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Critical review

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Adipose tissue as an endocrine-immune organ and endocrine-metabolic changes in patients with HIV-associated lipodystrophy syndrome

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Abstract

Introduction

The advent of Antiretroviral Therapy (HAART) as a treatment for Acquired Immune Deficiency Syndrome, in the 90's, showed increased survival rates and improved quality of life of HIV infected patients, making HIV infection a chronic disease. This critical review aims to discuss the mechanisms underlying lipodystrophy and their effects, focusing on adipose tissue as an endocrine and immune organ.

Discussion

The aetiopathology of lipodystrophy syndrome is complex, it involves an interaction of several factors. The use of HAART in patients plays a fundamental role in the aetiopathology of lipodystrophy syndrome, a complex pattern of insults in the adipose tissue occurs, and as a result, the adipocyte differentiation is impaired and metabolic changes take place through different mechanisms.

Conclusion

The HIV infected patients in chronic use of the Antiretroviral Therapy, commonly, develop the lipodystrophy syndrome as a result, mainly, of insults in the adipose tissue, although its genesis has not been clarified yet. Therefore, taking into consideration the many manifestations of the syndrome, such patients hold high risk endocrine-metabolic profile for cardiovascular events.

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Introduction

The advent of Highly Active Antiretroviral Therapy (HAART) as a treatment for Acquired Immune Deficiency Syndrome (AIDS), in the 90's, showed increased survival rates and improved quality of life of Human Immunodeficiency Virus (HIV) infected patients, making HIV infection a chronic disease, which lead to an increased prevalence of other pathologies, such as, HIV-associated lipodystrophy syndrome (HIVLS), a clinical picture which consists of changes in body fat distribution and endocrine-metabolic changes[1].

In HIVLS, there can be central lipohypertrophy, in which accumulation of fat in torso and/or abdomen, breasts and posterior cervical region can occur; peripheral lipoatrophy, in which thinning of adipose tissue may occur in the face, anterior and lateral cervical, lower and/or upper limbs or buttocks; or mixed lipodystrophy, in which both alterations can occur. These changes can take place under different intensities[2].

This syndrome can present, associated with changes in body fat distribution, other metabolic features, such as dyslipidemia and insulin resistance[1]. This critical review aims to discuss the mechanisms underlying lipodystrophy and their effects, focusing on adipose tissue as an endocrine and immune organ.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Physiopathology of HIVLS – lipoatrophy and lipohypertrophy

Several risk factors can be associated to lipodystrophy. The risk factors associated to greater risk of lipohypertrophy are: the use of antiretroviral therapy, duration of antiretroviral therapy[3], the use of protease inhibitors, female gender, greater amount of body fat before antiretroviral therapy[4] and undetectable viral load.

As to lipoatrophy, the risk factors are: age (patients over 40 years old), low body fat prior to antiretroviral therapy, lower levels of CD4+ T cells[5], the use of stavudine, duration of antiretroviral therapy treatment[6] and HIV infection time[7].

Studies indicated the use of HAART, age, dyslipidaemia, pre-infection[8], and CD4+ T cells values[4], as risk factors regardless of the clinical form.

There are distinct physiopathological mechanisms of lipodystrophy, which is the reason why there is greater knowledge regarding lipoatrophy.

Among the physiopathological mechanisms, mitochondrial toxicity is one of the most important. In addition to the impaired expression of genes associated with adipogenesis, the adipose tissue in patients with HIVLS, especially those who receive nucleoside analogues (NRTIs) show a reduction in the expression of mitochondrial DNA (mtDNA)[9]. It was suggested that suggests that depletion of mtDNA mediated by NRTI, plays a role in lipodystrophy's pathogenesis[10]. In spite of that, a simple explanation to NRTIs

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action based on the reduction of oxidative burst is not enough to adipocyte differentiation and increased lipolysis may be involved[11, 12]. It was reported that thymidine analogues, stavudine and zidovudine, caused a decrease in lipid content, mitochondrial activity and survival of adipocytes in vitro[11].

Protease inhibitors can also cause lipoatrophy by inhibiting lipogenesis and adipocyte differentiation, stimulating lipolysis and preventing the nuclear localization of sterol regulatory enhancer–binding protein 1 (SREBP1)[13].

Although the consequences of mtDNA depletion are not completely comprehended, it is known that damages to mitochondrial oxidative metabolism can lead to disturbs in gene expressions (adiponectin, for example) through retrograde signalling and oxidative damages in lipids management, favouring the accumulation of fat and mitochondrial lipotoxicity[9]. Thereby, impaired mitochondrial function appears as an additional characteristic to changes in lipoatrophic subcutaneous fat[14].

Through subcutaneous adipose tissue biopsy of HIV-1 infected patients with lipoatrophy, high levels of expression of inflammatory markers as tumor necrosis factor (TNF-α) were observed, IL-6, IL-8 and IL-18. The expression of the first two is positively correlated with apoptosis and negatively with the expression of adipogenic markers, considering the proinflammatory role of cytokines in adipocyte differentiation and viability.

Certain similar alterations in inflammatory markers were observed, such as induced TNF-α, while it differs from other subcutaneous adipose tissue markers, such as the deficiency in the induction of monocyte chemoattractant protein-1 (MCP-1)[15]. Still regarding immunohistochemistry, the expression of tumour growth factor beta (TGF- β), TNF-α and caspase 3 was analysed in the adipose tissue of patients with lipodystrophy and found an enhanced expression of caspase 3 and TNF-α, which has a correlation with the expression of TGF-β, suggesting a negative feedback

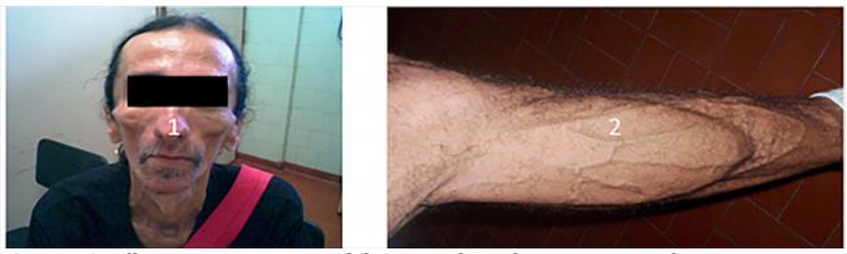

Figure 1: Illustrative images of lipoatrophic charateristics of HIV- associated lipodystrophy. 1 Patient with lipoatrophy in face, emphasizing facial lines, by loss of subcutaneous fat. 2. Patient with lipoatrophy in lower limbs, emphasizing appearence of blood vessels. Font: Ambulatory of lipodystrophy patients from University Hospital João de Barros Barreto (HUJBB), Belém-PA, Brazil. Photos: Prof. Dr. Rosana Libonati.

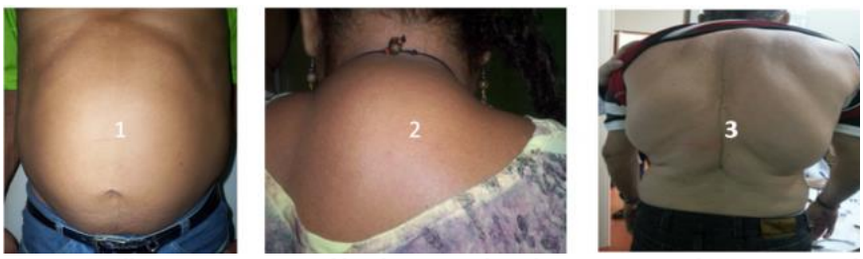

Figure 2: Illustrative images of lipohypertrophic characteristics of HIV-associated lipodystrophy. 1 Patient with abdominal lipohypertrophy. 2. Patient with dorsal cervical lipohypertrophy (buffalo hump). 3. Patient with lipohypertrophy in subscapular area. Font: Ambulatory of lipodystrophy patients from University Hospital João de Barros Barreto (HUJBB), Belém-PA, Brazil. Photos: Prof. Dr. Rosana Libonati.

between an inflammatory response and an anti-inflammatory response. The inflammatory response was more important in male patients[16]. The continued use of HAART, specially of protease inhibitors, leads to alterations of Peroxisome Proliferator -Activated Receptor-gamma (PPARγ) of macrophages stimulating their transformation to M1 or inflammatory or classical activated macrophage which can induce apoptosis, increase secretion of inflammatory cytokines, such as TNF-α and IL-6, and contribute to mechanisms of lipodystrophy's clinical expression[17].

The lipohypertrophy-associated mechanisms have not been established yet, however, lipolysis is more intense in the subcutaneous adipose tissue by inflammatory cytokines' activity, such as TNF-α e a IL-6, nervertheless, these effects were not the same as observed in the visceral adipose tissue[18]. Increased visceral adiposity is presented as a protective mechanism of the organism, due to acquired generalised lipodystrophy (AGL), in the attempt of minimize lipotoxic damage to other tissues[19, 20]. Table 1 summarizes the main mechanisms associated lipo-dystrophy.

HIV-associated lypodystrophy syndrome and endocrine and metabolic alterations

The HAART consists of a specific treatment developed to improve the health status of HIV-1-infected patients. It consists in a combination of a NRTI, non-nucleoside analogue of the viral reverse transcriptase (NNRTI), associated with protease inhibitor (PI). Almost half of HIV-1-infected patients under HAART (40%–50%) present changes in adipose tissue distribution (known as lipodystrophy) in addiction to systemic metabolic complications[1].

Lipodystrophy is classified into three clinical categories: lipohypertrophy, lipoatrophy, and mixed syndrome. This classification considers the redistribution of body fat in individuals living with HIV. Lipohypertrophy is characterized by accumulation of fat in the abdominal area, visceral fat accumulation, dorsal-cervical area

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(known as buffalo hump) and breasts. Lipoatrophy occurs when the patient has lost subcutaneous fat in the face, buttocks, and upper and lower limbs, making its blood vessels prominent. The mixed form refers to a combination of both lipohypertrophy and lipoatrophy[21,22] (Figure 1 and Figure 2).

It is necessary to remember that these alterations can reach patients differently. Besides, this group of patients are more susceptible to some metabolic alterations such as dyslipidaemia, insulin resistance and enhanced risk of cardiovascular disease.

A frequency of 21.1 % of diabetes mellitus, 48.7% of mixed dyslipidaemia, 32.9% of hypertriglyceridemia and 10.5% of low HDL was reported[22], however, in another study higher frequencies were observed, such as, 61.6 % of hypertriglyceridaemia and 75.8 % of low HDL[3], which suggests that these findings depend on the study of each individual case.

The association between the clinical signs of lipodystrophy with a specific drug of HAART is not well established yet. It is suggested that NRTIs favour lipoatrophy and PIs tend to promote visceral lipohypertrophy and systemic metabolic disturbances. Nevertheless, recent studies suggest they act in synergism to generate the characteristic signs of the redistribution of body fat and thus contribute to associated metabolic alterations[23].

The adipose tissue as a secretory organ releases hormones, such as leptin and adiponectin and cytokines such as TNF-α, IL-1 e IL-6 that present important immune function in inflammatory response, which will reflect in metabolic alterations in lipodystrophy syndrome[24]. Table 2 synthesizes the main factors secreted by the adipose tissue related to endocrine and immune response and the consequences of lipodystrophy in them.

In lipoatrophy, a decrease in the expression of PPARγ occurs[25], leading to alterations in the lipid metabolism, causing a reduction of lipoprotein lipase, which is the enzyme responsible for the absorption of fatty acids by the adipose tissue and fat replacement, that acts by hydrolysis of circulating triglycerides, which can also justify the hypertriglyceridaemia observed in lipodystrophy. The expression of the insulin-sensitive glucose transporter GLUT4, is also reduced, leading to impaired glucose uptake and consequent reduction in triglyceride synthesis[25].

Table 1: Physiopathogenical mechanisms of lipodystrophy related to HIV.

Source (first author, reference)	Lipodystrophy analyzed	Mechanism analyzed	Physiopathology
Villaroya[9]	Lipoatrophy	Mitochondrial toxicity	Reduced gene expression of mtDNA
Caron[11]; Hadigan[12]	Lipoatrophy	Increased lipolysis	Decreased Adipocyte differentiation
Caron[13]	Lipoatrophy	Inhibition of lipogenesis	Impair nuclear localization of SREBP1
Oliveira[16]	Lipoatrophy	Citokines activity	Increased expression. of TNF-α & caspase 3
Sattler[17]	Lipoatrophy	Citokines activity	Increased expression. of TNF-α and IL-6
Maraldi[19]; Gan[20]	Lipohypertrophy	Increased visceral adiposity	Organic protection against elevated concentrations AGL

Another major alteration that is probably related to the impairment of the PPARγ activity is the reduced expression of adiponectin. The known role of adiponectin in the improvement of glucose uptake mediated by insulin in peripheral tissues and liver to sensitize insulin-dependent suppression of glucose production causes such reduction to be considered a major contributor to insulin resistance[26].

In a study with 112 HIV infected patients treated with HAART, observed higher levels of adiponectin in patients without lipodystrophy, compared to individuals that showed body fat redistribution. This study suggests that adiponectin would be inversely correlated with visceral fat mass, triglycerides, insulin resistance and directly associated to HDL cholesterol and peripheral fat in HIV infected patients treated with HAART[27].

As to leptin, it is reduced in patients with lipoatrophy, low levels of leptin were independently associated with insulin resistance in patients with lipoatrophy, posteriorly to peripheral and total body fat adjustment. This has to do, probably, to reduction of total body fat and consequent reduction in leptin production by adipocytes. Individuals with lipohypertrophy showed the highest serum leptin levels, probably due to a state of leptin resistance or excessive production of leptin by adipose tissue[28].

Free fatty acids from lipolysis in visceral fat, in patients with lipohypertrophy, released in great quantities in portal circulation play an important role in the genesis of tissue resistance to insulin action, both hepatic and peripheral levels. The increase in waist-hip ratio, central adiposity, triglycerides and LDL and decrease in HDL were noticed in women with HIV-associated lipodystrophy, which is similar to metabolic syndrome. In addition to the cardiovascular risk factors, C-reactive protein and IL-6 were elevated and adiponectin was reduced[29].

It is interesting, as observed that pro-inflammatory cytokine, such as TNF-α, is elevated in patients with HIV-associated lipodystrophy, and it is an important factor in insulin resistance[30].

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Table 2: Adipose tissue and main altered adipokines in lipodystrophy related to HIV.

Factor secreted	Endocrine and immune response	Alterations in lipodystrophy
Adiponectin	Induces fatty acid oxidation and glucose uptake; improves peripheral insulin sensitivity	Low levels; insulin resistance; hypertriglyceridemia
Leptin	Mediates energy homeostasis; promotes satiety; decreases gluconeogenesis in the liver	Low levels
IL-6	Negatively correlated with the expression of adipogenic markers	Increased expression on lipoatrophy
TNF-α	Negatively correlated with the expression of adipogenic markers	Increased expression on lipoatrophy

Therefore, both lipoatrophy and lipohypertrophy are alterations of the adipose tissue that can lead to insulin resistance and dyslipidaemia, with major underlying inflammatory response.

Conclusion

HIV infected patients, in chronic use of HAART, commonly develop the lypodystrophy syndrome and have in the aggression towards the adipose tissue, its main form of attack, even though its genesis remains not completely clarified. Among them, we mention mytochondrial toxicity, with a highlight on the alterations of the adipose tissue, not only when it comes to endocrine functions (eg. adiponectin and leptin) and immune functions (interleukins), but also when it involves body distribution, resulting in clinical evidence of seemingly peripheral lipoatrophy and/or central lipohypertrophy. The HIV lypodystrophy syndrome enables endocrine-metabolic changes, such as insulin resistance and alterations in glucose tolerance profile, with a tendency to evolving into diabetes, and in some specific cases, the syndrome also enables non-alcoholic hepatic steatosis.

Dyslipidaemic alterations are present in the majority of patients, which makes it easier for the prevalence of the metabolic syndrome. Therefore, taking into consideration the manifestations of the syndrome, these patients hold a high risk endocrine-metabolic profile for cardiovascular events. Due to this fact, it becomes necessary the investment in strategies that aim for prevention and control of possible comorbidities in order to enhance the patients quality of life.

Abbreviations list

AIDS: Acquired immunodeficiency syndrome; HIV: Human Immunodeficiency Virus; HAART: Highly Active Antiretroviral Therapy; PI: Protease Inhibitor; NNRTI: Nonnucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleoside Reverse Transcriptase Inhibitor; HIVLS: HIV-associated lipodystrophy syndrome; PPAR-gamma: Peroxisome Proliferator-Activated Receptor-gamma; mtDNA: mitochondrial DNA; TNF-α: Tumour necrosis factor alpha; TGF-β: Tumour growth factor beta; MCP-1: Monocyte chemoattractant protein-1; SREBP-1: Sterol regulatory enhancer–binding protein 1; AGL: Acquired generalized lipodystrophy.

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