FFA, interleukin – 6 (IL-6) and TNF- $\alpha$  pro-

duction through the activation of the proinflammatory nuclear factor –  $\kappa$ B (NF $\kappa$ B) pathway. This PI-induced deleterious paracrine loop, between adipocytes and macrophages, similar to the observed in obesity, is not seen in VAT. These data indicate that SAT is more sensitive to the adverse effects of some PIs than VAT [8].

#### 4. Adipogenesis

Individuals can differ remarkably in body fat distribution and the known differences in FFA uptake of adipose tissue compartments play a role in this difference. Premenopausal female SAT takes up more FFAs than male [25] and upper-body SAT takes up FFAs more avidly than femoral fat in men, but not in women. Gene expression, mRNA transcription of FA transporters and consequently facilitated FA transport was greater in the upper body in men and in the femoro-gluteal region in women. This novel FFA disposal pathway may also play a role in the development or maintenance of body fat distribution. On the other hand, direct FFA uptake in subcutaneous fat differs from fatty acid uptake from a meal in two respects: 1) direct FFA uptake is more efficient in women than in men and 2) in men there is no preferential direct FFA uptake in upper-body subcutaneous fat compared with femoral fat in women. These gender-based differences are consistent with this process as a mechanism to develop or maintain variations of body fat distribution between men and women, both lean and obese. The greater direct FFA uptake in abdominal over femoral fat in men could be due to the greater facilitation of inward fatty acid transport. Contrary to what is generally believed, upper-body subcutaneous fat releases ~70 % of systemic FFAs in lean men and women, whereas the leg contributes only ~20%; fatty acid uptake from a meal follows a similar pattern [26]. In non-obese men, the direct uptake/storage of FFAs in upper-body and leg fat mirrors this regional difference in FFA release, whereas in lean women, direct FFA uptake was similar in upper-body and femoral adipose tissue. This imbalance between release and direct reuptake in women could redistribute fatty acids toward leg fat. In obese women, the total FFA reuptake in leg fat was also significantly greater than in upper-body fat. It may be that some populations of fat cells, such as the smaller adipocytes, take up but do not actively release FFAs, whereas larger fat cells briskly release FFAs and do not take up FFAs under post-absorptive circumstances. In summary, there is a mechanism for adipocyte fatty acid uptake and storage that has yet to be understood, but which is independent of lipoprotein lipase and it's not thought to exist in the post-absorptive state [25].

Macrophage infiltration of the human adipose organ is a well-documented phenomenon that induces a low-grade chronic inflammation that is associated with IR. This reaction appears to be related mainly to macrophage-produced cytokines (TNF- $\alpha$  and IL-6) capable of interfering with the normal activity of insulin receptors. The greater amount of macrophages and macrophage-secreted cytokines found in visceral fat is in line with the greater morbidity associated with these depots. Subcutaneous and visceral adipocytes have cell-autonomous properties due to inherently different progenitor cells that exhibit a different gene expression pattern. Subcutaneous white adipose tissue responds better to the anti-lipolytic effects of insulin, secretes more adiponectin and less inflammatory cytokines, and is differentially

affected by molecules involved in signal transduction as well as drugs, compared with visceral white adipose tissue [13].

Lipoatrophic adipose tissue is known to be characterized by smaller adipocytes, greater cell size variation, disruption of cell membranes, and signs of apoptosis as determined by immunohistochemistry staining, when compared with non-lipodystrophic adipose tissue. There is a marked difference in gene expression between dorsocervical and abdominal SAT, irrespective of the lipodystrophy status, that lies in the expression of homeobox genes involved in organogenesis and regionalization. Disparate expression of such fundamental regulators of transcription might ultimately contribute to different patterns of differentiation and affect the susceptibility of the adipose tissue depot to cART-induced toxicity, perhaps making the abdominal subcutaneous and femoro-gluteal depot more vulnerable to atrophy [27].

Morphologic alterations in lipoatrophy-prone areas of SAT have been confirmed at the level of gene expression [9]. Most studies report that these lipoatrophic areas show an abnormally low expression of the major adipogenic transcription factors peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), sterol-regulatory element binding protein-1 (SREBP-1), and CCAAT/enhancer-binding protein- $\alpha$  (C/EBP $\alpha$ ) [28-30]. Consequently, the expression of adipogenic differentiation-related genes is also decreased. For example, there is a reduction in the expression of genes for lipoprotein lipase and for the insulin-sensitive glucose transporter GLUT 4 [28, 29], resulting in impaired fatty acid and glucose uptake, respectively, and thus leading to a deficit in the lipid-accretion capacity of SAT. Another major alteration detected, which is probably related to the impaired adipogenic gene expression, is reduced expression of the adipokine genes adiponectin and leptin [28, 29]. In addition to impaired expression of adipogenetic-related genes, adipose tissue from patients with lipodystrophy, mainly those receiving NRTIs [31, 32] also show a reduction in mitochondrial DNA (mtDNA) levels. This decrease is associated with complex alterations in mitochondrial function, such as reduced expression of mtDNA-encoded transcripts and compensatory up-regulation of dysfunctional mitochondrial mass, that likely reduce the endogenous oxidative capacity of adipose tissue [33]. Moreover, increased oxidative stress and apoptosis have also been reported in lipoatrophic SAT [34]. Lipoatrophy is also accompanied by a state of chronic low-level inflammation [35]. High levels of expression of the inflammatory markers, TNF- $\alpha$ , IL-6; IL-8 and IL-18 have been reported in SAT from HIV-1-infected lipoatrophic patients [28, 30, 35-37]. Expression of TNF $\alpha$  and IL-6 mRNA in SAT of lipodystrophic patients correlates positively with tissue apoptosis and negatively with adipogenic marker expression, which is consistent with a role for pro-inflammatory cytokines in adipocyte viability and differentiation [30]. Unlike SAT, VAT did not exhibit impaired expression of adipogenic marker genes. However, it did show some similar changes in inflammatory markers, such as induction of TNF- $\alpha$ , whereas others differed from that of SAT, such as, for instance, lack of monocyte chemoattractant protein -1 (MCP-1) induction. In contrast, mitochondrial dysfunction in VAT was found to be similar to that in SAT. Therefore, mtDNA depletion and signs of altered mitochondrial function are common to atrophic (subcutaneous) and hypertrophic (visceral, dorsocervical) depots in HIV-1 lipodystrophy, indicating that mitochondrial impairment cannot explain in a simple manner the final outcome for adipose depots, either in terms of lipoatrophy or lipohypertrophy [23]. Taken together, these observations indicate that different responses occurring in subcutaneous and visceral fat depots in lipo-

dystrophic patients are likely to be related to intrinsic differences in fat physiology and/or capacity to react to the same insult. One adipose depot (visceral) enlarges in size and approaches its fat storage capacity threshold (as in obesity) merely because another adipose depot (subcutaneous) cannot [38]. A direct role for HIV-1 infection has been proposed by analyzing SAT from untreated HIV-1-infected patients (“naïve”) as compared to healthy controls. Early histological studies did not indicate clear mitochondrial or inflammatory-related disturbances [39], but subsequent gene expression studies have shown a significant decrease in the expression of the adipocyte differentiation controller PPAR $\gamma$  and some impairment in the expression of genes encoding mitochondrial proteins and proteins specifically related to adipocyte metabolism, including adiponectin and 11 $\beta$ -steroid dehydrogenase type-1, the enzyme responsible for glucocorticoid activation [9, 29]. Some signs of inflammatory response have also been reported [29]. All these alterations are further enhanced in SAT of lipodystrophic patients. Therefore, it appears that HIV-1 infection initiates a first wave of alterations in adipose tissue that is amplified by cART and ultimately results in lipodystrophy [9].

## 5. Congenital generalized lipodystrophies

Generalized lipodystrophies are rare disorders that may be congenital or acquired. The genetic lipodystrophies have been reported in about 1000 patients [2]. The congenital generalized lipodystrophy (CGL) Berardinelli-Seip syndrome (BSCL), is an autosomal recessive disorder initially reported by Berardinelli [3] and Seip [40] with frequent parental consanguinity [41-44]. It has been proposed that Berardinelli-Seip syndrome could be a Portuguese disease, later spread by the Portuguese across the world [45].

Patients with CGL are recognized at birth or soon thereafter due to a near-total lack of body fat and prominent muscularity that causes a severe and striking phenotype (Figure 2A and 2B). Diabetes develops during infancy or most often during the teenage years. Hepatosplenomegaly, umbilical prominence or hernia, acanthosis nigricans, voracious appetite and accelerated growth can occur. Female patients develop hirsutism, may have clitoromegaly, oligomenorrhea and polycystic ovaries. Other uncommon manifestations include hypertrophic cardiomyopathy, mild mental retardation, and focal lytic lesions in the appendicular bones after puberty [41, 42]. Diabetes and its complications, hyperlipidemia and recurrent attacks of acute pancreatitis, hepatic steatosis and occasionally cirrhosis are the causes of morbidity and mortality [2].

At least 4 molecularly distinct forms of congenital lipodystrophy have been defined, with the mutations of the enzyme acyltransferase 1-acylglycerol-3-phosphate O-acyltransferase 2 (AGPAT2) or (BSCL1- locus 1) and Berardinelli-Seip (BSCL2 - locus 2) being both responsible for 95 % of gene mutations. AGPAT2 has been mapped in chromosomes 9q34. AGPATs are critical enzymes involved in the biosynthesis of triglycerides and phospholipids from glycerol-3-phosphate. They catalyze acylation of fatty acids at the sn-2 position of glycerol moiety and convert lysophosphatidic acid to phosphatidic acid [2, 46]. AGPAT2 is highly expressed in the adipose tissue, and its deficiency may cause lipodystrophy by limiting triglyceride or phospholipid biosynthesis [47].



**Figure 1.** A: Two sisters with Berardinelli-Seip syndrome B: Women with Berardinelli-Seip syndrome

Type 2 CGL is due to BSCL2 gene mutations. This gene is located in chromosome 11q13 and encodes a protein called seipin [48]. Seipin appears to play a role in lipid droplet formation and may also be involved in adipocyte differentiation [49-51].

Patients with BSCL2 mutations have the most severe variety of CGL and are born without any body fat [2]. Two other genes were identified for CGL: caveolin 1 (CAV1) [52] and polymerase I and transcript release factor (PTRF) [53]. Caveolin 1 is the main component of caveolae, specialized microdomains seen in abundance on adipocyte membranes [54]. It binds fatty acids and translocates them to lipid droplets. PTRF (also known as cavin) is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3 [53].

## 6. Mortality in generalized lipodystrophies

Patients with generalized lipodystrophies are predisposed to develop acute pancreatitis, cirrhosis, endstage diabetic renal disease requiring transplantation, and blindness due to diabetic retinopathy. Many patients with FPL die of coronary heart disease or cardiomyopathy and rhythm disturbances [55-57]. Sudden death has been reported during childhood in CGL, type 4, likely due to arrhythmias [58]. Patients with HIV-lipodystrophy are predisposed to develop

ing coronary heart disease [59]. Patients with congenital Berardinelli-Seip lipodystrophy frequently develop hypertrophic cardiomyopathy that can lead to death from cardiac failure [41]. In individuals with BSCL, ventricular dysfunction and hypertrophic cardiomyopathy are often observed. In cardiac biopsies performed in eight individuals with BSCL, the presence of subendocardial fibrosis and an abnormal architecture in the left ventricular lumen was observed [60, 61]. Hypertrophic cardiomyopathy in BSCL patients has been correlated with high plasmatic insulin levels, which activate the type 1 insulin-like growth receptors, present in large quantities in the myocardial tissue, that stimulate cell growth [62, 63]. In addition, the presence of IR and hypertriglyceridemia in individuals with BSCL may predispose them to premature atherosclerosis. Individuals who have mutations on chromosome 11 (BSCL2) seemed to present more severe symptoms than those who had mutations in BSCL1, with a high incidence of premature deaths. Cardiomyopathy was three times more frequent in those with BSCL2 mutations than in individuals with alterations in BSCL1 [42].

## 7. Mandibuloacral Dysplasia (MAD)-associated lipodystrophy

MAD is characterized by skeletal abnormalities such as mandibular and clavicular hypoplasia and acroosteolysis [64], progeroid manifestations, partial or generalized lipodystrophy and metabolic complications, among other clinical features [65, 66]. Patients with MAD harbor mutations in lamin A/C (LMNA) or zinc metalloproteinase (ZMPSTE24) [67, 68]. ZMPSTE24 is involved in post-translational proteolytic processing of prelamin A to mature laminA [2].

## 8. Autoinflammatory syndromes

A syndrome of joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced (JMP) lipodystrophy was reported by Garg in three patients, belonging to two pedigrees, who were from Portugal and Mexico [69]. Three other patients have been reported from Japan [70, 71]. Mutations in PSMB8 may trigger an autoinflammatory response resulting in infiltration of adipose tissue with lymphocytes and other immune cells and adipocytes [2]. The other autoinflammatory syndrome is the chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. The mode of inheritance seems to be autosomal recessive, but the molecular basis remains unknown [2, 72, 73].

## 9. Familial Partial Lipodystrophy(FPL)

FPL is characterized by the onset of fat loss from the limbs and other regions of the body, usually during childhood, adolescence or adulthood. Many regions of the body, such as the face, neck, and intra-abdominal region are spared, and patients accumulate excess body fat in the non-lipodystrophic regions [74-76]. Metabolic complications, acanthosis nigricans, oligoame-

norrhoea, hirsutism, polycystic ovarian syndrome, mild to moderate myopathy, cardiomyopathy, and conduction system abnormalities indicative of multisystem dystrophy can occur [2, 55, 56, 77]. The identification of the first gene for FPL, Dunnigan variety, i.e. LMNA, on chromosome 1q21-22 [2, 78-81], an integral component of nuclear lamin, was made in 1998. Thereafter, four other genes were identified: PPAR $\gamma$  [82-84], a key transcription factor involved in adipocyte differentiation; v-AKT murine thymoma oncogene homolog 2 (AKT2) [85], involved in downstream insulin signaling; and cell death-inducing DNA fragmentation factor-like effector c (CIDEc) [86] and perilipin 1 (PLIN1) [87], both involved in lipid droplet formation [2, 88]. Adipocyte loss is due to premature cell death resulting from disruption of the nuclear envelope [87, 89]. Defective adipocyte differentiation seems to be the cause of the lipodystrophy of PPAR $\gamma$  and AKT2 mutations. Fibrosis of adipose tissue with small adipocytes is responsible for the lipodystrophy of PLIN1 mutations [2, 87].

There are other rare genetic syndromes whose molecular basis remains unknown, namely atypical progeroid syndrome [90], Hutchinson-Gilford progeria syndrome [91], SHORT-associated lipodystrophy [92], and Wiedemann-Rautenstrauch syndrome [93].

Patients with FPL syndromes display mixed lipodystrophy with subcutaneous lipoatrophy and central fat accumulation. Those with FPLD2 also have an increased amount of fat in the cervico-facial area compared to patients without these mutations. Therefore, a single protein mutation leads to two opposing fat localization phenotypes [8]. Importantly, mutations in LMNA are also responsible for metabolic laminopathies resembling the metabolic syndrome (MS) and Hutchinson-Gilford progeria, a severe syndrome of premature aging [94]. Prelamin A is implicated in increased oxidative stress and in the occurrence of cellular senescence [8].

## 10. Acquired lipodystrophies

### 10.1. Acquired Generalized Lipodystrophy (AGL) – Lawrence syndrome

The onset of subcutaneous fat loss in patients with AGL usually occurs during childhood [95]. The pattern and extent of fat loss is quite variable and most patients have generalized loss of fat, but a few of them have areas such as intra-abdominal and bone marrow fat spared. AGL patients are highly likely to develop severe hepatic steatosis and fibrosis, diabetes, and hypertriglyceridemia [2]. The pathogenesis of fat loss remains unknown. Panniculitis may precede loss of fat. Lipodystrophy can be associated with autoimmune diseases such as juvenile dermatomyositis [95]. Chronic hepatitis with autoimmune features and low serum complement 4 levels, suggesting involvement of the classical complement pathway in the pathogenesis of fat loss, has been reported [96].

### 10.2. Acquired partial lipodystrophy–Barraquer-Simons syndrome

Fat loss occurs gradually in a symmetric fashion, first affecting the face and then spreading downward. Most patients lose fat from the face, neck, upper extremities, and trunk, and subcutaneous fat from the lower abdomen and legs is spared. Many patients accumulate ex-

cess subcutaneous fat in the hips and legs. Metabolic complications are rare. Misra et al suggest that the fat loss involves autoimmune-mediated destruction of adipocytes because the patients have low serum levels of complement 3 and complement 3-nephritic factor, which blocks degradation of the enzyme C3 convertase [95]. It is possible that the C3-nephritic factor induces lysis of adipocytes expressing factor D [97].

### 10.3. Localized lipodystrophy

Localized lipodystrophies present focal loss of subcutaneous fat, usually causing one or more dimples, and in general occurs due to subcutaneous injection of various drugs (Figure 4), panniculitis, pressure, and other mechanisms [98].



**Figure 2.** Patient with lipohypertrophy related to subcutaneous administration of pegvisomant.

### 10.4. Lipodystrophy associated with HIV-infection

The impressive progress resulting from the discovery of drugs able to control HIV infection on a long-term basis, has offered most patients a prolonged lifespan, possibly as long as that observed in non-infected subjects [7]. Suppression of viral replication has become a treatment goal that can be reached with the use of cART. After the introduction of protease inhibitors (PIs) in 1996, as a component of highly active antiretroviral therapy, the morbidity and mortality associated with HIV has dramatically been reduced [99]. However, patients develop a syndrome of fat redistribution with peripheral fat loss (face, upper limbs and femoro-

gluteal) and visceral fat accumulation, generally associated with metabolic abnormalities [4, 100-103] and increased risk of CV diseases [104, 105], similar to what occurs in congenital lipodystrophies [4, 59]. Lipohypertrophy usually represents a central visceral fat accumulation in the abdomen and trunk, but can also be found in breasts (in women), dorsocervical region ("buffalo hump"), double chin, lipomas, and within the muscle and liver [59, 106]. Lipoatrophy and lipohypertrophy are frequently associated (mixed form), but they also can occur independently of each other [59]. This HIV-associated lipodystrophy has been proposed to be an age-related fat redistribution condition that could amplify age-related comorbidities and lead to their earlier occurrence [8]. Also, hyperlactenemia and bone demineralization can occur [107, 108].

Owing to a lack of a consensus on the definition of lipodystrophy and lipodystrophy syndrome in HIV-infected patients, its exact prevalence is not known [6]. In the early 2000s, about half of HIV-infected patients undergoing cART were diagnosed as lipodystrophic (20-80%) [109]. Abnormalities in peripheral and central fat masses are clinically evident in 20-35% of patients after approximately 12-24 months of cART [59, 107, 110, 111]. With the new anti-retroviral agents, the probability of developing lipoatrophy has decreased in western countries as the pattern of cART prescription has significantly changed [112]. In the study of Nguyen, lipodystrophy has become less frequent since 2003 [112]. Two widely used thymidine analogs from the first class of ART, stavudine and zidovudine, are responsible for lipoatrophy and now they have been replaced by a new generation of potent NRTIs. Although metabolic toxicity of boosted PIs is far less than of first-generation protease inhibitors (PIs), they are still considered responsible for increased CV risk. The new classes of ART, fusion inhibitors (F20), integrase inhibitors (raltegravir) or entry inhibitors (anti-CCR5, maraviroc) have not yet been shown to alter metabolic parameters or fat distribution [8, 112-117].

HIV-infected patients can have 4 different phenotypes of body fat composition: no lipodystrophy, isolated peripheral lipoatrophy, isolated central fat accumulation and a mixed form of lipodystrophy (or redistribution syndrome) [100]. About 50% of patients with HIV-associated lipodystrophy display mixed forms, with the loss of limb fat and marked expansion of VAT [113]. The high frequency of this association suggests that these two opposite phenotypes could be, at least in part, causally related [8]. Also, HIV patients may have a picture similar to partial lipodystrophy patients with peripheral fat atrophy and hypertrophied central fat depots. Thus, there are similarities between HIV lipodystrophy and genetic forms.

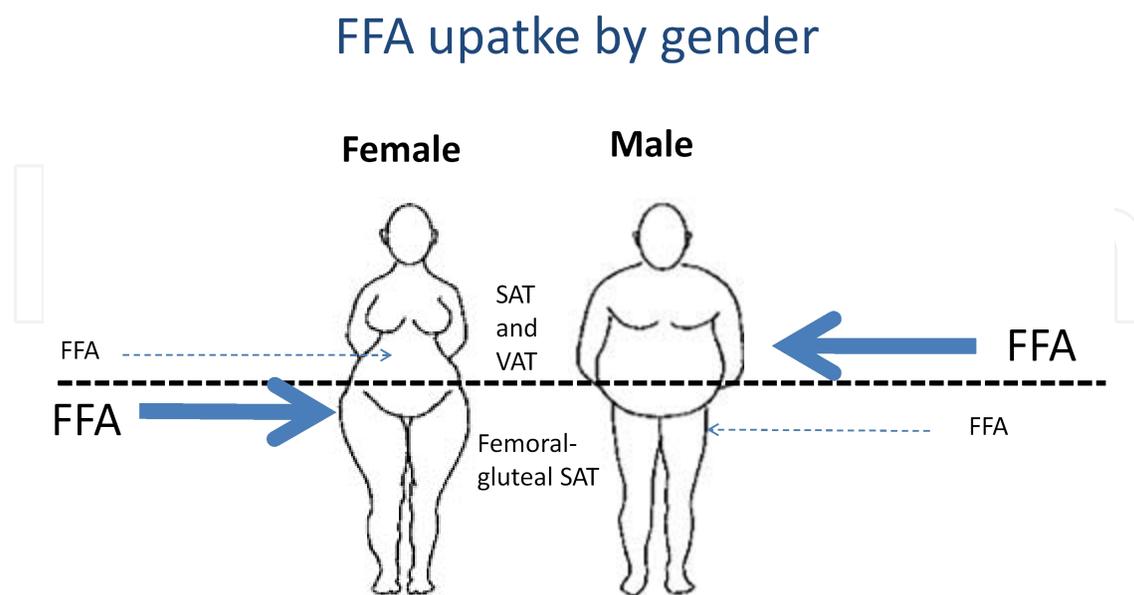
## 11. HIV-lipodystrophy and related factors

There is a possible role of the virus contribution for lipodystrophy i.e. the HIV or hepatitis infection affects fat tissue before any ART. Monocytes are relatively resistant to HIV infection, but differentiated macrophages are highly susceptible and tissue macrophages have been found to harbor HIV-1 [118]. Infected macrophages release pro-inflammatory cytokines. Systemic inflammation associated with HIV infection might promote monocyte migration across the vascular endothelium, leading to an increased number of activated macrophages in fat

[118]. Several studies reported that the severity of HIV infection is associated with an increased prevalence of lipodystrophy [59, 119], probably as a consequence of persistent HIV-infected macrophages in adipose tissue, which could enhance local inflammation.

ART-naïve HIV-positive patients have increased TNF- $\alpha$  expression compared with uninfected controls [29], which is consistent with increased inflammation. TNF- $\alpha$  alters adipocyte function and differentiation, in part through the inhibition of PPAR $\gamma$  expression [120]. Infected macrophages might also release viral proteins (such as Vpr and Nef) that can impact on adjacent adipocytes and lead to decreased PPAR $\gamma$  activity and inhibition of adipogenesis [121, 122]. Although lipodystrophy is uncommon in ART-naïve patients [113], the HIV infection of macrophages could itself result in low-grade fat inflammation and lead to the release of viral proteins that affect neighboring adipocytes and decrease their differentiation.

The development of lipodystrophy and metabolic toxicities is partially related to the individual drugs included in cART regimens, associated with other risk factors [123] such as gender and pre-HIV-infection body composition, disease-specific factors such as the nadir levels of CD4 $^+$  lymphocytes and the duration of HIV infection [110, 123, 124]. The most significant risk factors associated with lipodystrophy are exposure to and duration of nucleoside thymidine analogues (most commonly stavudine), age, severity of disease markers (CD4 lymphocyte count and plasma HIV viral load), therapy duration, and belonging to the Caucasian race. On the other hand, the most common statistically significant risk factors for lipohypertrophy are therapy duration, PI administration, markers of disease severity, and age. We cannot forget that along the years, patients have done multiple regimes and combinations of antiretroviral drugs, which makes it difficult to identify different risks with different drugs, and studies therefore report conflicting results [6].



**Figure 3.** FFA uptake by gender (SAT - abdominal subcutaneous adipose tissue; VAT – visceral adipose tissue; FFA – free fat acids)

## 12. Protease inhibitors

PIs affect multiple metabolic pathways and are associated with lipohypertrophy, lipoatrophy, atherogenic dyslipidemia and IR, [125, 126]. Studies in-vitro reported that PIs are able to alter a number of adipocyte functions, including differentiation, expression of transcriptase factors involved in adipogenesis, cell survival, cytokine production, mitochondrial function and IR [127]. PIs may cause lipodystrophy by inhibiting ZMPSTE24, resulting in accumulation of toxic farnesylated prelamin A [128], increased oxidative stress and altered adipokine and cytokine production [89, 127, 129]. The adverse effect of PIs could also result from the induction of endoplasmic reticulum stress or the inhibition of the proteasome [130, 131].

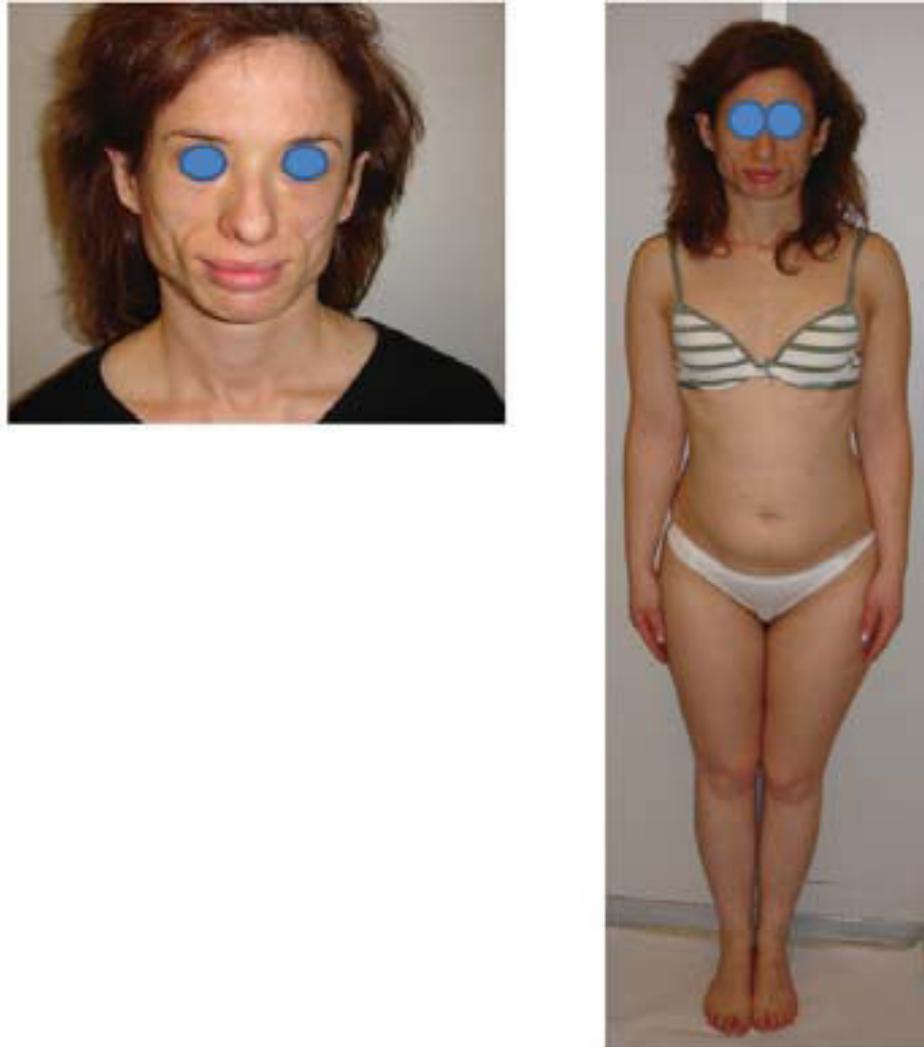
Different PIs might affect key intranuclear genes, causing reduction in levels of RNA encoding SREBP-1, which changes the expression of PPAR  $\gamma$  [28]. The levels reduction of intranuclear SREBP-1 leads to a decreased adipocyte differentiation and an altered release of adipocytokines [132]. PIs can inhibit lipogenesis and stimulate lipolysis [28, 132-135], and may induce IR by inhibiting glucose transporter 4 expression (GLUT4) [136].

## 13. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

NRTIs are analogs that inhibit the viral reverse transcriptase enzyme. The thymidine NRTIs (zidovudine, stavudine and didanosine) cause mitochondrial toxicity by mitochondrial DNA polymerase inhibition and by causing DNA mitochondrial mutations [31, 137, 138]. These disturbances result in apoptosis of peripheral adipocytes and lead to lipoatrophy [31]. NRTIs are also associated with fat hypertrophy in visceral depots [113, 139, 140]. Nucleoside analogues may inhibit adipogenesis and adipocyte differentiation, promote lipolysis, and exert synergistic toxic effects when associated to PIs [31, 141-143]. Moreover, NRTIs promote lipolysis and the subsequent efflux of non-esterified fatty acids from adipose tissue [142, 144].

## 14. Mitochondrial toxicity and fat redistribution

In western countries, long-term HIV-infected patients present several age-related comorbidities earlier than the general population [145], and display signs of premature aging [8]. New hypotheses were recently suggested about the pathophysiology of fat redistribution, proposing that mitochondrial toxicity was involved in lipoatrophy and in fat hypertrophy. HIV-associated lipodystrophy could be an age-related fat redistribution that could amplify age-related comorbidities and their earlier occurrence [8]. Mitochondria play an important role in adipocyte differentiation and function. At physiological low levels, ROS could act as secondary messengers to activate adipogenesis and lipogenesis, resulting in increased adipocyte number and size. In hepatic cells, oxidative stress activates the transcription factor SREBP1c, which is highly expressed in adipocytes and increases lipogenesis and lipid accumulation [146]. At higher levels, ROS could inhibit differentiation [8].



**Figure 4.** Acquired partial lipodystrophy - Barraquer-Simons syndrome

Excessive VAT releases increased visceral adipocyte-FFAs, adipokines and cytokines. Indeed, activated macrophages, which have an M1 proinflammatory phenotype, invade expanded adipose tissue; upon invasion, their production of proinflammatory cytokines and chemokines increases. This could lead to the decreased secretion of adiponectin by adipocytes in response to  $\text{TNF-}\alpha$  [36]. Increased abdominal fat lipolysis increases ectopic fat deposition within tissues (liver, skeletal muscle and heart). Subsequently, these derivatives overwhelm mitochondrial oxidative capacity and activate stress kinases, leading to IR. This situation, known as lipotoxicity, associates ectopic depots of triglycerides in non-adipose tissues that buffer excess fatty acid derivatives [147]. Moreover, a paracrine loop is present between adipocytes and macrophages; macrophage-secreted cytokines ( $\text{TNF-}\alpha$  and IL-6) activate the NF $\kappa$ B pathway in adipocytes, resulting in increased IL-6 and FFA production. Saturated FFA can, in turn, activate the Toll-like receptor-4 (TLR-4) on macrophages and adipocytes, thereby increasing the proinflammatory loop. This paracrine loop has been reported in obesity as a result of macrophages infiltrating fat [148].

## 15. Cortisol and fat redistribution

Patients with hypercortisolism also have an acquired form of lipodystrophy [1], characterized by fat hypertrophy in the upper body with increased VAT and decreased limb fat. Cortisol can activate adipocyte differentiation and hypertrophy, mainly in visceral fat depots, because of the higher expression of glucocorticoid receptors (GR- $\alpha$ ) and the 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD-1) that transforms inactive cortisone into active cortisol in adipocytes from central depots [22]. In addition, cortisol induces IR and increases lipolysis in adipocytes [22]. It has been hypothesized that glucocorticoid activation is involved in cART-linked central fat hypertrophy [8]. Higher ratios of urinary cortisol:cortisone metabolites and higher subcutaneous 11 $\beta$ -HSD-1 expression are observed in patients with severe lipodystrophy compared with those without [149]. In cART-naïve patients, 11 $\beta$ -HSD-1 expression increases in both abdominal and thigh SAT after 12 months of ART, but only in patients with lipohypertrophy or without lipoatrophy [150]. Because TNF- $\alpha$  expression in fat is related to that of 11 $\beta$ -HSD-1 [149], inflammation is linked to glucocorticoid activation [8]. TNF- $\alpha$  activates 11- $\beta$ -hydroxysteroid dehydrogenase (HSD)-type 1, and this enzyme's activity is higher in visceral fat compared with subcutaneous fat. Visceral fat is able to locally produce cortisol, which could act inside the adipocytes and increase lipid accumulation [151]. Other hormones, such as growth hormone and testosterone, can modulate the activity of 11 $\beta$ -HSD-1. It is interesting to note that HIV-infected patients with lipodystrophy often present with a relative decrease in growth hormone [152] and testosterone levels. Moreover, when patients with visceral fat hypertrophy are treated with growth hormone, a reduced amount of visceral fat is reported, together with improved metabolic status [153].

## 16. Aging

In the general population, age is associated with central fat redistribution, mitochondrial impairment and increased levels of pro-inflammatory cytokines [154]. Aging adipocytes release more pro-inflammatory cytokines than young ones [155]. Aging is physiologically associated with fat redistribution, oxidative stress and low-grade inflammation. In the general population, the interaction between the proinflammatory state and genetic background potentially triggers the onset of age-related inflammatory diseases such as atherosclerosis, sarcopenia and frailty. Decreased immune response leading to immunosenescence is also probably involved in early aging [8, 156]. Aging and some cARTs result in mitochondrial dysfunction and oxidative stress, which lead to cellular senescence. Moreover, some PIs induce the accumulation of the pro-senescent protein prelaminA [8].

## 17. Genetic factors and HIV-lipodystrophy

A role for genetics is also probable in HIV-lipodystrophy. TNF- $\alpha$  gene promoter polymorphism is associated with lipodystrophy, but this association has not been confirmed in larg-

er studies [157]. Interestingly, stavudine-induced lipoatrophy is linked to the HLA-B100\*4001 allele, which is located in close proximity to the TNF- $\alpha$  gene; this observation further supports the theory that there is a role for inflammation in lipoatrophy [158]. Apo C3-455 also plays a role in lipoatrophy, and two variants of the adipogenic  $\beta$ 2 receptor seems to be involved in fat accumulation, whereas PPAR $\gamma$  variants are not involved [159]. The toxicity of ART also depends on a patient's metabolism, in part genetically determined.

## 18. Role of inflammation

Even if infectivity of adipocytes by HIV has been contested, the ability of the virus to modify adipocyte phenotype has been shown in some studies [160, 161]. Moreover, macrophages and dendritic cells present in lipodystrophic adipose tissue could be infected, which could modify their characteristics [7]. Macrophage infiltration is observed in adipose tissue from patients with HIV-related lipodystrophy together with decreased adipokine and increased pro-inflammatory cytokine production [162]. Some anti-retrovirals increase oxidative stress and generation of reactive species, which results in decreased production of adiponectin and leptin by adipocytes and increased production of pro-inflammatory cytokines [7].



**Figure 5.** Patient with mixed lipodystrophy (absence of subcutaneous peripheral fat in arms, legs and face and increased abdominal fat mass)

## 19. Lipotoxicity

Lipotoxicity is a possible explanation for the development of metabolic syndrome (MS) and diabetes in multiple pathological situations, from obesity to lipodystrophies of distinct origin. According to the lipotoxicity theory, excess availability of fatty acids or a limited capacity to metabolize them in organs and tissues elicits most of the alterations that are characteristic of MS, especially IR. The toxicity of fatty acids toward  $\beta$ -cells may lead to altered insulin production. Actually, high FA levels can induce a reduction in GLUT2 on  $\beta$  cell surfaces and induce a decrease in insulin secretion [19]. Increased availability and, ultimately, increased accumulation of fat into skeletal muscle tends to promote IR; and fatty acid levels in liver that exceed the capacity of this organ to oxidize or export them, lead to the increased accumulation of fat that is often associated with MS. All of these events could result from alterations in fat metabolism or excess intake of fat-enriched nutrients, but they could also arise as a result of intrinsic alterations in the capacity of adipose tissue to store and thereby buffer the excessive accumulation of fatty acids in other tissues and organs [163]. One hypothesis consistent with the appearance of MS in ART-associated lipodystrophy syndrome is lipotoxicity resulting from limitations in the capacity of subcutaneous fat to store the appropriate amounts of fat and the subsequent diversion of fatty acids to ectopic sites [164]. Several arguments in support of lipotoxicity as a major contributor to MS in distinct human pathologies come from the paradoxically common metabolic alterations found in the obesity and in lipodystrophies of genetic origin. According to the lipotoxicity theory, the fat stored in adipose tissue is biologically inert and the observed metabolic alterations are primarily caused by the increased exposure of cells to non-esterified fatty acid. Thus, in obese patients, it is not the amount of fat stored in adipose tissue that elicits metabolic dysfunctions, but rather the balance between the availability of those fatty acids to tissues and organs and the capacity of the organs to eliminate them through triglyceride storage in adipose tissue, or oxidation [165]. A complementary concept is the idea that there is a threshold for adipose tissue expansibility; once it's reached, as it occurs in obese individuals, appropriate storage of fatty acids inside adipocytes in their inert and esterified form is impaired, determining the extent of lipotoxicity [164]. Either a total or partial lack of adipose tissue storage capacity causes an increase in circulating lipid levels and is associated with ectopic lipid accumulation in non-fat tissues such as liver, skeletal muscle and pancreas. These alterations lead to non-alcoholic fatty liver diseases, hepatic and muscle IR and development of type 2 diabetes. Adipokine deficiency further contributes to metabolic alterations (e.g. hyperphagia) owing to an associated leptin deficiency, which also contributes to positive energy balance and potential lipotoxicity through increased fat intake [94].

## 20. Insulin resistance

IR occurs in about one-third of patients on certain PI-based regimens, although the thymidine NRTIs have also been associated [166]. Asymptomatic type 2 diabetes mellitus is diag-

nosed in 5-10 % of patients [126]. The new-generation PIs appear to have a milder IR effect and the prevalence of diabetes is lower than described in the early 2000s. Its prevalence, however, remains higher than in the general population at the same age. In particular, patients with severe lipodystrophy are more prone to develop IR [7]. The pathogenesis of glucose metabolism disorders is still unclear and, although a direct effect of potent antiretroviral combinations is certainly involved, it is likely that multiple factors play a role, including genetic predisposition, cytokine and hormonal alterations, changes in the immune system, non-antiretroviral drug-induced toxic effects, opportunistic diseases, and perhaps the HIV infection itself [167]. Risk factors for the development of IR in HIV-positive population include duration of ART, PI treatment, concurrent fat redistribution syndrome, dyslipidemia, increasing age, hepatitis C virus co-infection, as well as pharmacological treatment with pentamidine or megestrol acetate [100, 167-169].

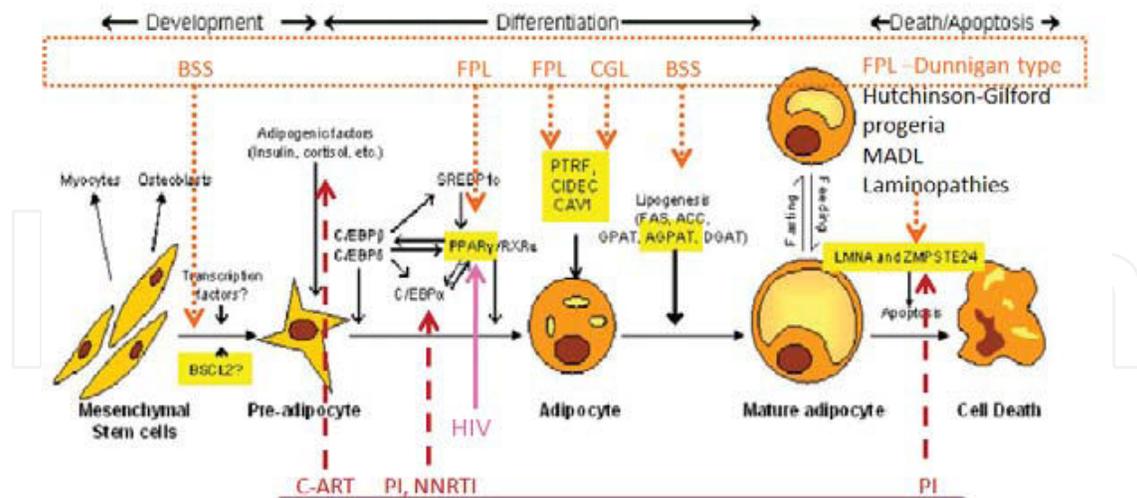
PIs (including indinavir, amprenavir, nelfinavir, and ritonavir) have been shown to induce IR in vitro by reducing glucose transport mediated by the glucose transporter 4, a receptor involved in glucose uptake [136]. The deleterious impact of some PIs on adipocytes through the inhibition of GLUT4 transporters was directly demonstrated in healthy controls, after given these molecules for a few weeks [169-171]. Several PIs can interfere with nuclear transcription factors, leading to decreased adiponectin levels, which also leads to IR [123]. Some PIs might also cause mitochondrial toxicity [172]. Additionally, the increase in FFA levels associated with PIs, as well as with fat redistribution, might also have a role in the development of IR (*see* lipotoxicity) [173].

## 21. Dyslipidemia

A number of HIV-infected patients present dyslipidemia, increased cholesterol, low-density lipoprotein (LDL)-cholesterol and triglycerides together with decreased HDL. This profile has been associated with the presence of a MS, resulting from an increased visceral fat amount with IR [7].

In patients receiving cART, the prevalence of hyperlipidemia ranges from 28 to 80% in different studies [167, 174], and it includes hypertriglyceridemia in the majority of cases [123]. Dyslipidemia is frequently, but not always, associated with fat redistribution syndrome: although lipid and glucose metabolism alterations are more common in patients with body-fat abnormalities, they are also observed in those without these morphological changes [167].

Several pathogenetic mechanisms have been proposed to explain cART-associated hyperlipidemia, which seems to result from a complex and multifactorial pathologic process: possibly HIV infection itself, leading in some cases to permanent low grade inflammation with abnormal levels of some pro-inflammatory cytokines; lipodystrophy itself, as in the genetic forms, with decreased lower-body fat depots and increased visceral fat; and antiretroviral molecules (PIs, NNRTIs and some NRTIs) [7].



**Figure 6.** Genetic and acquired lipodystrophies (CGL – congenital generalized lipodystrophy; BSS – Berardinelli-Seip syndrome; cART- combined antiretroviral therapy; NRTI – nucleoside and nucleotide reverse transcriptase inhibitors; PI - protease inhibitors; FPL- familiar partial lipodystrophy; MADL- mandibuloacral dysplasia associated lipodystrophy; adapted from Agarwal&Garg. *Ann Rev Genomics Human Genet* 2006; 7: 175-199]

Various mechanisms involved in ART-related dyslipidemia have been described: reduction in the catabolism of VLDL, increased VLDL production, impaired catabolism of FFA, increased liver triglyceride synthesis, increased secretion of apolipoprotein B-containing lipoproteins, reduced expression of LDL receptors, reduced degradation of SREBP, and reduction in FXR (farnesoid X receptor) [175]. The first hypothesized mechanism is based upon the structural similarity between the catalytic region of HIV-1 protease and two human proteins involved in lipid metabolism: the cytoplasmic retinoic acid-binding protein type 1 (CRABP-1) and the low-density lipoprotein-receptor-related protein (LRP). PIs probably bind to CRABP-1 and erroneously inhibit the formation of cis-9-retinoic acid, leading to increased apoptosis of peripheral adipocytes, decreased lipid storage and increased lipid release into the bloodstream. Similarly, PIs may inhibit the normal functioning of LRP and interfere with fatty acid storage in the adipocytes [167, 176]. Furthermore, data from in vitro and in vivo studies suggest that PIs may prevent proteasomal degradation of nascent apolipoprotein B, a key protein component of circulating triglycerides, leading to increased production of VLDL particles. An upregulation of metabolic pathways leading to an excessive production of VLDL can also be caused by the PI-induced intra-hepatocyte accumulation of nuclear transcription factors involved in the metabolism of apolipoprotein B, such as SRBPs. In addition, the levels of lipoprotein particles containing apolipoprotein C-III and apolipoprotein E are increased in PI-treated patients [176-179].

## 22. Metabolic syndrome

In the general population, MS is described as an association of increased upper-body fat, particularly in the visceral area, with IR responsible for and revealed by metabolic altera-

tions, including increased LDL, decreased HDL, increased triglycerides, increased glycemia or diabetes and increased blood pressure [180-182]. All these parameters constitute a constellation of major CV risk factors [180]. This situation also includes low-grade inflammation and a prothrombotic state [7].

The pathophysiology of MS is complex – genetic factors, aging and weight gain associated with sedentariness and food habits constitute major risk factors. Also, decreased mitochondrial function related to aging [183] and an age-related redistribution of fat towards the central, visceral areas are involved, leading to IR and metabolic abnormalities [7].

The components of the HIV lipodystrophy syndrome(s) bear a striking resemblance to those of MS [123]. Both can present hyperinsulinemia, glucose intolerance, central or abdominal obesity, hypertension, atherogenic lipid profile, hyperuricemia, prothrombotic and proinflammatory states [123].

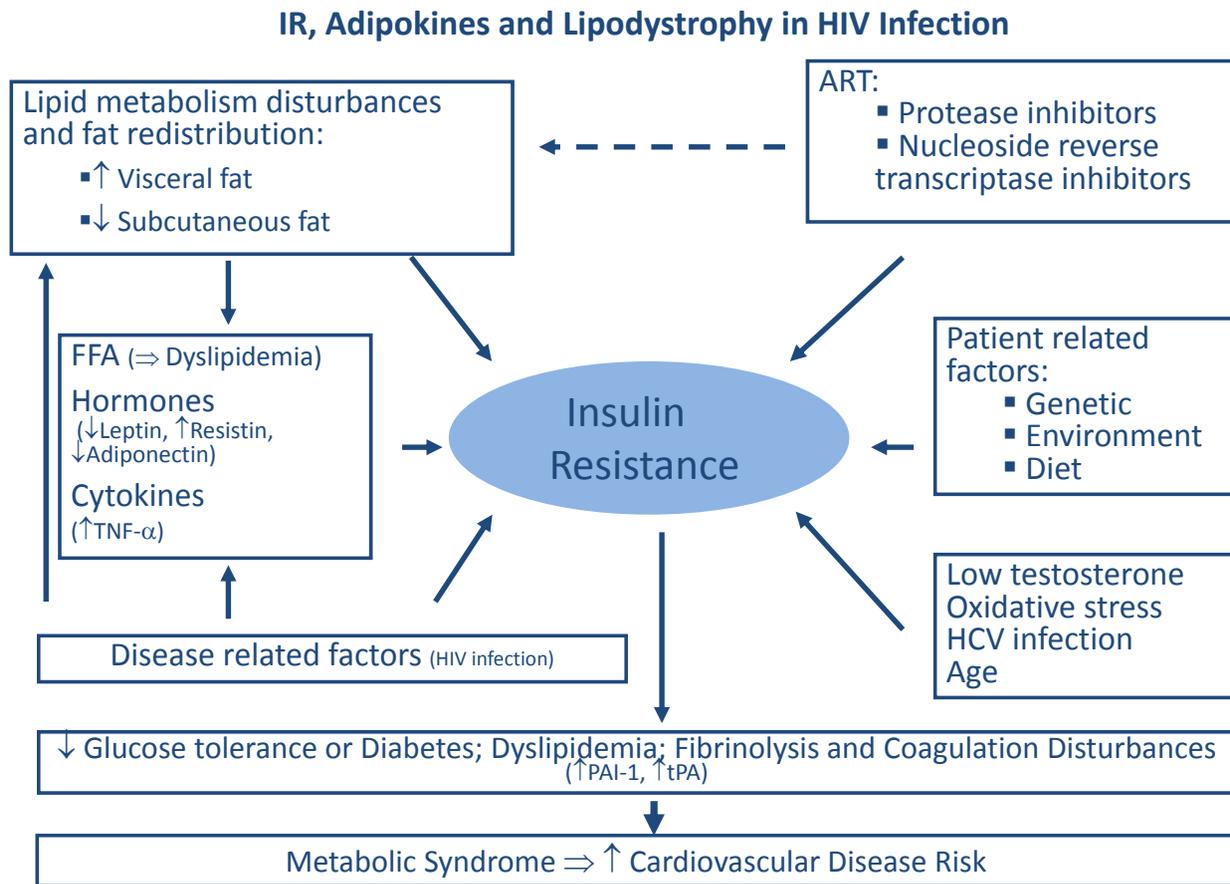
Liver lesions of nonalcoholic steatohepatitis (or NASH) are a complication of MS, with a possible evolution towards severe liver complications such as cirrhosis. HIV-infected patients, with IR in the context of a severe lipodystrophy, present an increased risk of liver lesions [184]. Moreover, as HCV infection has been associated with steatosis and hepatic IR resulting from viral or metabolic effects, HCV co-infection could aggravate the metabolic and liver status of HIV-infected patients [185]. HIV-infected patients with MS are more likely to have higher values of carotid intima-media thickness (cIMT) and detectable coronary artery calcium score [186].

### **23. Clinical sequelae associated with HIV and HIV-lipodystrophy**

Different studies suggest that the CV risk is increased among HIV-infected patients on cART and the responsible mechanisms are complex: in addition to the direct effect of the virus on the vasculature, the toxicity of antiretroviral drugs and the set of metabolic alterations aggregated in the MS are involved [187]. Whether the increased CV risk is due to HIV infection itself, to ART, or to a synergistic interaction between these factors, remains to be established [167]. HIV infection itself may increase CV risk. The HIV surface glycoprotein gp120 can stimulate endothelial cell production of tissue factor, an early step in the development of atherosclerosis [188]. Both HIV infection and ART promote atherosclerosis and its clinical manifestations through inflammatory mechanisms involving endothelial cells, either directly or indirectly, and also by inducing lipid alterations [189, 190].

Furthermore, some data suggest that endothelial dysfunction, impaired fibrinolysis, and excess inflammation are more common in HIV-positive patients than in general population, which may contribute to an increased CV risk [191]. At the same time, cIMT and coronary calcification assessments suggest increased incidence of atherosclerotic disease and premature occurrence of arterial atherosclerotic lesions among HIV-infected individuals [192]. Surrogate markers of atherosclerosis, including abnormal cIMT [193, 194], altered endothelial reactivity [195], abnormal coronary calcium scores [196], higher than expected C-reactive

protein levels and abnormal proinflammatory and prothrombotic indices [197], all suggest a state of increased atherosclerotic risk [123].



**Figure 7.** The relationship between HIV infection, lipodystrophy, ART, insulin resistance, adipokines, metabolic alterations, metabolic syndrome and cardiovascular disease risk

Endothelial cells have been shown to be variably permissive for HIV infection. The HIV virus itself is able to penetrate coronary artery and brain microvascular endothelial cell membranes and to initiate inflammatory and biochemical intracellular reactions [198, 199]. The activation of endothelium induced by either HIV infection itself or by a leukocyte-mediated inflammatory cascade triggered by the same virus leads to an increased expression of endothelial cellular adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), E-selectin, P-selectin, thrombomodulin, tissue plasminogen activator (tPA), and PAI-1. A significant association between increasing serum concentrations of adhesion molecules and risk of future myocardial infarction has been shown in apparently healthy men and women, and these molecules are now considered as soluble biomarkers of endothelial inflammation and early atherosclerosis [200, 201]. Increased serum levels of ICAM-1, VCAM-1, E-selectin, and thrombomodulin were demonstrated in patients with advanced HIV infection and opportunistic diseases. A correlation between ICAM-1 concentrations and the progression of disease as well as the reduction of CD4 lymphocyte count was also reported. If

circulating adhesion molecules indicate vascular endothelium injury, it seems clear that endothelium injury is associated with the progression and severity of HIV disease [202]. cART should reduce the endothelial damage by controlling HIV infection, but it would also contribute to stimulating endothelial activation by deranging both lipid and glucose metabolism [167]. Some PIs, as ritonavir and indinavir are able to directly cause endothelial dysfunction, with mitochondrial DNA damage and cell death, independently of lipid profile [203]. cART may promote atherosclerosis both by direct effects on endothelial cells and by indirect effects associated with metabolic disturbances [167].

Elevated serum levels of PAI-1, tPA, and CRP, as well as reduced serum levels of adiponectin could be considered biochemical markers of endothelial dysfunction, metabolic alterations, and CV risk in HIV-infected patients [192]. Some authors suggested that the pathogenetic mechanism responsible for carotid lesions associated with HIV infection may be more similar to an inflammatory process than to the classical atherogenesis [204, 205]. Some retrospective and prospective studies have shown that the incidence of myocardial infarction in HIV-positive subjects treated with ART tends to be higher than in the general population, particularly in those receiving a PI-based treatment [206]. However, reports from large observational studies demonstrate that there is still considerable controversy regarding the association of cART, particularly PI-based combinations, with increased incidence of coronary heart disease risk [167].

Moreover, prospective studies involving large cohorts of HIV-infected patients have documented an increased incidence of myocardial infarction and cerebrovascular diseases in association with a prolonged exposure to cART. However, the absolute risk of CV events remains low, and should be balanced against the remarkable benefits of cART in terms of improvement in immune function and related morbidity and mortality [167].

In other words, incidence of CV disease in successfully cART-treated HIV-infected patients is low. However, the risk of CV disease is increased compared with that of uninfected people. This fact is due in great part to a higher prevalence of underlying traditional CV risk factors that are mostly host dependent. HIV may additionally contribute through immune activation, inflammation, and immunodeficiency. In a more modest way than HIV infection, the type of ART may also contribute, mainly through the impact on metabolic and body fat parameters, and possibly through other factors that are currently unclear. From the CV perspective, the benefits of ART outweigh any potential risk [207, 208].

## 24. Conclusions

Human lipodystrophies are a heterogeneous group of diseases with generalized or partial fat loss. They include rare genetic conditions or more frequent acquired forms, and may be old, or more recent, such as HIV-related lipodystrophy. Almost all lipodystrophies are associated with metabolic alterations including IR, diabetes, dyslipidemia and early CV disease. In this new context of increased aging of HIV-infected patients, increased metabolic and CV complications are to be expected due to high incidences of smoking status, over-nutrition

and reduced exercise, lipodystrophy, dyslipidemia, altered glucose tolerance with IR and low-grade infection with the ongoing drug-induced inflammation. It is important to be aware of these alterations and to apply risk-modification strategies to reduce CV risk in the HIV-infected patients.

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