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Facial Lipoatrophy and AIDS

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1. Introduction

Since AIDS has become a chronic and manageable disease, it is essential to recognize and treat the conditions associated with the infection itself and with the adverse effects of antiretroviral drugs. Facial lipoatrophy associated with HIV / AIDS has become epidemic. Therefore, all of those involved in assisting this group of patients should recognize the signs of lipodystrophy syndrome as well as the recommended treatment options, which should always be incorporated into the therapeutic arsenal for patients with HIV/AIDS.

2. Lipodystrophy associated with HIV/AIDS

2.1 Background

From 1996, a series of new anatomical and metabolic changes began to be described in patients with HIV/AIDS, especially in those undergoing highly active antiretroviral therapy. The patients presented peripheral fat atrophy as well as central fat accumulation. At the same time, it was observed that redistribution of body fat was accompanied by insulin resistance and several abnormalities in serum lipids. These changes were later described in general terms as HIV-associated lipodystrophy and/or HIV lipodystrophy syndrome (HLS).

The HLS was officially described by the Food and Drug Administration (FDA), the United States agency regulating the release and use of drugs, in 1997.

The first morphological signs of HLS were described about two years after the introduction of protease inhibitors (PI). However, the introduction of PI coincides with the inclusion of a second nucleoside analog reverse transcriptase inhibitor called stavudine.

Initially, HLS was called Crixbelly, since the first cases of redistribution of body fat were observed after the use of Crixivan® (Indinavir), a drug belonging to the PI class. The association between the use of Indinavir and the redistribution of body fat was described in 1998, with the use of computed tomography showing the increase in visceral fat in these individuals. With the emergence of new PI, it was concluded that the redistribution of body fat was not an exclusive effect of Indinavir, and the name was abandoned.

After observing clinical similarities between patients with Cushing's syndrome and patients with HLS, Miller at al. (1998) began to call it "pseudo-Cushing's syndrome". However,

subsequent studies showed no changes in the hypothalamic-pituitary-adrenal axis of HIV-seropositive patients, and this nomenclature was also abandoned.
Currently, several synonyms are used for HLS, such as body fat redistribution syndrome, metabolic syndrome associated with antiretroviral therapy or, more recently, HIV/ART-associated dyslipidemia.

2.2 Clinical aspects

The first body changes to be noticed were accumulation of fat in the abdominal region and on the back of the neck, the so-called buffalo hump.
Other anatomical changes include lipoatrophy of the face, arms and legs and prominence of superficial veins, associated or not with accumulation of fat in the abdomen, neck and breast. The metabolic changes include lipid changes and abnormalities in glucose homeostasis. Metabolic changes may be associated or not with anatomical changes.
Lipid changes found in HLS are an increase in serum triglycerides (TG) and/or total cholesterol levels at the expense of low-density lipoproteins (LDL), with a tendency to decreased levels of high-density lipoproteins (HDL).
Hypertriglyceridemia is mainly due to elevated levels of *de novo* lipogenesis and to delayed clearance of TG in the postprandial period. Studies have also revealed that a significantly higher proportion of patients receiving PI presented increased fasting serum levels of apolipoproteins B and E, possibly due to their increased synthesis, which could be related to the manifestation of hyperlipidemia. Moreover, the so-called metabolic syndrome, in which abdominal obesity - a component of HLS - correlates with changes in lipid metabolism, was present in 18% of the patients undergoing ART, especially in patients using PI.
Glucose abnormalities may manifest as glucose intolerance, peripheral insulin resistance or diabetes mellitus (DM).
The mechanisms of action through which ARV such as protease inhibitors cause insulin resistance are a reduction in glucose uptake mediated by insulin in skeletal muscle and adipocytes, interfering with glucose transmembrane transporters GLUT-4, and their effect on the transcription factor sterol regulatory element binding protein-1c (SREBP-1), affecting the metabolism of glucose as they produce imperfect expressions of the gamma receptor activated by peroxisome proliferator (PPAR-gamma).
The lactic acidosis that occurs in the syndrome is mainly caused by nucleoside analog reverse transcriptase inhibitors. It is secondary to the mitochondrial dysfunction caused due to inhibition of mitochondrial deoxyribonucleic acid (DNA) polymerase by this class of drugs. The establishment of lactic acidosis is slow and the symptoms are not specific.
It is unclear whether the loss of bone mineral density is a component of the same syndrome. Avascular necrosis has been considered a complication of HLS, since hyperlipidemia and the HIV infection itself are known risk factors for osteonecrosis of the femoral head.
Metabolic changes are associated with increased risk of cardiovascular events.
Hyperinsulinemia associated with insulin resistance is a risk factor recognized in patients not infected with HIV and may contribute to increased risk of acute myocardial infarction in patients using ARV.
Thus, HIV-positive patients, with significantly higher prevalence of elevated fasting glucose and triglyceride levels and low levels of HDL cholesterol are at increased risk of

atherosclerosis, coronary heart disease and diabetes mellitus. The risk of developing diabetes is 6 to 10% in these patients, and is further increased in obese patients coinfected with hepatitis C or with a family history of DM . There are reports of an increase of 16% in the incidence of myocardial infarction per year of antiretroviral treatment.

Among the fat redistribution anatomical changes, three groups are identified: lipoatrophy, lipohypertrophy and mixed forms.

Lipoatrophy and lipohypertrophy may occur independently or may occur together in the same patient.

There is central or localized accumulation of fat in lipohypertrophy. Accumulation of fat may occur in the abdomen, neck, back, breast and other sites in a localized form. The abdomen acquires a global aspect and fat tissue is commonly deposited intra-abdominally, in viscera or between them. Increased intra-abdominal pressure may predispose to abdominal hernias that may eventually require surgical correction.

Accumulation of fat in the upper trunk surrounding the chest and extending up to the armpits was observed in male patients, as well as accumulation of fat in the anterior cervical region and in the suprapubic region in men and women.

An increase in the breasts of female patients mostly occurs due to a fat component and is not necessarily associated with glandular hypertrophy. In male patients, gynecomastia can occur (glandular hypertrophy) or pseudo-gynecomastia (fat accumulation).

Lipohypertrophy is more associated with older patients who are initiating treatment, using protease inhibitors, and who have more elevated body mass.

Loss of peripheral subcutaneous tissue is observed in lipoatrophy. In addition to that, upper and lower limbs get thinner, the skin gets thinner and allows almost anatomical visualization of muscle groups and superficial blood vessels. This condition may give the patient a pseudo-athletic aspect. Evidence of blood vessels is also often confused with venous insufficiency (pseudo varicose veins).

For some authors, the heterogeneity of the findings concerning HIV-associated lipodystrophy may reflect the existence of more than one syndrome.

2.3 Diagnosis

There is still no universally accepted definition for HLS, which explains the difficulty in determining a case as wells as its prevalence, etiology and treatment.

The most commonly used method to determine a case of lipodystrophy includes the subjective description of changes in body fat. Two multicenter studies were conducted in an attempt to define a case of lipodystrophy. The Lipodystrophy Case Definition Study compared patients with and without clinical evidence of lipodystrophy, in agreement between patients and physicians. Laboratory, anthropometry and radiology data, such as dual X-ray absorptiometry (DEXA) and computed tomography (CT), were compared between the two groups of patients. The definition of lipodystrophy generated had sensitivity and specificity of 80%, but has proved to be too complex to be used in clinical practice. The Fat Redistribution and Metabolic Changes in HIV Infection Study compared laboratory testings and anthropometry and radiology data on distribution of body fat among HIV-infected and non-infected patients. The study showed that the only change in body fat associated with HIV infection was generalized lipoatrophy. The results do not explain the high prevalence of intra-abdominal obesity in HIV-positive patients, but is in accordance with other studies, which claim that lipoatrophy is the hallmark of body changes in HIV-infected individuals.

Some diagnostic criteria were proposed in the First International Workshop on Lipodystrophy and Adverse Reactions to Drugs, held in June 1999 in San Diego. The clinical criteria described were sunken face, depressed temples, sunken eyes, prominent zygomatic arch, emaciated appearance, prominent non-varicose veins in the arms and legs, loss of skin folds, loss of the contours and fat from the gluteal region. Accumulation of fat was categorized into 5 areas: increased abdominal girth, breast enlargement, dorsocervical fat accumulation, facial fat accumulation (although possibly rarer than facial lipoatrophy), and the presence of lipomas. Methods for evaluation and monitoring of fat deposition include patient's report, clinical evaluations, anthropometric measurements and imaging studies.

Objective criteria for diagnosis of lipodystrophy have not been established yet. The absence of standardized values in relation to fat in the general population and the heterogeneity of clinical manifestations of lipodystrophy make the diagnosis even more difficult. A gold standard technique for measuring body fat is not available yet. However, some methods such as anthropometry, bioelectrical impedance analysis (BIA), DEXA, computed tomography, magnetic resonance imaging (MRI) and ultrasound have been used.

Anthropometry and impedance analysis cannot measure localized fat. CT and MRI methods are costly, which restricts their use. The use of US is promising because it is simple, noninvasive, available and low-cost, although it is more operator-dependent than the other techniques. The fact that measurement of absolute values of localized fat does not elucidate the occurrence of body-fat changes is also a limiting factor.

High-resolution MRI allowed the identification of a clear disruption in the adipose tissue of HIV patients, and changes in the tissue architecture seem to appear earlier than changes detected by DEXA or by clinical examination.

The US showed moderate agreement between its findings and the lipoatrophy reported by the physician or patient in clinical evaluation. According to the authors, the anatomy of the face, the patient's age and quality of the skin affect how subcutaneous fat is perceived externally. Even so, they see the US as a potentially useful tool in evaluating patients due to its low-cost, accessibility and absence of radiation.

Considering all of these limitations, describing the loss or accumulation of fat in specific areas and determining the degree of intensity through clinical evaluation and in a way that doctors and patients agree continue to be the best way to define the problem individually.

Most studies on lipodystrophy syndrome are based on the presence of symptoms subjectively reported by patients, clinical signs found in the physical examination carried out by a doctor or on a combination of both. These observations may or may not be confirmed by diagnostic methods.

Objective measurement of facial fat is more difficult to obtain than measurement of body fat. A questionnaire of the FRAM study (2006) asked patients to assess any change in fat in the region of the cheeks, near the nose and mouth, and give it a score from 1 to 6. A similar score system varying from 1 to 7 was used by health professionals to assess fat in the region of the cheeks of the participants. A longitudinal ratio of the data obtained from patients and healthcare professionals can be used, as well as monitoring based on serial photographs, if the patient consents.

The diagnosis of lipoatrophy is still often based on the patient's perception and on clinical evaluation, which have shown a good correlation.

2.4 Epidemiology

It is very difficult to evaluate the prevalence of HLS, since there is no clear definition of the disease, with well-defined criteria for characterizing a case. Also, there are no accurate

diagnostic methods for detection of fat redistribution or quantification of loss or gain of body fat.

As the condition is characterized by several changes in body composition, whether atrophy, hypotrophy or hypertrophy, which may be present together or separately, it becomes more difficult to fit the patients into well-defined groups.

The prevalence of lipodystrophy reported in the literature varies widely, with articles that describe rates of 7 to 84% among patients with HIV/AIDS using antiretrovirals or not. Such variations are possibly due to the diagnostic criteria used, despite the lack of standardization for these criteria.

Generally speaking, the prevalence of at least one body change is approximately 50%.

A study conducted by Cabrero et al. (2010) with 965 patients in 98 different health facilities showed that the patients noticed some kind of body change in 55.1% of the cases. Concerning the physicians' perception in relation to body changes, this ratio changes to 55.2% of the cases. The most commonly reported change was lipoatrophy, which was mentioned by 46.8% of the patients and 49.4% of the physicians, followed by lipohypertrophy. There was no gender difference in terms of perception of body changes. The concordance between patients and physicians in terms of the changes detected was 83%.

Hendrickson et al. (2009) also agree that lipoatrophy is one of the most common manifestations associated with the use of ARV and cite a frequency range of 13 to 63%.

Viskovic et al. (2009) believe that lipoatrophy is the most common and disfiguring of the body changes of the syndrome. They evaluated 151 patients with HIV, of whom about 39% reported lipoatrophy in some place, while about 45% of the physicians noticed fat loss in the clinical examination. Among the patients, 11% reported facial lipoatrophy, while the doctors noticed clinically detectable facial lipoatrophy in 15% of the patients.

2.5 Physiopathogenesis

The exact mechanism that leads to the development of anatomical and metabolic changes is still unclear. Several hypotheses have been suggested and, separately, none of them explain all aspects of these changes, which are probably multifactorial in origin. Some hypothesis are: mitochondrial toxicity related to the use of NRTIs; dysregulation of the tumor necrosis factor α (TNFα); inhibition of cytochrome P 450, related to protease inhibitors; hypercorticolism (pseudo Cushing's syndrome); local effects of HIV on production of cortisol and changes in other steroid hormones, among others.

When HLS arose, it was initially associated with the use of PI, a frequent component of ART. Studies have suggested that PI mediated lipoatrophy by changing the regulatory element of steroids and binding to protein 1, which is involved in the differentiation of adipocytes.

Ledru et al. (2000) have also showed that PIs have an effect on cellular proteases, which contributes to the accumulation of T cells, which produce TNFα. This seems to favor lipodystrophy as it contributes to changes in lipid metabolism. Other authors have also shown that TNFα levels and its receptors seem to be associated with the development of lipodystrophy in patients undergoing ART.

More recently, NRTI, another frequent component of ART, has been implicated as a cause of lipodystrophy.

Among the NRTIs, lipoatrophy is more associated with the use of stavudine and zidovudine. Lipoatrophy occurs in 30% of the patients after 2 years of use of stavudine, while it occurs in only 6% of the patients using tenofovir.

NRTIs deplete the deoxyribonucleic acid (DNA) of mitochondria, inhibiting mitochondrial DNA polymerase, which may result in apoptosis of adipocytes. It has been suggested that thymidine analogue NRTIs (stavudine, zidovudine) are more toxic to the mitochondrial DNA than the new non-thymidine analogue NRTI, such as abacavir; although all of the drugs belonging to this class can cause depletion of mitochondrial DNA.

Lipohypertrophy is more associated with the use of PIs; although efavirenz, an NNRTI, is involved in the appearance of pseudo-gynecomastia. Even though lipoatrophy is more associated with NRTI, efavirenz is also implicated in the progression of lipoatrophy.

Pacenti et al. (2006) identified genes modulated by PI and NRTI in early adipogenesis and suggest that the regulation of transcription factors and modulation of the Wnt gene are the route through which PIs lead to inhibition of adipocyte differentiation and negative regulation of the expression of specific markers for adipocytes such as leptin, MRAP, Cd36/FAT and S100A8. The effect of NRTIs on adipocyte differentiation and on gene expression profiling was milder than that of PI, although NRTI have shown modulation in the expression of tissue inhibitors of metalloproteinases and of transcription factors, such as Aebp1, which can act on the determination of the phenotype of adipocytes. The authors conclude that abnormal expression of these genes may underlie lipodystrophy associated with ART.

Genetic predisposition is another important factor in the pathogenesis of lipodystrophy. Ranade et al. (2008) identified a subgroup of patients who were especially vulnerable to the metabolic side effects of ART. After genetic analysis, they identified the resistin gene as being implicated in susceptibility to HIV-associated lipodystrophy.

Mitochondrial DNA haplogroup H was also identified as having strong association with the presence of atrophy in patients treated with nucleoside analog reverse transcriptase inhibitors. On the other hand, haplogroup T has shown borderline significance as a protective factor in the development of lipoatrophy in the same group of patients.

Some studies suggest that fat redistribution and metabolic abnormalities associated with HIV infection are related to changes in the endocrine function of adipose tissue. The adipose tissue, besides its function of storing fat, is an active endocrine tissue and the major determinant of insulin sensitivity, modulating the metabolism of glucose and lipids through the secretion of adipocytokines.

Verkauskiene et al. (2006) have shown that HIV-infected children with signs of redistribution of body fat have lower levels of adiponectin, associated with insulin resistance and dyslipidemia. In this study, leptin concentration showed no significant effect on the redistribution of body fat.

Lipoatrophy may occur in the absence of PI or NRTI therapy, with studies suggesting that antiretroviral drugs are not the only causal factor. In the HIV Outpatient Study (2001), 1,077 patients were evaluated in relation to changes in body fat distribution. Lipoatrophy was associated with the use of indinavir, a PI, for more than two years and with the use of stavudine, an INTR. However, independently, risk factors unrelated to drug use were strongly associated with lipoatrophy, including advanced age (> 40 years), white race, CD4 count <100 cells/mm3, decreased body mass index, and higher duration and severity of the HIV disease itself. The number of non-pharmacological risk factors increased the likelihood of developing lipoatrophy. The results suggest that the cause of lipoatrophy is multifactorial and that it may be a result of HIV infection of long duration. The expression of tumor necrosis factor α (TNF) by subcutaneous adipocytes *in vitro* is higher among patients with lipoatrophy, and this suggests that sustained activation of inflammatory cytokines in HIV infection may mediate lipoatrophy.

Interleukin 6 (IL-6) is a multifunctional cytokine that acts as an inflammatory, immune and metabolic mediator. Thus, its involvement in various events related to HIV infection is questioned. Increased production of IL-6 in patients infected with HIV and undergoing antiretroviral therapy is known. Saumoy et al. (2008) evaluated the influence of the IL-6-174G>C genotype on the risk of developing fat redistribution syndrome in HIV-infected patients undergoing combined antiretroviral therapy, but no significant difference was found.

Beyond the risk factors for HIV facial lipodystrophy which have already been identified, as the use of protease inhibitors, age, low CD4, high viral load, duration of ARV, white race and being female, other influences which have not yet been identified may also be associated with the development of HLS.

Whatever the etiology of HLS, be it caused by drug therapy, genetic predisposition, immune reconstitution, activation of cytokines, direct action of HIV infection, hormonal influences or other unidentified influences, the fact is that fat loss is apparently irreversible.

3. Facial lipoatrophy

3.1 Definition

Among the areas affected by lipoatrophy, one of the most common components of the syndrome, the face is the region where fat loss is more evident and impressive.

Facial lipoatrophy consists of a progressive loss of facial fat, mainly due to decreased malar fat (Bichat's fat pad) and temporal fat. Facial lipoatrophy stimulates the appearance of new skin furrows, the intensity of facial expression lines, in addition to intensifying areas of depression and visualization of the skull. All of this leads to wrinkling of the face, which precociously ages the individual; in women, loss of facial fat leads to a loss of femininity of the face. Moreover, the aspect of an emaciated and haggard face started to be seen once again as a 'facies of the disease', bringing back the old stigma of the "face of AIDS", in addition to the fear of involuntary disclosure of the diagnosis.

3.2 Classification

The lack of criteria for diagnosing and assessing fat loss in facial lipoatrophy (HIV facial wasting) is also a complicating factor in the establishment of a classification of disease severity.

The Facial Lipoatrophy Severity Index (FLSI) was developed by Brazilian physicians based on the parameters used for the classification of psoriasis severity. This tool aims at objectively measuring the degree of atrophy and improvement with treatment.

The FLSI evaluates three regions of the face. The malar region corresponds to the zygomatic and buccal areas, limited by the infraorbital border and lower edge of the mandible. Other anatomical structures considered are the zygomatic bone, the body of mandible projection, the zygomaticus major muscle, the canine fossa and maxilla.

The temporal region corresponds to the anterior temporal fossa, limited by the temporal line of the frontal bone and zygomatic arch (zygomatic process of the temporal bone and temporal process of the zygomatic bone).

The pre-auricular region corresponds to the masseter, between the zygomatic arch and the angle and lower edge of the mandible.

The depth and extent of the affected area in the malar, temporal, and preauricular regions are individually assessed. The depth of the atrophic areas is scored from 0 to 4, with 0 being absence of atrophy, 1, mild atrophy, 2, moderate atrophy, 3, severe atrophy, and 4, very severe atrophy. The extent of the affected area is scored from 0 to 5, with 0 being absence of

involvement, 1, involvement of less than 20% of the region assessed, 2, from 21 to 50%, 3, from 51 to 70%, 4, from 71 to 90%, and 5, from 91 to 100%.
A partial number is calculated for each area assessed by multiplying the score relative to depth by the one relative to the affected area and by a correction factor.
The correction factor was determined for each region of the face and corresponds to the degree of importance of each one of them in facial lipoatrophy. Correction factors are 0.7 for the malar region, 0.2 for the temporal region and 0.1 for the preauricular region.
Since fat loss is not symmetrical, the most affected side is considered in the assessment.
The partial scores of the three regions are then added, yielding a final score.
The Brazilian Ministry of Health classifies facial lipoatrophy into grades I through IV, based on the application of the FLSI.
Grade I, or mild facial lipoatrophy, corresponds to an FLSI from zero to 5.9. In such cases there is a slight depression, but there is no evidence of anatomical structures in the region nor loss of facial contour. The skin is normal to digital pressure.
Grade II or moderate facial lipoatrophy corresponds to an FLSI from 6.0 to 10. Depression is more visible with early visualization of anatomical structures, especially the zygomatic arch and increase of nasolabial folds. There is no loss of facial contour or projection of the maxilla. Upon digital pressure, the skin is normally depressed but return to the resting state is delayed.
Grade III or severe FL corresponds to an FLSI from 10.1 to 15. Structures in the malar region are well observed, such as the zygomatic bone, visualization of the canine fossa, partial visualization of the zygomaticus major muscle and mild or moderate depression of the lower edge of the mandible. Loss of facial contour and projection of the maxilla may occur. Upon digital pressure, the skin depresses slightly and is very slow to return to the resting state.
Grade IV, or very severe FL, corresponds to an FLSI from 15.1 to 20. There is almost complete visualization of the anatomical contours, revealing the bone and muscles of the face. There is loss of facial contour, with visualization of the upper and lower surfaces of the zygomatic arch in the temporal and preauricular regions. Upon digital pressure, the skin hardly depresses.
The FLSI can vary from 0 to 20, and the Brazilian Ministry of Health recommends treatment for patients with a score equal to or greater than 6.
Other classifications are adopted in the international literature, all of them with a degree of subjectivity for being evaluator-dependent.

3.3 Psychological impact

Changes in body image can be extremely disruptive in terms of psychosocial well-being, increasing the stigma of the disease. Although it is also visible in the arms, legs and buttocks, lipodystrophy is most apparent on the face.
With the progression of the symptoms, patients begin to show facies that are typical of lipodystrophy syndrome. This brought back the stigma of AIDS and the need for specialists working with HIV/AIDS patients to identify these changes and seek treatment options.
Patients have described facial lipodystrophy as a visible marker to identify HIV carriers, perceived as the "face of AIDS," or the "Kaposi's sarcoma of the 21st century." Moreover, it causes problems in social and family relationships, which in some cases trigger disturbances in social relations, leading to the isolation of patients. One of the major consequences of lipodystrophy is treatment dropout due to the psychosocial effects of body fat redistribution.

Given the prevalence of changes caused by fat redistribution, it is clear that HIV-associated facial lipoatrophy is becoming epidemic. It stigmatizes those affected causing a major impact on their quality of life. Usually, these patients have good disease control and good health, but their facial features suggest otherwise and the psychological effects are often devastating.
Patients with facial lipoatrophy are exposed and cannot afford to keep their condition a secret. This may result in discrimination at work, affect relationships and sexual function and even adherence to treatment. This influences the patients' sense of well-being, as well as their body image and self-esteem. In some cases, patients become socially isolated.
It is a fact that facial lipoatrophy causes a major psychological impact and can reduce patient compliance with treatment.

3.4 Treatment

Since the causes of HIV-associated lipodystrophy are not well known and it is not yet clear how the syndrome develops, it is difficult to delineate treatment attempts. So far, some treatments are available for facial lipodystrophy, either conservative or interventional, pharmacological or surgical, with varying results and side effects.

3.4.1 Conservative treatments

Among the conservative treatments of FL, the possibility of adjustment of antiretroviral therapy has been considered, allocating drugs that are less associated with the development of HIV facial wasting. Change of antiretroviral therapy in response to lipoatrophy should be cautious due to the risk of viral rebound or adverse reactions to the drugs introduced.
Some studies have shown that the exchange of a thymidine analogue nucleoside reverse transcriptase inhibitor for a non-thymidine analogue results in a slight increase in peripheral fat after 24 weeks, measured by DEXA and CT, although the effect has not been shown to be clinically evident. The replacement of stavudine with abacavir or tenofovir showed maintenance of the immunological pattern, with the advantage of stabilization of anatomical changes, and even their slight improvement. A prolonged interruption to treatment (greater than 6 months), however, does not yield a clinically evident improvement in lipoatrophy in some studies.
Nonetheless, physicians should consider the sensitivity of the virus to the drugs and disease severity, as well as the potential risks of drug therapy when changing treatment regimens.
One of the possible interventions in drug therapy is the use of antidiabetic agents.
Thiazolidinediones (rosiglitazone, pioglitazone) are antidiabetic agents that improve insulin resistance in type 2 diabetes mellitus. They can lead to fat gain in some patients and may increase fat mass in some familial forms of lipoatrophy. Some studies show conflicting results about the increase of subcutaneous fat tissue with the use of rosiglitazone. Large-scale studies are needed.
Studies with metformin are not consensual and most have a short follow-up. Some data suggest reduction of subcutaneous fat with its use, including visceral and limb fat, being more useful in patients with glucose disorders.
Anabolic actions are among the most important effects of the growth hormone (GH). The therapeutic use of human GH began 49 years ago. Recombinant GH has been used since 1985, which enabled pituitary hormone replacement therapy with less risk to patients. The most common indications for the use of GH are deficient growth, either idiopathic or secondary, adults with GH deficiency or insufficiency, and weight loss due to AIDS. The

FDA has approved a type of growth hormone to treat muscle wasting in HIV-positive patients when they present with hormonal suppression. The use of this treatment in public health programs is limited by high cost, about $ 36,000 per year. The international literature reports that short-term treatment increases total body weight and lean body mass, with consequent improvement of physical capacity and quality of life. The regimen to be employed among HIV/AIDS patients and the duration of treatment are not well established.

Although commonly used to fight body mass loss, anabolic steroids may actually reduce subcutaneous fat and worsen HIV-associated lipoatrophy. Although human GH has been widely used in HIV-associated fat accumulation, particularly in the abdominal (visceral) region, its use to treat facial lipoatrophy is controversial. Honda et al. (2007) evaluated the use of subcutaneous GH in HIV-1 patients who had moderate to severe facial lipoatrophy. The authors concluded that GH is effective and relatively safe for the treatment of moderate to severe facial lipoatrophy and that the cost-effectiveness of its use should be further discussed.

The use of GH is also limited by the fact that the benefits obtained with its use do not persist for more than 12 weeks after its interruption and by a decreased sensitivity to insulin, already impaired in the syndrome.

Some new drug treatments have been suggested for HIVLS, but more scientific studies to gauge their true clinical applicability are needed.

Leptin is an amino acid which is a product of the human leptin gene. It regulates the energy, neuroendocrine and functional homeostases of the body. Recombinant human leptin is an emerging possibility to treat lipoatrophy caused by its genetic deficiency and may have some application in lipoatrophy associated with HIV/AIDS.

As one of the causes of lipoatrophy is mitochondrial toxicity caused by ARVs, antioxidants and mitochondrial cofactors could also be of value in its prevention or treatment.

Nutritional counseling and physical exercises are adjuvant therapies for metabolic and body alterations in HIVLS. Aerobic exercises reduce the levels of TGC and cholesterol, especially LDL and, through the burning of fat, they help to reverse some bodily changes related to the central accumulation of fat. Resistance exercises help with muscle mass gain, improving the appearance of the chest, arms and legs, in addition to being useful to treat osteopenia. A diet rich in fiber and adequate in energy and protein can prevent the development of body fat deposits. However, these measures have no impact on facial subcutaneous fat that has already been lost.

3.4.2 Surgical treatments

Disorders of body fat distribution associated with antiretroviral therapy are currently considered irreversible. Several studies have explored therapeutic strategies, but none of these strategies allow for sufficient recovery of adipose tissue to a consistent clinical perception.

To the HIV/AIDS Treatment and Training Foundation in Spain, surgery is the only option to reverse the manifestations of lipodystrophy, which can be atrophy, hypertrophy, or a combination of both.

One promising technique to treat facial lipoatrophy is subcutaneous filling – the cutaneous fillers.

The use of dermal fillers was introduced in 1981, when bovine collagen began to be implanted into the skin to smooth away the appearance of facial wrinkles. Since then, new materials have been developed to improve effectiveness and safety parameters.

The ideal filler should be a nontoxic material that does not induce hypersensitivity or foreign body reactions, which does not degenerate over time or induce calcification, and which is chemically inert and easily implanted. These substances must be biocompatible, must not cause allergic reactions, and must be easily managed and stable over time. Moreover, the cost of treatment should be accessible to patients.

3.4.2.1 Dermal fillers

Injectable fillers are currently important tools in the non-invasive arsenal of rejuvenation procedures, in the correction of congenital or acquired facial defects and, more recently, in the treatment of facial lipoatrophy associated with HIV/AIDS.

According to their availability, chemical composition and degradation, fillers can be classified as temporary or permanent, organic or inorganic, and autologous or heterologous.

With regard to durability, some studies rely on a third sub-group, which would be that of semi-permanent fillers. Some authors define semi-permanent products as those with durability between one and two years. Permanent fillers would then last over 2 years and temporary fillers, less than one year.

Some fillers, when implanted, increase facial volume by direct filling and expansion of receptor sites. This is the case of silicone, collagen, and certain polyacrylamides. Others also create volume directly, but promote a foreign body reaction for a given period of time, stimulating progressive and long-lasting collagen deposition. PMMA, polylactic acid and calcium hydroxyapatite are examples of this second category.

Hoping to find a filler with greater durability, researchers tested a series of non-resorbable particles in mice, and polymethylmethacrylate (PMMA) molecules were the best tolerated, with the lowest rate of allergic reactions.

Polymethylmethacrylate was synthesized for the first time in 1902. It was patented in 1928 as Plexiglas and it was mainly used as bone cement in the medical field. Initially available in the form of pellets, in 1937 the material could also be found in the form of granules and molding powder.

Neurosurgeons began using PMMA during the Second World War to perform cranioplasty because of the resistance and lightness of the material. PMMA is still used in the reconstruction of cranial defects because of its excellent tissue compatibility, the ease with which it is handled in surgery, its strength and radiolucency, as well as its accessibility, low thermal and electrical conductance and lightness. In 1946, PMMA represented approximately 95% of the prostheses in the market.

Medical research progressed and PMMA also began to be used for the fixation of femural orthopedic prosthesis. The use of PMMA as bone cement was introduced by Charnley and Smith in the 60s. Since then it has been widely used in surgery to fill the spaces between the prosthesis and bone.

The inert chemistry and biocompatibility of polymethylmethacrylate have been accepted since Jude introduced the first hip prosthesis made of this material in 1947.

The first hard PMMA ophthalmic lenses were made by Kevin Tuohey in 1948. Its use in ophthalmology has also brought a lot of knowledge about this material.

So far, PMMA continues to be used as bone cement in orthopedics, as repair material in craniofacial neurosurgery, as a material for intraocular lenses in ophthalmology and as dental cement in dentistry.

The PMMA molecule appears to be chemically inert, so conducting prior allergy testing is not necessary when the product is used in isolation. Animal experiments have shown that

the keys to skin biocompatibility are the spherical shape of particles, their smooth and regular surface and the size of polymethylmethacrylate microspheres. The size of the molecules is important because very small particles can be easily phagocytosed and the largest ones do not pass easily through a No. 26 needle. Repeated rinsing of the microspheres reduces impurities and increases tolerance to the product by reducing the number of foreign body giant cells around the injected particles of PMMA.

Since PMMA microspheres are not biodegradable and are too large to migrate or be phagocytosed by macrophages, a permanent tissue increase is expected, consisting of 80% of the volume of autologous connective tissue. Lemperle et al. (1991) suggested that PMMA particles are resistant to phagocytosis and degradation and are not carcinogenic. This study attributes resistance to phagocytosis to the smooth surface of the particles and reports that, after four months, a delicate fibrous capsule is formed around each particle, which prevents displacement of the implant.

The PMMA implant has immediate and long term results, considering it is a biocompatible and inert filler, which give it characteristics of a permanent implant.

The injected microspheres cause a stimulus in the tissue that ultimately induces formation of new collagen fibers.

The tissue stimulation induced by PMMA microspheres is caused by a mild inflammation produced by monocytes, histiocytes and fibroblasts at the site of application, which can subsequently produce collagen fibers. Allen et al. (1992), in a longitudinal study, noticed the cellular reactions after the injection of inert implants. Such reactions were followed by a series of events of variable magnitude. In the first 24 hours, neutrophils and small round cells predominate; within 48 hours, there is a predominance of monocytes and, in 7 days, there is formation of foreign body giant cells. In two weeks, the cellular response is already moderate; in 4 weeks, fibroblasts appear; in 6 weeks, foreign body giant cells are noted and deposition of collagen is intensified; in eight weeks, chronic inflammatory cells are scattered along a massive deposition of collagen. Thereafter, the cellular reaction to the foreign body is stabilized and in six months giant cells and a small level of cellular response are present with a reduced amount of dense collagen; there is also conversion of fibroblasts into fibrocytes. From then on there was greater permanence of the implant in place. Collagen compounds mixed with PMMA microspheres then became a source of great expectations for researchers and the medical community.

In presentations made available internationally, PMMA microspheres were first suspended in gelatin. Of the 578 patients who initially received the product, 15 developed granulomas within 6 to 18 months after application. It was concluded, therefore, that impurities stimulated macrophages and were the cause of the formation of granulomas. In addition, some patients had palpable nodules that were attributed to the rapid absorption of the gelatin carrying the microspheres, which allowed them to agglutinate. This vehicle was then replaced by a collagen solution, which is more viscous and more durable in the tissue. After applying the product to the deep dermis, collagen is degraded by the body within 1 to 3 months and is completely replaced by the patient's own collagen within a similar period of time, ensuring increased volume.

The collagen used in foreign formulations is of bovine origin. The antigenicity of bovine collagen is reduced by the action of a pepsin, which removes the more antigenic end portion of the collagen molecule, without destroying the helical nature of the collagen fibers.

Commercial formulations available in most countries are a suspension of 20% purified PMMA microspheres of 30 to 42 micrometers in diameter in a 3.5% bovine collagen solution. It also contains 0.3% lidocaine to reduce discomfort after application. This product has been

approved and made available in over 50 countries since 1994, with an estimated 400,000 patients treated so far and a complication rate of 0.01%. It has been marketed under the trade name Artecoll since 1996 in the European Union, 1998 in Canada and in Mexico, since 1999. The product was approved by the FDA in October 2006, and is marketed in the U.S. under the name Artefill, with the same composition as that of Artecoll, but with reduced nanoparticles and more uniform-sized spheres.

Because bovine collagen is a foreign protein, 3% of patients may develop an immune reaction, possibly a type IV allergic reaction, although antibodies to bovine collagen can be seen in the serum of patients. Thus, a prior allergy test is essential. A small amount of pure collagen solution, usually 0.05 to 0.1 ml, is injected intradermally on the surface of the forearm. Reading is done in 72 hours and again after 1 month. Edema and/or erythema make the test positive. About 1.2% of patients with negative test results develop an immune reaction in a subsequent application, so a second test should be performed 30 days after the first. Some authors suggest a new test for treatments after a period of 12 months.

The association of bovine collagen to PMMA substantially increases the cost of the product, which becomes a limiting factor for situations in which large amounts of the filler are needed, such as in the treatment of facial lipodystrophy, and very impractical for use in public health programs.

Several countries use associated PMMA –Artfill, Artecoll- and the number of patients treated worldwide surpassed 250,000 in 2005. Among these, only 0.01% had granuloma formation.

Most papers published in the international literature on PMMA implants are about collagen-associated products (Artecoll or Artfill).

The Brazilian Sanitary Surveillance Agency (ANVISA), similar to the FDA in the United States, has approved the use of PMMA without association with collagen for the treatment of HIV-associated facial lipodystrophy. However, this product has also been used to treat nasolabial folds, to correct the atrophy of bone eminences, especially malar and mental, to treat Parry-Romberg syndrome (progressive hemifacial atrophy), and to correct the nasal dorsum, scars and atrophic ear lobe.

The injectable product used in Brazil consists of polymerized microspheres of PMMA ranging from 30 to 50 micrometers in size, coated with magnesium carboxygluconate hydrolactic gel. The ratio microspheres/gel is 3:10. It is available in 10 ml vials or ready-to-use syringes of 1 or 3 ml, stored at room temperature. It was initially introduced in Brazil in 1996. Since there are no animal components in its structure, prior allergy testing is not needed.

The great advantages of the PMMA used in Brazil are the fact that it does not require prior allergy testing and presents no risk of prion disease transmission. Because it is a permanent filler, the results are lasting. In addition, it has a very low cost compared to other fillers on the market. The cost of Metacryll, one of the PMMA-based products sold, is about US$20/ml. Studies have shown safety and efficacy with the use of this product, with a high rate of satisfaction among patients and low incidence of side effects. In fact, an increase in the number of CD4 + cells after treatment of FL with this implant has been described. Improvements in the quality of life, social relationships, and psychological state of the patient are reported after treatment of FL, with improvement of the immune system.

The literature describes the use of many other fillers in the treatment of FL. In the United States and Canada, some forms of injectable liquid silicone have been successfully used to treat HIV-associated facial lipoatrophy. The term silicone was assigned to a family of polymers with one basic element: silicon. These polymers vary in their viscosity from an oil

to a jelly. The pure silicone recommended for dermal filling is siloxane, which is a class of chemical compounds with alternating chains of silicon, oxygen and methane. The pure, sterile and filtered form is recommended for use as filler.

The combination of puncture and silicone deposition leads to an inflammatory reaction with polymorphonuclear cell migration, followed by a moderate lymphocytic infiltrate. This infiltrate can be observed for six months. There is a discreet phagocytic activity and a small number of giant cells can be seen, which do not evolve to the formation of granulomas. The low volumes of silicone injected soon settle in the deep dermis and subcutaneous tissue and are surrounded by pseudocapsules of preexisting collagen, which later give rise to a newly-formed thin collagen capsule.

Immediate reactions include erythema, edema, and possibly ecchymosis. Soon after injection, small papules may appear at the site of the injection, but they disappear after a few hours or within 3 weeks. There are reports of dyschromias, but they are infrequent. Excessive elevation may occur due to overcorrection or excess volume injected. Cases of erythema and granuloma formation are associated with impurity of the material, inadequate location or injection of large volumes. Migration of the silicone, which is often the main fear among professionals and patients, only occurs when volumes above 1 ml are used in a single site, which is often necessary in the treatment of FL.

In some studies, injectable liquid silicone appeared to be the most cost-effective treatment in the United States. However, a longer follow-up of treated patients is needed to determine the efficacy, permanency, and long-term safety of liquid silicone injection in the treatment of HIV-associated facial lipoatrophy.

A limiting factor to this procedure is that its use is prohibited in many countries.

Polylactic acid filler was the first to be approved by the FDA for the treatment of facial lipoatrophy associated with the use of ARVs. FDA approval was based on four studies that documented the safety and efficacy of the product in 278 patients with facial lipoatrophy.

Polylactic acid is a synthetic polymer which is biodegradable and immunologically inert. Once injected, the microparticles of polylactic acid may stimulate collagen production, which allows a gradual and progressive increase in the volume of the lipoatrophic area. Polylactic acid belongs to the family of alpha-hydroxyl acids and has been available for over 30 years for various uses in medicine.

Polylactic acid is injected into the deep dermis in order to increase the number of fibroblasts and their activity, resulting in increased collagen synthesis. It has two modes of action. Initially, there is a temporary increase in volume of the treated area and it is essential that patients be well advised not to be disappointed when this initial volume decreases. The initial volume is created by injection of the volume of sterile water used to reconstitute the polylactic acid, which is resorbed in 48 to 72 hours. The second mode of action is the stimulation of collagen formation.

It may take several sessions before the desired effect on the contour of the face is noted. Polylactic acid is completely degraded in nine months.

Carey et al. (2007) conducted a randomized, multicentric study with a follow-up of 24 and 96 weeks, comparing adult patients with facial lipoatrophy induced by ARVs who were injected with polylactic acid in their deep dermis with a control group. These authors showed that treatment of facial lipoatrophy with polylactic acid in adult patients infected with HIV provided only a modest increase in facial thickness, but not in facial volume. In contrast, patients' perception of improved well-being, quality of life and cosmetic benefits was significant. Polylactic acid does not interfere with fat loss from other regions of the body. The authors further point out that other comparative studies are needed to establish the optimal treatment for HIV-associated facial lipoatrophy.

However, because polylactic acid is a biodegradable product, its effects are temporary and retreatment may be eventually necessary. Furthermore, multiple application sessions are necessary for its administration. Still, subcutaneous nodules have been described after injection of this material. There is also the high cost of this procedure. Thus, other alternative options for patients with facial lipoatrophy are important.

Hyaluronic acid is a polysaccharide component of soft tissue and it is identical in all species and types of tissue. There are commercial formulations that have already been approved by the FDA.

Injectable hyaluronic acid is obtained by bacterial fermentation and has a low incidence of adverse reactions. This incidence has fallen further in recent years, from 1/1400 patients in 1999 to 1/1800 patients in 2000. This decrease is explained by the production of more purified forms of hyaluronic acid by the pharmaceutical industry.

Hyaluronic acid has been used successfully to treat HIV-associated facial lipoatrophy. However, as with other temporary fillers, large volumes are often needed to achieve full correction, which tends to decrease after 6 to 12 months. The high cost of large volumes and the need to repeat treatment are major limiting factors.

Calcium hydroxyapatite gel is an injectable filler composed of 30% calcium hydroxyapatite microspheres and 70% of a carrier aqueous gel. Although synthetic, its components are identical to the mineral portion of bones and teeth. It is a biocompatible, non toxic and non-antigenic material.

It was approved by the FDA in 2006 for correction of the signs of facial fat loss in HIV patients. This implant provides an immediate correction. The carrier gel is absorbed in a few weeks, leaving the microspheres that serve as matrix for neocollagenesis and formation of new tissue. The major limiting factors for its use are also its high cost and the fact that it is a new filler about which there are no long term studies.

Polyacrylamide gel is a non-biodegradable polymer, non-allergenic and non toxic, composed of 96% non-pyrogenic water and 4% polyacrylamide. It is the only filler in which a thin layer of collagen capsule develops around the gel, isolating it from the host tissue. As a result of the encapsulation process, the implant can be readily identified and if removal is needed, it can be easily removed by the expression of the capsule, expelling the material from its interior. Therefore, polyacrylamide is considered an injectable prosthesis.

Polyacrylamide gel is nonbiodegradable and it is suggested to be biologically inert. The cosmetic effects of polyacrylamide filling are permanent, avoiding the need for further treatment.

A practical limitation of therapy with facial fillers is the cost associated with these products. The cost of polyacrylamide in 2007 in Canada was about US$ 175.00 per milliliter; patients require about 10 to 25 ml of the product. The total cost of the treatment would therefore range from US$ 1,750.00 to US$ 4,375.00 . In addition to the cost, which makes the use of this filler very impractical, the rate of infection described in the literature is higher than with the use of other fillers.

Cost is really a limiting factor in the choice of fillers, especially considering that in the case of FL the volumes needed are higher than those for other cosmetic indications. In a study of treatment of HIV/AIDS facial lipoatrophy with large particle-size hyaluronic acid, trade name SubQ, the estimated value per patient was 950 Euros, considering that each patient received an average of 6 ml of the product and the cost of 1 ml of the material was 160 Euros. Other formulations of hyaluronic acid have a starting cost of US$ 123 per unit, with a total average cost of US$ 687 for treating an area of the face. Polylactic acid has an approximate cost of US$ 123 per ml, with a total average price of US$ 3,690 per facial area

treated. Silicone has a total cost of $ 8,750 for facial area treated, as described in the literature. Hydroxyapatite costs about $ 280 / ml, with an average cost of treatment reported in the literature of $ 7560 for facial area.

Because HIV-associated lipoatrophy is caused by loss of subcutaneous fat of the own patient, it would seem logical that the transfer of autologous fat was the most appropriate therapeutic option. A recent study reported 29 patients with HIV-associated facial lipoatrophy who received autologous fat transplantation by the Coleman's method. The technique was deemed reliable and photographic records done 6 months after treatment showed the permanency of the fat graft. However, the authors noted that most patients with HIV-associated facial lipoatrophy have no suitable fat donor areas, so many are not candidates for this procedure. Jones (2005) performed fat grafts in 10 patients with HIV-associated facial lipoatrophy with the same methods and similar results. Nevertheless, in almost all cases, correction did not last for more than 12 months. Another recent study also suggested that, although the filling with autologous fat is effective for this condition, patients with HIV-associated facial lipoatrophy have minimal fat donor sites and that this treatment requires new filling sessions over time. HIV patients often lose subcutaneous fat in the abdomen and buttocks, which are usually fat donor sites.

Comparative studies with groups treated with different fillers available in the market should be conducted to better establish the cost effectiveness of each product; the high cost of most fillers in the market limits their use in the treatment of FL.

In an attempt to obtain new fillers to be used mainly in treatments for rejuvenation of the face, new products may be developed and made available in the market. The cost of newly launched products, the durability of the materials, and the existence of research to ensure their effectiveness and safety are important factors that should bolster the use of fillers in medical practice, in particular, their use in the treatment of FL.

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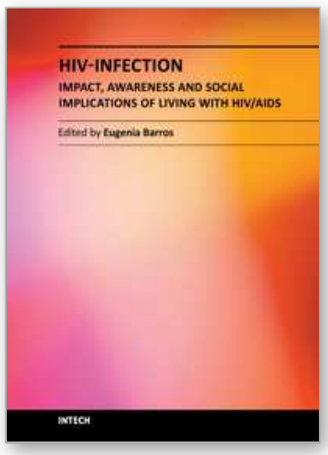
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The past few decades have seen the escalation of HIV-infections and the 'frantic' search for new drugs to treat the millions of people that live with HIV-AIDS. However because HIV-AIDS cannot be cured, but only controlled with drugs, and the Antiretroviral (ARV) treatment itself results in some undesirable conditions, it is important to generate wider awareness of the plight of people living with this condition. This book attempts to provide information of the initiatives that have been used, successfully or unsuccessfully, to both prevent and combat this 'pandemic' taking into consideration the social, economic, cultural and educational aspects that involve individuals, communities and the countries affected.

How to reference

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