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1. Introduction

Dyslipidemia is a change in serum lipids levels, which is associated with increased risk of cardiovascular events when are found elevated (American Heart Association, 2002, Sposito et al., 2007). Before introduction of antiretroviral therapy (HAART), patients with acquired immunodeficiency syndrome (AIDS) developed a dyslipidemia characterized by isolated elevation of triglycerides (TG) and decrease in total cholesterol (TC) and its fractions (Gkrania-Klotsas & Klotsas, 2007; Mulligan, 2003). With the advent of HAART, especially with the use of protease inhibitors (PI), this situation changed to a lipid profile with elevated TG, TC, lipoproteins of very low and low density (VLDL-C and LDL-C) and decrease in high density lipoprotein (HDL-C), leaving these patients at risk for developing diabetes, hypertension and other complications (Chen et al., 2002; Furtado et al., 2007; Garg, 2000; Gkrania-Klotsas & Klotsas, 2007; Kotler, 2008; Mulligan, 2003; Sattler, 2008; Segarra-Newnham, 2002; Schering & Tovar, 2006; Yu et al., 2005).

Studies estimate that the prevalence of dyslipidemia in patients with HIV (Human Immunodeficiency Virus) during use of antiretroviral therapy can vary from 33% to 82% and may be influenced by several factors including study type, sample type and time of HAART (Gkrania-Klotsas & Klotsas, 2007; Schering & Tovar, 2006; Yu et al., 2005).

2. HIV lipodystrophy syndrome

According to UNAIDS and World Health Organization (WHO) (2009) there was a large increase in the prevalence of HIV carriers in the world, reaching 33.4 million in 2008, value explained by the maintenance of annual incidence and the increase of the survival (Lihn et al. 2003; Mallewa et al., 2008). However, was noted a illness pattern change of these patients which ever left to be affected by a clinical feature characteristic of opportunistic diseases to develop HIV lipodystrophy syndrome (HIVLS) (Kramer et al., 2009; Ministry of Health of Brazil, 2008; Samaras et al., 2009; Stankov & Behrens, 2010).

Body composition abnormalities have been reported in 40-50% of HIV-positive outpatients. This proportion is higher in patients receiving antiretroviral therapy. The rate of lipodystrophy can be high depending on the characteristics of the cohort (sex, age and possibly race), the type and duration of antiretroviral therapy (Grinspoon & Carr, 2005).
The HIVLS presents three distinct forms according to distribution pattern: lipoatrophy, with fat loss in limbs, face and buttocks; lipohypertrophy, with localized increase of abdominal, breast and dorsocervical subcutaneous cellular tissue, besides visceral deposit and lipoma formation; and the mixed form with signs of both syndromes earlier (Sattler, 2008; Mello et al., 2008) (Figure 1).

Legend: A) facial lipoatrophy with facial furrows accentuated, bony prominence, and loss of Bichat’s fat (malar fat). B) Lipoatrophy of the lower limbs with prominent veins. C) Visceral lipohypertrophy, with increased waist circumference and little subcutaneous tissue. D) Dorsocervical lipohypertrophy. Photos of the collection of Dr. Rosana Libonati.

Fig. 1. Morphological changes in HIV patients with lipodystrophy syndrome, Pará, Brazil.

In addition to fat distribution alterations, metabolic changes are expressed as a mixed dyslipidemia with hypertriglyceridemia, total hypercholesterolemia, low density lipoprotein (LDL-C) elevation, reduction of high density lipoprotein (HDL-C), besides the induction of insulin resistance culminating in establishment of type II diabetes (Furtado et.,
Dyslipidemia in Patients with Lipodystrophy in the Use of Antiretroviral Therapy

2007; Chen et al., 2002; Garg, 2000; Sattler, 2008, Yu et al., 2005). The changes in the concentrations of plasma lipids are more observed in patients receiving protease inhibitors (PI) (Yu et al., 2005).

Prospective studies investigating body composition in patients starting HAART for the first time have showed increases in fat during the initial months of treatment, followed by a progressive declining in the following three years. In one study, the decline was estimated at 14% per year in white men who received treatment regimens containing zidovudine/lamivudine or stavudine/lamivudine plus protease inhibitor or non-nucleoside reverse transcriptase inhibitor. In contrast, trunk fat increases initially and then remains stable for two or three years, resulting in relative central adiposity. These changes are clinically evident in 20 to 35% of patients after about 12 to 24 months of combination antiretroviral therapy (Grinspoon & Carr, 2005).

The type, duration and current use or not of antiretroviral therapy are strongly associated with the lipoatrophy severity. Therapy based on two nucleoside analogue reverse transcriptase inhibitors and one protease inhibitor has strong association with severe lipoatrophy (Mallon et al., 2003).

Now, the mechanism by which the protease inhibitor causes lipodystrophy remains unknown. Several protease inhibitors prevent preadipocytes differentiation and mild to moderate apoptosis in subcutaneous adipose tissue. Adipose tissue of patients with lipodystrophy has reduced expression of mRNA of several key factors involved in adipogenesis, including Sterol regulatory element binding protein (SREBP1c) and Peroxisome proliferator-activated receptor gamma (PPARγ). In vitro studies have shown that protease inhibitors can inhibit lipogenesis and adipocyte differentiation, stimulate lipolysis and prevent nuclear localization of SREBP-1c (Garg, 2000; Grinspoon & Carr, 2005).

The nucleoside analog more strongly associated with lipoatrophy is stavudine, particularly when used in combination with didanosine. Lipoatrophy associated with nucleoside analogue may be due in part by mitochondrial injury caused by inhibition of the mitochondrial DNA polymerase γ within adipocyte and mitochondrial DNA depletion, although the extent and specificity of this effect remains unknown. The nucleoside analogue can inhibit adipogenesis and adipocyte differentiation, promote lipolysis and exert synergistic toxic effect with protease inhibitors in vitro and in vivo (Grinspoon & Carr, 2005).

In nine studies assessing risk factors for lipoatrophy, were statistically significant more common duration and exposure to thymidine analogues, most commonly stavudine (d4T) (6/9), age (5/9), markers of disease severity (CD4/HIV RNA) (5/9), duration of therapy (3/9) and Caucasian (3/9). A prospective nonrandomized study in 40 HIV-positive patients starting antiretroviral therapy for the first time resulted after an average of 96 weeks, using multivariate analysis, that treatment with d4T is an independent factor for lipoatrophy (Lichtenstein, 2005).

In eight studies assessing lipohypertrophy, the most significant risk factors were duration of therapy (3/8), a marker of disease severity (3/8), age (3/8) and protease inhibitor use (4/8).

An additional study evaluating 2258 HIV-positive patients evaluated change in adipose tissue for both gender. Logistic regression showed that men have a significantly lower adjusted risk than women have (OR: 0.47, CI 95%: from 0.38 to 0.58) and a significantly lower risk of lipohypertrophy and mixed redistribution, while the risk of lipoatrophy was similar between genders. Therefore, a rigorous multivariate analysis controlling for numerous variables reveals multiple risk factors, suggesting that the pathogenic mechanism
for fat redistribution seems to be the result of complex interactions between host, disease and drugs factors (Lichtenstein, 2005).

As for the diagnosis of HIVLS, there is not one standard pattern used to subjective body changes mentioned by the patients, anthropometric measurements and metabolic changes demonstrated in fasting laboratory tests (Diehl et al., 2008). Other tests that assist in conducting the HIVLS patients are: bone densitometry, for the investigation of osteopenia/osteoporosis; Dual-emission X-ray absorptiometry (DEXA), which allows an analysis of body composition, especially fat in the limbs, Computed Tomography, to observe presence of visceral fat deposits, and upper abdominal ultrason for hepatic steatosis assessment (Mallon et al., 2003).

Therefore, the main consequences of HIVLS are increased cardiovascular risk and consequent development of hypertension, diabetes mellitus, atheromatous disease, stroke, myocardial infarction (Kramer et al., 2009). Psychological disorders as well as, like stress and low self-esteem by stigmatizing body changes (Santos et al., 2005; Seidl & Machado, 2008), which not cease to be risk factor for these events already mentioned by activation of sympathetic and glucocorticoids systems, and neuropeptide Y production potentiating the metabolic changes (Licht et al., 2010; Rasmusson et al., 2010).

3. Pathophysiology of dyslipidemia secondary to antiretroviral therapy

Since the implementation of antiretroviral therapy (HAART), in the 90s of last century, the treatment of AIDS has increased the mean life expectancy of HIV-infected population. Until then seen as a death sentence in a matter of short time, the disease have been faced like chronic, and with more optimism. However, despite a decrease in morbidity and mortality, HAART led to a problem that has become a major challenge that patients with AIDS must control: dyslipidemia (Cahn et al., 2010).

The dyslipidemia associated with HAART has been characteristic of elevated total cholesterol (TC), low-density lipoprotein (LDL-C) and triglycerides (TG), in addition to decreased high-density lipoprotein (HDL-C), which results in increased predisposition to the development of hypertension, insulin resistance, diabetes mellitus and cardiovascular complications. There are evidences that cardiovascular manifestations proportions in HIV-infected patients on HAART are higher than in general population (Almeida et al., 2009). This does not mean that the occurrence of dyslipidemia has emerged only with the implementation of antiretroviral drugs to treat AIDS. Before the existence of HAART had been reported lipid profile changes with high levels of triglycerides and low rate of VLDL-C and HDL-C (Sprinz et al., 2010; Grunfeld et al., 1992).

Several studies investigate ways of relating to HAART the effects of dyslipidemia like type of drug used by the patient and how the treatment regimen it has been implemented, but is still lacking a precise explanation for the lipid profile origin. Protease inhibitors (PI) are associated with dyslipidemia and insulin resistance for a considerable time, specifically ritonavir, and a variety of hypotheses (albeit not conclusive) it is presented to explain this association (Noor, 2007; Dubé et al., 2003).

One proposed mechanism to emergence of dyslipidemia is the lipoprotein lipase inhibition by PI, responsible for LDL-C increased, due to difficulty in capturing chylomicrons, resulting in lower hepatic clearance of triglycerides (Sprinz et al., 2010, as cited in Carr & Mooser, 2001). Another hypothesis is that PI has the ability to inhibit steps in lipid metabolism by binding to cellular retinoic acid binding protein type 1 (CRABP-1) and
related protein receptor LDR-c, resulting in hyperlipidemia by higher release of lipids in the circulation. More specifically, the PI on CRABP-1 receptor leads to a reduction of 9-cis retinoic acid and dimerization with the receptor activated by peroxisome proliferator-activated receptor gamma (PPAR-γ), which is involved both in apoptosis of adipocytes and in differentiation between these two. (Sprinz et al., 2010; Carr et al., 1998). A third theory, restricted to ritonavir, antiretroviral therapy suggests it increases the activity of sterol regulatory element binding protein 1 (SREBP-1c), increasing lipogenesis, the rate of VLDL-C and apolipoprotein B liver. Thus, the increase in triglycerides caused by ritonavir that could be related to elevation in hepatic lipoprotein, inhibiting degradation mediated by apolipoprotein B and SREBP-1c in liver (Riddle et al., 2001; Liang et al., 2001).

As regard the insulin resistance promoted by PI, this class of antiretroviral drugs has been related to inhibition of GLUT-4 in the transmembrane transport of glucose, leading to reduced glucose uptake mediated by insulin in peripheral tissue (skeletal muscle and adipocytes), which can lead the modification of lipid levels (Noor, 2007). The fact that some patients had a clinical and laboratory profile more or less lowered depending on the effects that PI has on the lipids metabolism may be related to genetics, suggesting that certain people are more prone to PI effects through manifestation of certain genes so far not identified (Shahmanesh et al., 2001).

With regard to nucleoside reverse transcriptase inhibitors (NRTIs), it is speculated that can lead to reduced synthesis of mitochondrial DNA, leading to decreased oxidative phosphorylation, resulting in subcutaneous adipocyte apoptosis, dyslipidemia, and increased insulin resistance (Maagaard & Kvale, 2009). The reverse transcriptase inhibitor non-nucleoside (NNRTI), particularly Efavirenz, are also related to the onset of metabolic disorders, including dyslipidemia – but they have lower participation. When compared to patients receiving Nevirapine, patients who make use of Efavirenz have higher levels of triglycerides and HDL-C (Sprinz et al., 2010, as cited in Carr et al., 1998).

The type of antiretroviral used in HAART case amends significantly the lipid profile of patient it might be replaced. However, make use of a change in medication or combination of drugs (a strategy that appears more practical than prescription of lipid, at least at first glance) does not always result in improving lipid metabolism, considering the dyslipidemia in HIV infection is related to a multifactorial framework (Sprinz et al., 2010).

Although there are doubts considering the mechanisms linked to development of dyslipidemia in patients receiving HAART, and about assumptions not fully understood, this is still the most effective treatment in patients with AIDS and should not be proscribed for patients. To minimize risks that dyslipidemia implies to health, we recommend the same precautions, both dietary and behavioral (avoiding a sedentary lifestyle) and drug (statins/fibrates) for the general population. The use of fibrates is primarily indicated for reduction of hypertriglyceridemia, while statins are used to reverse the hypercholesterolemia. However, must be careful in prescribing of statins, since there is risk of drug interactions with HAART (Sprinz et al., 2010).

4. Treatment of dyslipidemia secondary to antiretroviral therapy

Hyperlipidemia is a major risk factor for developing of atherosclerosis. Epidemiological studies in adults show a direct association between high levels of total cholesterol and LDL and the incidence of mortality and morbidity in coronary artery disease (CAD) and is LDL-C a predictor of CAD risk at any age, besides low HDL and diabetes mellitus (Giddings, 1999).
Dyslipidemia in HIV infection is related to a multifactorial framework (Sprinz et al., 2010), so treatment should be done with non-pharmacological and pharmacological measures.

4.1 Hypercholesterolemia
4.1.1 Non-pharmacologic therapy
The HIV-infected patients with dyslipidemia they should be screened before using those drugs as therapy, with the implementation of the change of lifestyle of these patients through diet, exercise, tobacco control, diabetes mellitus and hypertension (Dubé et al., 2003). In one study, the diet associated with exercise in 11% reduced cholesterol levels of patients infected with HIV (Henry et al., 1998). In another study showed that diet accompanied by resistance exercise at least three times a week reduced the cholesterol level by 18% and triglycerides by 25% (Jones et al., 2001).

The first measure to be taken will always be non-pharmacologic therapy, unless there is urgent need for intervention, as patients at high risk for coronary artery disease (obesity, diabetes, family history of cardiovascular disease) and extremely high levels of LDL-C greater than 220 mg / dL (Dubé et al., 2003).

4.1.2 Pharmacological therapy
The pharmacological treatment for dyslipidemia it is performed with HMG-CoA reductase inhibitors, or statins, are the main representatives of pravastatin and atorvastatin groups. They have been used extensively in clinical practice as first-line treatment for hypercholesterolemia in the general population and in HIV-infected patients, promoting reduction of cardiovascular risk in patients without no history of coronary artery disease and of progression of coronary artery stenosis with decrease of cardiovascular events recurrence, working in primary and secondary, respectively (Dube et al., 2003).

In one study, patients with altered levels of total cholesterol (TC) and triglycerides (TG), using pravastatin 20 mg/day occurring 19% decrease in the level of TC and 37% in the level of TG (Baldini et al., 2000). In another study, diet was associated with therapy with pravastatin 40 mg/day in patients with TC levels greater than 240 mg/dL, indicating a 17% decline in the levels of TC and 19% in the level of LDL-C (Moyle, 2001). Therefore, Palacios et al., in 2002, analyzing a group of patients with TC levels greater than 240 mg/dL under atorvastatin 10 mg/day was found a 27% decrease in the level of TC, 41% of TG and 37% in the LDL-C.

Thus, statins are the first choice in the treatment of elevated LDL-C (> 220 mg / dL) and patients with high total cholesterol associated with hypertriglyceridemia (TG between 200 to 500 mg/dL), initial dose may be used 20-40 mg of pravastatin or atorvastatin 10 mg monitoring possible liver toxicity with laboratory tests (Dube et al., 2003). Protease inhibitors and non-nucleoside inhibitors of reverse transcriptase enzyme use in its metabolism the cytochrome P450 pathway (Smith et al., 2001), the same route used by simvastatin, lovastatin and atorvastatin, then the first two are prescriped to patients under antiretroviral therapy and the latter can be used with caution.

Fibrates are used as second choice in the treatment of hypercholesterolemia. In patients with normal TG and elevated LDL-C levels, a slight decrease in LDL-C ranging from 5 to 20% in the studies carried out. Therefore, the therapeutic fibrates use should be reserved for treatment of hypertriglyceridemia (TG> 500 mg/dL) in these patients (Dube et al., 2003).
4.2 Hypertriglyceridemia

4.2.1 Non-pharmacologic therapy

The non-pharmacologic therapy should be first applied to all patients with hypertriglyceridemia, through modification of lifestyle; diet should be instituted to reduce fat intake, weight reduction, reduction or elimination of alcohol intake, smoking cessation control of hyperglycemia and diabetes with insulin sensitizers such as metformin. In studies, it has been found that diets associated with exercise and resistance training promotes decrease of 21% and 27%, respectively, TG levels in HIV-infected patients (Henry et al., 1998; Yarashesky et al., 2001). Patients who demonstrate extreme elevations in TG level (> 1000 mg / dL) and with a history of pancreatitis should be treated associating pharmacologic and non-pharmacologic therapy (Dube et al., 2003).

4.2.2 Pharmacologic therapy

Drug therapy should be instituted in all patients with TG levels greater than 500 mg/dL with the introduction of Gemfibrozil with starting dose of 600 mg half an hour before meals (lunch and dinner) or fibrates at a dose 54 to 160 mg/day (Dube et al., 2003). In a study carried out in patients with TG levels higher than 400 mg/dL using fibrate dose of 200 mg/day was observed 14% and 54% decrease of TC and TG levels, respectively (Palacios et al., 2002). Therefore, in another study, patients with TG levels higher than 266 mg/dL, using Gemfibrozil 600 mg/day associated with diet, evolved with a reduction of TG values in 18% (Miller et al., 2002). The use of statins in general is not recommended for the treatment of hypertriglyceridemia (TG > 500 mg / dL) alone, is recommended when triglyceride levels are between 200 to 500 mg/dL associated with increased total cholesterol (Dubé et al., 2003).

5. Experience of the assistance service of metabolic diseases secondary to antiretroviral therapy for patients with dyslipidemia

Assistance Service of Metabolic Diseases Secondary to Antiretroviral Therapy (HAART) of the João de Barros Barreto University Hospital (HUJBB), Brazilian national reference in transmissible infectious diseases and AIDS, actually, assist about 99 HIV carriers’ patients with lipodystrophy syndrome. Into this service, the authors develop a Project titled Lipodystrophy and Antiretroviral Therapy, financed by The State of Pará Research Foundation (FAPESPA), Research Program for the Unified Health System (PPSUS). One of the Project’s purposes was the implantation of the lipodystrophy ambulatory care. The HUJBB lipodystrophy ambulatory care works with team composed by an endocrinologist, a nutrition doctoral student, two medicine M.Sc students, four medical undergraduate students. The medical accompaniment is performed once a week. In the first service is diagnosed the clinical form of lipodystrophy and requested the proper tests (total cholesterol, HDL, LDL, triglycerides, fasting glucose test, oral glucose tolerance, insulin, abdominal ultrasonography to hepatic steatosis diagnostic and computed tomography for evaluation of visceral lipohypertrophy and electrocardiogram). The first patient’s return is around 45 days and subsequently every three months for medical accompaniment. Each medical consultation is also performed medical history, measurement of blood pressure, heart auscultation, anthropometric evaluation (measurements of weight, height, skin folds) and bioimpedance. In addition, if need be the patient is referred to other professionals of the multidisciplinary team HUJBB.
Of the accompanied patients with lipodystrophy syndrome in this ambulatory care, 77% (n = 77) have dyslipidemia and presents the following profile: 67.9% were male, mean age of 44.5 years, average time of HIV infection of 8, 3 years, average time of use of antiretroviral therapy for 6.9 years and body mass index of 24.5 kg/m². Regarding risk factors, it is observed that 18.2% are smokers, 40.3% alcoholics, 71.4% sedentary and 45.5% had hepatic steatosis. Regarding the classification of nutritional status (WHO, 1995) 58.4% are eutrophic, thin 6.5% and 35.1% overweight/obesity. Among the co morbidities studied, it appears that 24.7% and 21.1% are hypertensive and diabetics, respectively. When stratifying the lipodystrophy syndrome, according to the clinical manifestations, 35.1%, 10.4% and 54.5% of patients had lipoatrophy, hypertrophy and mixed syndrome, respectively. Concerning average serum lipid levels, there is high levels blood of cholesterol and triglycerides, low HDL-C, and LDL-C within the normal range. In regard to dyslipidemia classification (Sposito et al., 2007), have been observed that 48.7% of patients have mixed hyperlipidemia, 32.9% hypertriglyceridemia, low HDL-C 10.5% and 7.9% isolated hypercholesterolemia (Table 1 and 2). In the assessment of cardiovascular risk by Framingham Risk Score was found that more than 30% of the sample had medium and high cardiovascular risk.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Sample</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>52</td>
<td>67.5</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>25</td>
<td>32.5</td>
</tr>
<tr>
<td>Smoking</td>
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<td>14</td>
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<tr>
<td>Alcoholism</td>
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<tr>
<td>Sedentary</td>
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<td>71.4</td>
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<td>Diabetes mellitus</td>
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<td>21.1</td>
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<td>SH *</td>
<td>77</td>
<td>19</td>
<td>24.7</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Diabetes</td>
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<td>48.1</td>
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<tr>
<td>Hypertension</td>
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<td>55</td>
<td>71.4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Hepatic steatosis</td>
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<td>Nutritional status**</td>
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<td>Thinness</td>
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<td>Eutrophic</td>
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<td>Overweight/Obesity</td>
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<td>Mixed</td>
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<td>54.5</td>
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<tr>
<td>Classification of dyslipidemia***</td>
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<tr>
<td>Mixed Hyperlipidemia</td>
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<td>48.7</td>
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<td>Hypertriglyceridemia</td>
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<td>32.9</td>
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<tr>
<td>Low HDL</td>
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<td>10.5</td>
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<tr>
<td>Isolated hypercholesterolemia</td>
<td>6</td>
<td></td>
<td>7.9</td>
</tr>
</tbody>
</table>

Legend: SH - systemic hypertension; ** WHO, 1995; *** Sposito et al., 2007

Table 1. Patients profile with lipodystrophy and dyslipidemia accompanied by the Assistance Service of Metabolic Diseases Secondary to Antiretroviral Therapy, João de Barros Barreto University Hospital, Pará, Brazil.
Table 2. Distribution of mean and median values of some variables in patients with lipodystrophy and dyslipidemia accompanied by the Assistance Service of Metabolic Diseases Secondary to Antiretroviral Therapy, João de Barros Barreto University Hospital, Pará, Brazil.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample</th>
<th>Mean ± SD</th>
<th>Median</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>77</td>
<td>44.5 ± 9.6</td>
<td>45.0</td>
</tr>
<tr>
<td>ART Time (years)</td>
<td>77</td>
<td>6.9 ± 4.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Time of HIV (years)</td>
<td>77</td>
<td>8.3 ± 5.4</td>
<td>8.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>76</td>
<td>24.5 ± 4.2</td>
<td>23.9</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>72</td>
<td>103.4 ± 27.7</td>
<td>98.5</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>76</td>
<td>218.9 ± 59.7</td>
<td>220.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>76</td>
<td>373.3± 393.8</td>
<td>280.5</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>60</td>
<td>40.8 ± 13.34</td>
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<tr>
<td>Male HDL-c</td>
<td>36</td>
<td>37.4 ± 11.7</td>
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</tr>
<tr>
<td>Female HDL-c</td>
<td>24</td>
<td>46.0 ±14.2</td>
<td>46.5</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>58</td>
<td>115.6 ± 45.4</td>
<td>117.9</td>
</tr>
</tbody>
</table>

Legend: ART – Antiretroviral Therapy, BMI – body mass index, SD standard deviation.

The ambulatory care authors conducted an intervention study with outpatient HIV-positive patients with lipodystrophy syndrome, in use of HAART in the period October 2006 to December 2007. Patients were evaluated every quarter for four visits. This study followed all the guidelines contained in Resolution 196/1996 of the National Committee for Ethics in Research (CONEP), being approved by the Ethics in Human Research of the Center for Tropical Medicine, Federal University of Para, according to opinion of approval No. 058/2006, to date of October 19, 2006. The sample consisted of patients with positive serology for HIV, use of HAART for at least 12 months, with clinical diagnosis of lipodystrophy. We selected only adult patients, aged 20 to 60 years, of both sexes. All were invited and agreed to participate by reading and signing the Free and Informed Consent Term - FICT.

We excluded all patients with mental illness, malignant tumors, and chronic users of glucocorticoids, Diabetes Mellitus and dyslipidemia diagnosed before starting HAART and those who did not achieve at least three follow-up visits clinical and nutritional care at the Ambulatory care of Lipodystrophy HUJBB.

To collect data we used a treatment protocol for metabolic evaluation, nutritional counseling and patient outcomes, among several details registered there were: patient identification, socio-economic, personal and family morbidity history, time of HIV diagnosis, time of HAART treatment, clinical history and biochemical tests. Among the lipodystrophy syndrome metabolic changes were required tests to total serum cholesterol, LDL-C, HDL-C and triglycerides for dyslipidemia analysis (Sposito et al., 2007).

We studied 29 patients, 17 (59%) and 12 (41%), male and females, respectively, with an average age of 46.07 (± 9.04) years. In males, the average age was 47.59 (± 7.66) years, median 46 years, whereas in females the mean age was 43.92 (± 10.67) years, median 44. The most prevalent age group for both sexes was 41 to 50 years.

In regarding to lipodystrophy syndrome classification, was observed that 11 (37.91%), 2 (6.9%) and 16 (55.17%) patients demonstrated lipoatrophy, lipohypertrophy and mixed syndrome, respectively. There is no sex association with lipoatrophy and mixed syndrome (p= 0.4138, OR= 0.3750, IC 95%= 0.0744 – 1.8891), whilst lipohypertrophy syndrome had predominance in females. It is assumed when calculating Odds Ratio to lipohypertrophy presence, was noted that female chance present lipohypertrophy is 2.66 times more, however, the results have not been significant (p=0.4130, IC 95% 0.5294 a 13.4334), data shown in Figure 2.
The HAART temporal analysis showed that there was a growing evolution of lipoatrophy and lipohypertrophy presence in association with prolonged use of HAART ($p = 0.0485$, $p = 0.0393$, respectively).

Among the 29 patients, 6 were taking hypolipidemic. The lipid profile found in patient’s evaluation, including those who had made use hypolipidemic therapy, was no statistically significant changes on the total cholesterol and LDL-C, however, for the HDL-C and triglycerides had significant differences between the first and last clinical follow-up nutritional (Figure 3).

**Legend:** (A) Total cholesterol, (B) LDL-C, (C) and HDL-C (D) triglycerides, distributed by quarters. Dependent t-test for paired samples.

**Fig. 3.** HIV patients Serum lipids who did not use hypolipidemic, distributed by quarters, 2006-2008 Para-Brazil.
When analyzing only the sample of patients who were taking hypolipidemic (n = 7), there was no statistically significant changes in the levels of serum total cholesterol, LDL-C and triglycerides (Table 3).

<table>
<thead>
<tr>
<th>Biochemical Tests</th>
<th>1º</th>
<th>2º</th>
<th>3º</th>
<th>4º</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>207.7 (±40.2)</td>
<td>264.0 (±128.2)</td>
<td>216.7 (± 69.2)</td>
<td>219.3 (±60.9)</td>
<td>0.6626</td>
</tr>
<tr>
<td>Total LDL cholesterol</td>
<td>91.7</td>
<td>136.6</td>
<td>108.8</td>
<td>89.7</td>
<td>0.2539</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>597.0 (±300.1)</td>
<td>996.0 (±1300.0)</td>
<td>488.3 (±637.6)</td>
<td>415.0 (±209.3)</td>
<td>0.0503</td>
</tr>
</tbody>
</table>

* Legend: Friedman test.

Table 3. Comparison of mean only of lipid profile of patients who were taking hypolipidemic therapy for the clinical follow-up of four nutritional consultations, Pará, Brazil 2006-2008.

In assessing relation between lipids and lipodystrophy syndrome, there was no significant association, as sample data in Table 4.

<table>
<thead>
<tr>
<th>Lipodystrophy Syndrome</th>
<th>Total Cholesterol</th>
<th>Lipohypertrophy</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipatrophyn (%)</td>
<td>Lipohypertrophyn (%)</td>
<td>Mixedn (%)</td>
<td>p value</td>
</tr>
<tr>
<td>Normal levels</td>
<td>3 (27.27)</td>
<td>0 (0.00)</td>
<td>7 (43.75)</td>
</tr>
<tr>
<td>Abnormal levels</td>
<td>8 (72.73)</td>
<td>2 (100.00)</td>
<td>9 (56.25)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>Normal levels</td>
<td>9 (81.82)</td>
<td>1 (50.00)</td>
</tr>
<tr>
<td>Abnormal levels</td>
<td>2 (18.18)</td>
<td>1 (50.00)</td>
<td>2 (12.50)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Normal levels</td>
<td>1 (9.09)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Abnormal levels</td>
<td>10 (90.91)</td>
<td>2 (100.00)</td>
<td>11 (68.75)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Normal levels</td>
<td>3 (27.27)</td>
<td>1 (50.00)</td>
</tr>
<tr>
<td>Abnormal levels</td>
<td>8 (72.73)</td>
<td>1 (50.00)</td>
<td>11 (68.75)</td>
</tr>
</tbody>
</table>

Legend: N - number of patients. Test: Partitioning Chi-square.

Table 4. Association between lipid profile and lipodystrophy syndrome, Pará, Brazil 2006-2008.
In assessing comparison of mean of lipid profile of all patients before and after the clinical and nutritional intervention (first and fourth visit), there was a significant difference between the levels of total cholesterol, LDL-C, HDL-C and triglycerides between the lipoatrophy and mixed syndrome (p > 0.05) (Table 5). No analysis was performed on the lipohypertrophy syndrome due to the presence of only two patients.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lipoatrophy</td>
<td>Mixed</td>
<td>p-value</td>
<td>Lipoatrophy</td>
<td>Mixed</td>
<td>p-value</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>196.91 (±35.05)</td>
<td>183.00 (±41.84)</td>
<td>0.3744</td>
<td>198.14 (±39.26)</td>
<td>185.58 (±45.97)</td>
<td>0.5538</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>112.42 (±40.61)</td>
<td>94.54 (±34.67)</td>
<td>0.2308</td>
<td>110.37 (±50.44)</td>
<td>86.33 (±32.10)</td>
<td>0.2313</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>37.91 (±11.65)</td>
<td>40.28 (±15.92)</td>
<td>0.6809</td>
<td>42.14 (±9.25)</td>
<td>44.92 (±14.64)</td>
<td>0.4504</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>299.36 (±27.77)</td>
<td>310.75 (±259.21)</td>
<td>0.9133</td>
<td>220.86 (±193.46)</td>
<td>218.90 (±179.92)</td>
<td>0.9829</td>
</tr>
</tbody>
</table>

Table 5. Comparison of mean of lipid profile of all patients, including who were taking hypolipidemic therapy before and after the intervention in lipodystrophy syndrome, Pará, Brazil 2006-2008.

The manifestation of lipodystrophy syndrome with regard to gender did not present significant differences for lipoatrophy or mixed syndrome. However, the syndrome was related to female lipohypertrophy corroborating other studies (Galli et al., 2002; Heath et al., 2002) and disagreeing with most published data has been shown increased risk of lipoatrophy syndrome among women. Tien et al. (2003) in prospective study of lipodystrophy syndrome risk among HIV-infected women and non-infected observed a risk 2.1 times more of develop lipoatrophy in infected women with virus than non-infected, whereas it did not differ lipohypertrophy syndrome between the two groups and the most prevalent de form lipodystrophy was mixed syndrome (81%). Van Griensven et al. (2007) evaluated the lipodystrophy syndrome prevalence among patients using stavudine in antiretroviral therapy and found lipoatrophy syndrome prevalence in 9.8% of patients on stavudine and 4.9% with lipohypertrophy syndrome. The HAART temporal analysis showed that there was a growing evolution of the appearance of lipoatrophy and lipohypertrophy associated with HAART prolonged use, as demonstrated by studies of Lichtenstein et al. (2005) and Goujard et al. (2003).

As regards the evaluation of metabolic changes associated with use of HAART coupled with the treatment of nutritional guidance, it must be pointed out that some factors may have affected the outcome of this work as the low adherence to medical treatment, nutrition, failure to follow the previous recommendations for achieving of biochemical tests and the small sample size of patients available for this study. This difficulty in adhering to medical treatment and/or diet therapy was also found by other authors (Quintaes & Garcia, 1999; Ceccato et al. 2004; Parenti et al., 2005; Barros et al. 2007; Chencinski & Garcia, 2006). The reluctance of patients to nutritional treatment may be related to low purchasing power (Barros et al., 2007), cultural and dietary habits proper to the Amazon region, who abuse food that are rich in lipids. In addition to psychosocial factors of patients, where the prejudice, social isolation and emotional disorders such as anxiety and depression
commonly observed in patients infected with HIV make it difficult to change lifestyle (personal and food) as suggested by Quintaes & Garcia (1999) Chencinski & Garcia (2006). There was also that patients profile evaluated before intervention reflected increase in serum total cholesterol and triglycerides, and lowering HDL-C as described in the literature (Caar et al. 1998; Hadigan et al. 2006; Having Hofstede et al., 2003; Abreu et al., 2006), disagreeing with main studies analyzed only about LDL-C, where most patients remained within normal range. Lipid disorders and association with lipodystrophy syndrome were common in all patients, especially in mixed syndrome, according to studies by Thiebaut et al. (2000) and Haugaard et al. (2005).

The lipid abnormalities evolution in patients after clinical and nutritional intervention during study noted significant changes of lowering triglycerides and increase in HDL-C, regardless of hypolipidemic use. The increased levels of HDL-C have been associated with decreased cardiovascular risk, as has been discussed in the work of Manninen et al. (1988). Where was reported that for every 1% increase in HDL-C was 3% reduction in coronary events and Pedersen et al. (1998) who said that for each 1% increase in HDL-C there was 1% reduction in coronary events, both independently of changes in LDL-C levels. The lipid profile of patients before and after nutritional intervention clinically observed that patients who had shown serum levels of triglycerides, total cholesterol and fractions (LDL-C and HDL-C) normal at first, had increasing them at the end of treatment. These patients had borderline values facilitating risk of increased total cholesterol, LDL-C and triglycerides and decreased HDL-C associated with nutrition acceptance less than 75%. Other patients in the first consultation showed values above the reference levels for total cholesterol, LDL-C and triglycerides as well as lowering HDL-C, reaching normal values due to good acceptance to nutritional care. The remaining patients showed levels of total cholesterol, LDL-C fractions, HDL-C and triglycerides changed during the research; probably was not able to perceive the importance of nutritional treatment. There were also cases of patients who had their lipid profile within the normal range, suggesting that not only the use of HAART interfered with these metabolic changes, but also other factors may be implicated as genetic predisposition. In regarding to lipodystrophy syndrome, the cholesterol and LDL-C means demonstrated it more significant in lipoatrophy than mixed syndrome compared before and after intervention. Triglyceride levels showed independent growing in despite to lipodystrophy syndrome, while HDL-C showed changed levels in mixed syndrome.

The physiopathology by which HAART determines HIV lipodystrophy syndrome, dyslipidemia therefore remains unknown. Second Andrade & Hutz (2002), the lipid serum levels are multifactorial characteristics, determinate by genetic and environmental factors, highlighting the genetic variability found in those genes that can affect the response to drugs used in hyperlipidemia treatment.

The authors of the lipodystrophy ambulatory care are developing a research paper about a case-control study conducted from December 2009 to July 2012. For data collection is being performed a clinical, epidemiological and nutritional evaluation where are registered information about patient identification, socio-economic conditions, personal and family history of morbidity, time of HIV diagnosis, HAART treatment duration, medication used - HAART, viral load, CD4 counts, clinical history, biochemical tests for dyslipidemia classification, anthropometric analysis and, APOAI and APOAV apolipoprotein polymorphism evaluation. This study aims to investigate these polymorphisms in an attempt to discover the main causes responsible for this metabolic disorder, the dyslipidemia.
6. Conclusion

The HAART has as one of its major collateral effect the lipodystrophy syndrome. There is necessity of more studies to deep into physiopathology of this syndrome; and metabolic and cardiovascular complications secondary to HAART. Dyslipidemia stands out as one of the most prevalent metabolic changes in patients with HIV, what makes it essential to feasibility of research in therapeutic care to clarifying of the clinical management. It is noted that nutritional guideline and/or hypolipidemic use, when have there been acceptance to treatment, takes place improvements of the lipid profile, can also there be normalization of those levels, in particular of the triglyceride levels. However, the adherence neither always takes place, what difficult the management of those patients.

7. References


Dyslipidemia in Patients with Lipodystrophy in the Use of Antiretroviral Therapy


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Dyslipidemia in Patients with Lipodystrophy in the Use of Antiretroviral Therapy


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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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