

Metabolic Disorders in HIV-infected Children Metabolic Disorders in HIV-infected Children

Spagnuolo M¹, Liguoro I and Guarino A

Department of Translation Science of Medicine University, Federico II, Naples, Italy

Corresponding author: Spagnuolo M¹, Department of Translation Science of Medicine University, Federico II, Naples, Italy, Tel: + 39 081 746 4337; Fax: + 39 081 746 4337; E-mail: mispagnu@unina.it

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Abstract

The introduction of highly active antiretroviral therapy (HAART) for the treatment of acquired immunodeficiency syndrome (AIDS) has resulted in greater survival of patients infected with the human immunodeficiency virus (HIV). However, the use of these drugs has been associated with lipodystrophic syndrome (LS), which is characterized by metabolic alterations (dyslipidemia, insulin resistance, diabetes, and lactic acidosis) and abnormal corporal fat distribution. Clinically, LS may manifest as three different forms: lipohypertrophy (accumulation of fat in the central part of the body), lipoatrophy (loss of fat in the extremities, face and buttocks) and mixed (lipohypertrophy + lipoatrophy). Although its physiopathology has not been elucidated, some mechanisms have been described, including leptin and adiponectin deficiency, mitochondrial dysfunction and use of antiretroviral drugs. The type, dose and duration of the antiretroviral treatment, as well as age and puberty are the main risk factors. LS are also associated with increased incidence of cardiovascular illnesses, atherosclerosis and diabetes mellitus. Follow up must be periodic, consisting of measurement of body fat distribution, evaluation of the lipid profile and insulin resistance.

Keywords: Hiv; Lipodystrophy; Highly active antiretroviral treatment; Children and adolescents

Introduction

Highly active antiretroviral therapy (HAART) has significantly improved the clinical outcome of HIV infection. However, HAART has been associated with potentially severe side effects in HIV-infected adults as well as in children. HIV-1-infected patients on HAART frequently develop a metabolic syndrome - in particular lipodystrophy syndrome (LS), which is characterised by peripheral lipoatrophy and visceral fat redistribution and is associated with metabolic alterations including dyslipidaemia, insulin resistance and cardiovascular risk [1-10]. The atherogenic profile of this syndrome may increase the risk of cardiovascular disease (CVD) even in young HIV-infected patients.

The pathophysiology of HAART-related lipodystrophy is still unknown, but the protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs), that are considered the mainstay of therapy, probably play a major role in this process [11-19]. It is also known that some antiretroviral molecules can inhibit differentiation and induce insulin resistance and apoptosis in adipose cells [20-26]. PIs are responsible for a decrease in cytoplasmic retinoic-acid protein-1, low-density lipoprotein receptor-related protein (LRP) and peroxisome proliferator activated receptor type-gamma (PPAR- γ) [27-32]. Instead, NRTIs and thymidine analogues cause mitochondrial dysfunction, as demonstrated by a decrease in subcutaneous adipose tissue mitochondrial DNA content. Both phenomena are responsible for a decreased differentiation of adiposities, increased levels of free fatty acids and lipoatrophy [33-41]. Even if it is now clear that the type and duration of NRTIs therapy is the dominant risk factor for the pathological changes of adipose tissue that underlie lipodystrophy [42-50], the pathogenesis of HAART-associated metabolic syndrome

is complex and several other factors may be involved, such as adipocytokines leptin, adiponectin and resistin [51-109].

A better understanding of the molecular mechanisms responsible for this syndrome will lead to the discovery of new drugs that will reduce the incidence of lipodystrophy and related metabolic complications in HIV-infected patients receiving HAART.

HIV and metabolic syndrome

Evidence for the increased prevalence of disorders of glucose metabolism in HIV-infected patients was initially derived from patient cohorts with HAART-associated lipodystrophy [44-50]. One such study reported the prevalence of diabetes at 2% in PIs recipients with lipodystrophy, rising to 7% after 14 months of further observation. Other previous studies also reported high rates of disorders of glucose metabolism in HAART-associated lipodystrophy, with diabetes in 7% and impaired glucose tolerance in 35% of HIV-infected patients [110-118]. A more recent study reported a prevalence of 17% using National Cholesterol Education Program Adult Treatment Panel Three (ATP-III) criteria in 710 patients in Spain, considering several risk factors such as BMI and past or current exposure to PIs [119-125]. Prospective reports showed that 10% of HIV-infected HAART recipients developed diabetes during a four-year follow-up period. After adjusting for age and body mass index (BMI) and comparing to controls, the resulting difference represented a greater than four-fold increase in the relative risk of developing diabetes [1,126]. Potentially related complications are also represented by hypertension, nephrotic syndrome, acanthosis nigricans and polycystic ovary syndrome [127].

The effect of initiation of HAART on diabetes incidence in treatment-naive patients has been recently reported by the Data Collection on Adverse Metabolic Syndrome, with referral to the constellation of the phenotypes of abdominal obesity, hyperlipidaemia,

elevated fasting glucose and hypertension [128-134]. Hyperinsulinaemia and insulin resistance can occur as a result of therapy with a PIs or as a consequence of the HIV infection. Initially, it was believed that PIs do not influence carbohydrate metabolism in pre-pubertal children due to the higher insulin sensitivity observed in this phase [135]. Nonetheless, recent studies have shown that these drugs lead to insulin resistance, both by decreasing the pancreatic beta cell response and through interference with the glucose transportation promoted by the GLUT-4 transport protein [125,135]. Therefore, treatment of HIV-infected children with PIs leads to the development of insulin resistance, similar to the situation observed in adults; the difference between the age groups is the difficulty in detecting this alteration.

The debate surrounding the predictive value of metabolic syndrome pivots around whether, as a composite, it predicts a multiplicative or additive increase in the risk of these conditions [136-139].

HIV and lipodystrophy

Lipodystrophy is observed with increasing frequency in HIV-infected adults and is considered a major public health problem because of its long-term cardiac and metabolic complications. However, there is limited information about abnormal fat distribution and complications in children. As yet, there are no well-defined criteria for the diagnosis of lipodystrophy in children [126].

The prevalence of lipodystrophy in HIV-infected children varies from 1 to 10% in the retrospective questionnaire-based surveys [129-134] and from 12 to 33% in studies conducted using anthropometry [50-110]. The frequency of lipodystrophy was determined by the sum of the three equally represented phenotypes (central lipohypertrophy, peripheral lipoatrophy and a combined pattern) and according to the European Paediatric HIV and Lipodystrophy Study Group, 46.7% of all children had clinical signs of fat redistribution [117,140].

Anthropometry can assess subcutaneous fat by measurement of skin-fold thickness in the biceps, triceps, subscapula and abdomen over the crest iliac, as well as by measurement of the circumference of the arm, leg, waist and hips. There is consensus that waist circumference is a good surrogate marker for visceral adipose tissue [1]. Jacquet defined peripheral fat wasting as facial, buttock or limb atrophy associated with arm skin-fold thickness below the third percentile of the reference values for sex and age, and truncal adiposity as breast enlargement or relative abdominal obesity with the skin-fold ratio at the trunk >2 standard deviations (SD) from the reference mean for sex and age [128-131].

The assessment of fat redistribution in HIV-infected children is also complicated by the normal dynamic alterations in body composition that occur during childhood and adolescence, therefore imaging could be considered more reliable than anthropometrics in diagnosing such modifications. Both dual-energy X-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI) have been also validated to assess fat distribution in children [132-134]. DEXA provides information about regional fat distribution, but cannot be used on the face, while computed tomography (CT) and MRI scanning discriminate between subcutaneous and visceral fat and may be useful techniques for detecting facial fat changes [136,137]. Furthermore, a recent study using DEXA and MRI showed that peripheral lipoatrophy is detectable in childhood even in the absence of clinical signs of lipodystrophy and that true central obesity is present only in children

with body-shape changes [129]. Although anthropometric measurements are easily obtained in children, CT represents the gold standard method for evaluation of fat distribution. However, it has several drawbacks, namely exposure to X-rays and need for sedation in infants and younger children that limit its use as a routine diagnostic tool. Therefore, it is preferable to evaluate body fat distribution in children using ultrasound rather than CT because of the lack of side effects, feasibility and lower costs [141].

The European Paediatric Lipodystrophy Group identified the following risk factors for lipodystrophy: severe clinical disease (US Centres for Disease Control and Prevention [CDS] stage C), female gender, older age, use of PIs, dideohydroxythymidine (d4T – stavudine) and efavirenz (belonging to Non-Nucleoside Reverse Transcriptase Inhibitors – NNRTIs – class) [142]. Besides, McComsey identified the puberty as the time in which HIV-infected children on HAART most likely develop lipodystrophy [43].

Pathogenesis of HIV lipodystrophy

Although the most compelling risk factor identified thus far has been HAART, genetic predisposition, virally mediated mechanisms involving HIV-1 accessory proteins, altered hormonal milieu and levels of inflammatory cytokines may also contribute to this syndrome and are currently under investigation

Drugs

Lipodystrophy has been closely linked to the use of PIs and, more recently, other antiretrovirals, including NRTIs and NNRTIs. Several mechanisms have been postulated to explain these adverse effects. PIs have the capacity to: inhibit the intrinsic activity of glucose transporter 4 (GLUT4) [34-41] alter degradation of sterol-regulatory-element-binding protein 1 (SREBP-1) and apolipoprotein B, resulting in lipodystrophy and increased lipid production; inhibit the function of LRP, leading to reduced TG clearance from the circulation [83]. NRTIs inhibit DNA polymerase gamma, an enzyme essential for mitochondrial DNA replication, resulting in mitochondrial DNA depletion, adipocyte death and lipoatrophy [143]. It has been also demonstrated that treatment with a NRTI-containing regimen of lamivudine or zidovudine in the absence of significant changes in body fat distribution, led to a 25% decrease in insulin-mediated peripheral glucose disposal and a 22% increase in fasting lipolysis [144]. However, a very recent study showed that substitution of stavudine with zidovudine could result in decreased severity or resolution of lipodystrophy among HIV-infected children and adolescents [145].

Pro-inflammatory cytokines

The increased levels of pro-inflammatory cytokines such as tumour necrosis factor (TNF)- α and interleukin (IL)-6 may further contribute to the development of lipodystrophy. TNF- α stimulates 11- β -hydroxysteroid dehydrogenase type-1, which converts inactive cortisone to active cortisol, resulting in increased lipid accumulation in adipocytes and insulin resistance. HAART drugs and inflammatory cytokines are also associated with a decrease in adiponectin levels [117-125] and this positively correlate with insulin resistance in HIV-infected patients with lipodystrophy.

Adipokines

Adipose tissue, previously seen as an inert energy storage organ, is now considered to be an endocrine organ in its own right. The hormonal changes caused by increases (in lipohypertrophy) or reduced subcutaneous fat (in lipoatrophy) may be central to the

metabolic abnormalities observed in HIV-infected patients with lipodystrophy.

Adiponectin levels are significantly lower in patients with fat redistribution and inversely correlate with serum TGs and insulin resistance [120-125]. These findings are independent of age, leptin levels, HIV medication and severity of disease. Low adiponectin levels may reflect a direct toxic effect of HAART on subcutaneous adipose tissue, but may also simply reflect the accumulation of visceral adipose tissue. Decreased adiponectin (as well as leptin expression) due to decreased adipocyte differentiation could be involved in the whole-body insulin resistance and metabolic manifestations observed in HIV lipodystrophy [126-131].

Recently, several experimental and clinical observations have implicated resistin, a 12.5 kDa polypeptide hormone produced by adipocytes and immunocompetent cells, in the development of insulin resistance [18,19,132,133].

The administration of resistin to animals resulted in impaired glucose and lipid metabolism in some studies [132] but these findings were challenged by subsequent reports of no association between adipose tissue resistin expression and insulin resistance [134]. Findings in humans have also been highly variable. Elevated resistin levels have been noted in obese and diabetic subjects, and increased resistin has been associated with insulin resistance in lean and obese subjects [135,136]. In a recent study of patients with HAART-induced metabolic syndrome, resistin levels decreased after administration of rosiglitazone, an insulin sensitiser, but no correlation between resistin and insulin resistance or markers of inflammation and coagulation was found [137-159]. The study by Spagnuolo et al. in agreement with another report, confirmed that circulating resistin levels are related to adiposity, but are unlikely to play a major role in the Homeostasis Model Assessment—Insulin Resistance (HOMA-IR) and metabolic abnormalities associated with HAART-induced metabolic syndrome [159].

It is noteworthy that serum resistin levels were below the mean in a child without ultrasound signs of fat redistribution and on restricted caloric intake. In fact, this suggests that a dietary approach may be beneficial in HIV-related LS.

Lipoatrophy has been associated with low circulating leptin levels through loss of subcutaneous adipose tissue, in which leptin is predominantly expressed. Observational studies in adults have demonstrated that also in HIV lipodystrophy leptin levels are positively correlated with adipose tissue mass [138-140]. Lipoatrophy is associated with relative hypoleptinaemia, but it is now evident that the metabolic, neuroendocrine and immunological effects of leptin deficiency may become manifest only once leptin falls below a threshold level [141,143]. The clinical cut-off for hypoleptinaemia remains to be clearly defined and may vary depending on the assay used. However, several studies including subjects with mixed patterns of fat redistribution at enrolment have failed to find significantly lower leptin levels than in controls [150].

In addition to its metabolic effects, it is clear that leptin has an important role in immune regulation. Leptin affects both cell-mediated and humoral immunity [150-153]. Leptin has been shown to have direct effects on cells of the innate immune system, upregulating phagocytic function in macrophages, stimulating pro-inflammatory cytokine secretion and stimulating chemotaxis in polymorphonuclear cells. The presence of the leptin receptor ObRb on these immune cells indicates that the role of leptin is likely to be direct and not mediated

by other hormonal changes, through activation of the JAK-STAT3 pathway in lymphocytes; other pathways such as MAPK and PI3K may also be involved [154-159].

Genetics

The genetic basis of HIV lipodystrophy (HIVLD) is also unclear. Some studies have implicated nucleotide variation in apolipoprotein CIII (ApoCIII), the β_3 adrenergic receptor or TNF- α . However, these studies focused on only one trait (e.g. triglycerides [TGs] or insulin resistance) and examined selected single nucleotide polymorphisms (SNPs) in a single gene [119].

HIV and dyslipidaemia

The main metabolic disorders presenting in lipodystrophy are dyslipidaemia, insulin resistance and lactic acidosis. It is usually of the mixed type, characterized by a decrease in high-density lipoprotein (HDL) cholesterol and increases in total cholesterol, LDL cholesterol and TGs. According to the European Paediatric Lipodystrophy Group, in 2004, 51% of children with lipodystrophy presented dyslipidaemia, 37% hypercholesterolaemia and 34% hypertriglyceridaemia [160]. Although dyslipidaemia can occur in children not treated with antiretroviral drugs, their usage, especially the PIs, favours the development of dyslipidaemia [161]. Among the PIs, ritonavir is the most commonly associated with dyslipidaemia [162-165].

Hyperlipidaemia has been described in HIV-positive children; HIV infection itself can modify the lipid profile, causing hypertriglyceridaemia and hypocholesterolaemia, stimulating a chronic inflammatory response by the inflammatory cells [165-168]. Moreover, many studies conducted on both adults and children with HIV infection have demonstrated that the introduction of an antiretroviral drug can induce dyslipidemia when it is not yet present or may worsen an already existing lipid disorder [169].

In the last few years, several studies on HIV-infected children have found an association between the use of PIs and increased levels of cholesterol and TG. In these studies, the prevalence of elevated total cholesterol ranged from 15 to 68%, while the prevalence of elevated TG ranged from 11 to 79% [163]. Tassiopoulos and colleagues conducted a longitudinal evaluation of cholesterolaemia on 2,122 perinatally HIV-infected children (Pediatric AIDS Clinical Trials Group 219C). The authors observed that a total of 277 of 2,122 children (13%) developed hypercholesterolaemia during a median follow-up of 50.4 months for an incidence rate of 3.4 cases per 100 person-years (95% confidence interval [CI] 3.0–3.9). After adjustment for age, boosted PIs use, PIs and NNRTIs use were associated with an increased risk of hypercholesterolaemia [164]. More recently, Chantray and colleagues observed that initiation or change in HAART was associated with significant increases in mean fasting total and LDL cholesterol during the 48 weeks of study observation. At week 48, the proportion of children with an abnormally high total cholesterol concentration significantly increased from 6% at entry to 21% ($p=0.001$) [165].

Management of dyslipidaemia in HIV-infected adults includes lifestyle changes, switching strategies and administration of lipid-lowering drugs. In terms of lifestyle changes, diet therapy is the primary approach to treating children and adolescents without HIV infection and with elevated blood cholesterol levels [170]. Although recent observational studies suggest that diet and physical exercise could improve lipid profile in HIV-infected patients [171,172], some RCTs did not corroborate this hypothesis [173,174]. However, a very

recent randomized study evaluated patients who had just begun HAART and prescribed a hypocaloric diet and were strictly followed, while controls had no diet and no nutritional follow-up [175]. This kind of approach resulted to prevent HAART-related dyslipidemia and lipodystrophy.

Modification of HAART – switching from a PI or to a PI-sparing regimen – is one strategy for managing dyslipidaemia in HIV-infected adults, but scant data exist about the efficacy of these strategies in children. McComsey and colleagues [166] published a prospective, open-label, multicentre trial conducted on 17 children who were switched from a PI-containing regimen to efavirenz. After 48 weeks, the switch to efavirenz resulted in significant improvements in total cholesterol, LDL and TG, while maintaining excellent virological control. Vigano et al. [167] published a 48-week randomised, prospective study in 28 HIV infected children. Individuals were randomized to switch from PI to efavirenz and from stavudine to tenofovir at baseline (group 1) or at week 24 (group 2). This study showed a significant improvement in lipid profile after replacing a PI (nelfinavir, lopinavir and ritonavir) with efavirenz and replacing stavudine with tenofovir.

There are currently no published data regarding the pharmacological treatment of dyslipidaemia in HIV-infected children. From the studies on HIV-positive adults with dyslipidaemia, statins should be used cautiously due to the potential for significant drug interactions when used with PIs (rhabdomyolysis and hepatitis) [169].

HIV and Cardiovascular Disease (CVD)

CVD is the prevalent cause of mortality in the general population and a relevant factor among HIV-infected adults [176]. Subjects who develop CVD usually have multiple risk factors (lack of exercise, obesity, smoking, diabetes, dyslipidaemia, etc.). HIV replication may increase cardiovascular risk, since it is an independent risk factor for lipid changes similar to those associated with increased risk of CVD in the general population [167]. The Strategies for Management of Antiretroviral Therapy (SMART) study showed that interruption of HAART is associated with increased cardiovascular risk in HIV-infected patients [168]. The Data Collection on Adverse events of Anti-HIV Drugs (DAD) study showed a relative increase in the incidence of myocardial infarction (MI) of 26% per year of exposure to HAART [177-181].

Few studies have looked at CVD risk factors and early manifestations of atherosclerosis in HIV-infected children and adolescents [177-186]. Bonnet et al. performed a cross-sectional study to evaluate vascular dysfunction in 49 HIV-infected children compared with 24 age- and sex-matched healthy controls. Among the HIV-infected children, 32 were receiving HAART and 15 were naive to therapy. HIV-infected subjects showed cross-sectional compliance, less distended carotid arteries and higher diastolic wall stress than controls, while the intima-media thickness (IMT) of common carotid arteries was similar in cases and controls [181]. Charakida et al. showed that HIV infection in childhood is associated with adverse structural (increased IMT) and functional changes in the vasculature, and, among HIV-infected children, age and treatment were significantly associated with increased IMT. In particular, vascular abnormalities were more pronounced in children exposed to PI therapy. These findings support a role for both HIV infection itself and antiretrovirals, especially PIs, in the pathogenesis of early vascular disease, in particular atherosclerosis [178].

McComsey et al. found greater values of carotid IMT and higher levels of some cardiac biomarkers in antiretroviral-treated HIV-infected children compared with age-, sex-, race- and BMI-matched healthy controls. On regression analysis, only duration of ART predicted IMT measurements, while traditional atherosclerosis risk factors, HIV disease factors and duration of PI did not [164].

Vigano et al. evaluated a cohort of 23 adolescents and young adults vertically infected with HIV compared with age-, sex- and BMI-matched healthy controls. Common carotid IMT (CCIMT) was higher in HIV-infected than in control children ($p < 0.001$). Predictors of CCIMT were HIV infection, male gender and vitamin B12 supplementation. Among the HIV-infected subjects, CCIMT was associated with the duration of exposure to a PI-based and NNRTI-based regimen plus single or double NRTI (treatment duration 11–20 years). The authors concluded that HIV infection and long duration of HAART are risk factors for higher CCIMT in adolescents and young adults [165].

HIV and bone

Many factors may negatively affect bone metabolism: direct interaction of HIV with cells of the bone, chronic T-cell activation, abnormal cytokine production affecting osteoblast and osteoclast function, disturbances of calcium homeostasis, parathyroid hormone function, vitamin D metabolism and adverse effects of HAART, especially PIs. Several studies on bone mineral measurements in HIV-infected children indicate a significant reduction of bone mineral content and bone mineral density (BMD).

Bone mineral accrual of HAART-treated children is impaired in comparison to healthy children [187,188]. In a prospective 12-month study, the BMD accrual of HAART-treated patients was comparable to that of healthy control patients at the vertebral site, but was lower than controls in the whole skeleton [187]. In another study, 60% of the patients had no change or decreased BMD SD-scores [188]. However, the use of tenofovir (one of the new molecules) has been linked to a reduction of bone mineral measurements in primates [189] and adult patients [190]. The available data in children are still poor and conflicting. Larger studies are needed to understand the effect of new drugs on bone mineral accrual in children.

HAART-treated children showed higher levels of markers of bone formation (bone alkaline phosphatase [BALP] and pro-collagen type 1 N-terminal pro-peptide [PINP]) and of bone resorption (N-telopeptide cross-links [NTx]) compared with antiretroviral-naive children and controls [191]. Children not receiving PIs showed reduced serum concentrations of osteocalcin and high levels of urinary NTx [187].

Serum concentrations of insulin-like growth factor-I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP3) in these patients were comparable to those of healthy controls. In another study, HIV-infected patients with severe symptoms showed significantly lower osteocalcin concentrations compared with patients with mild symptoms and healthy controls [192].

An open issue is the role of ART or HIV infection per se in the genesis of poor bone health in HIV-infected youths. Most studies have been performed in children who were receiving different antiretroviral drugs; the cohorts studied are heterogeneous in terms of treatment regimens employed, and thus it is not possible to reach definitive conclusions on the role of different classes of drug on skeletal health.

Few studies have reported results on untreated HIV-infected children [192,193]. In the first trial, 5 vertically infected patients were examined, and their DEXA measurements were compared with those of treated patients and healthy controls [192]. Vertebral and whole-body BMD values were found to be significantly higher than those of HAART-treated patients, and comparable to those of healthy children.

These results seem to indicate that HIV infection per se may not play an important role in the alteration of bone health in children, but more data are needed to clarify this issue.

Conclusion

Research should be undertaken into the metabolic risk.

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