Metabolic Disorders in HIV-infected Children

Metabolic Disorders in HIV-infected Children

Spagnuolo MI*, Liguoro I and Guarino A
Department of Translation Science of Medicine University, Federico II, Naples, Italy

*Corresponding author: Spagnuolo MI, 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

Received date: October 14, 2014; Accepted date: November 20, 2014; Published date: November 26, 2014

Copyright: © 2014 Spagnuolo MI, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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), lipodystrophy (loss of fat in the extremities, face and buttocks) and mixed (lipohypertrophy + lipodystrophy). 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-y) [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 adipocytes, 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 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 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, didehydrodeoxythymidine (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 lipodystrophy [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 sensitizer, 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 hyperleptinaemia, 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 hyperleptinaemia 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 OB-Rb 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 β3 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 hypercholesterolaemia, 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 dyslipidaemia 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 cholesterol and triglycerides 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, Chantry 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 in preventing HAART-related dyslipidemia and lipodystrophy.

Modification of HAART – switching from a PI or to a PI-sparing regimen – is one strategy for managing dyslipidemia 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 dyslipidemia in HIV-infected children. From the studies on HIV-positive adults with dyslipidemia, 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 naïve 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-naïve 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.

References

1. McComsey GA, Leonard E (2004) Metabolic complications of HIV therapy in children. AIDS 18: 1753-1768.
2. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, et al. (2004) Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA 292: 191-201.
3. Leonard EG, McComsey GA (2003) Metabolic complications of antiretroviral therapy in children. Pediatr Infect Dis J 22: 77-84.
4. Brambilla P, Bricalli D, Sala N, Renzetti F, Manzoni P, et al. (2001) Highly active antiretroviral-treated HIV-infected children show fat distribution changes even in absence of lipodystrophy. AIDS 15: 2415-2422.
5. Beregszaszi M, Dollfus C, Levine M, Faye A, Depghmoun S, et al. (2005) Longitudinal evaluation and risk factors of lipodystrophy and associated metabolic changes in HIV-infected children. J Acquir Immune Defic Syndr 40: 161-168.
6. Farley J, Gona P, Crain M, Cervia J, et al. (2005) Pediatric AIDS Clinical Trials Group Study 219C Team. Prevalence of elevated cholesterol and associated risk factors among perinatally HIV-infected children (4-19 years old) in Pediatric AIDS Clinical Trials Group 219C. J Acquir Immune Defic Syndr 38: 480-7.
7. Taylor P, Worrel C, Stainberg SM, Hazra R, Jankelevich S, et al. (2004) Natural history of lipid abnormalities and fat redistribution among human immunodeficiency virus-infected children receiving long term protease inhibitor-containing, highly active antiretroviral regimens. Pediatrics 114c: 235-242.
8. Tong Q, Sankalé JL, Hadigan CM, Tan G, Rosenberg ES, et al. (2003) Regulation of adiponectin in human immunodeficiency virus-infected patients: relationship to body composition and metabolic indices. J Clin Endocrinol Metab 88: 1559-1564.
9. Gan SK, Samaras K, Thompson CH, Kраegеn EW, Carr A, et al. (2002) Altered myocellular and abdominal fat partitioning predict disturbance in insulin action in HIV protease inhibitor-related lipodystrophy. Diabetes 51: 3163-3169.
10. Kosinski L, Kuritzkes D, Lichtenstein K, Eckel R (2003) Adipocyte-derived hormone levels in HIV lipodystrophy. Antivir Ther 8: 9-15.
11. Mynarčík DC, Combs T, McNurlan MA, Scherer PE, Komaroff A, et al. (2002) Adiponectin and leptin levels in HIV-infected subjects with insulin resistance and body fat redistribution. J Acquir Immune Defic Syndr 31: 514-520.
12. Jan V, Cervera P, Maachi M, Baudrimont M, Kim M, et al. (2004) Altered fat differentiation and adipokine expression are inter-related and linked to morphological changes and insulin resistance in HIV-1-infected lipodystrophic patients. Antivir Ther. 9:555–564.
13. Samaras K, Gan SK, Peake PW, Carr A, Campbell LV (2009) Proinflammatory markers, insulin sensitivity, and cardiometabolic risk factors in treated HIV infection. Obesity (Silver Spring) 17: 53-59.
14. Samaras K (2009) Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. J Acquir Immune Defic Syndr. V50: 499-505.
15. Purnell JQ, Zambon A, Knopp RH, Pizzuti DJ, Achari R, et al. (2000) Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. AIDS 14: 51-57.
16. Jemsek JG, Arathoon E, Arlotti P, Perez C, Sosa N, et al. (2006) Body fat and other metabolic effects of atazanavir and efavirenz, each administered in combination with zidovudine plus lamivudine, in antiretroviral-naive HIV-infected patients. Clin Infect Dis 42: 273-280.
17. Vonkeman HE, ten Napel CH, van Oeveren-Dybacz AM, Vermes I (2000) Beta3-adrenergic receptor polymorphism and the antiretroviral therapy-related lipodystrophy syndrome. AIDS 14: 1463-1464.
18. Maher B, Alfirevic A, Vilar FJ, Wilikins EG, Park BK, et al. (2002) TNF-alpha promoter region gene polymorphisms in HIV-positive patients with lipodystrophy. AIDS 16: 2013-2018.
19. Foulkes AS, Wohl DA, Frank I, Paleo E, Restine S, et al. (2006) Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. PLoS Med 3: e52.
20. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, et al. (2000) Molecular portraits of human breast tumours. Nature 406: 747-752.
21. Ramaswamy S, Ross KN, Lander ES, Golub TR (2003) A molecular signature of metastasis in primary solid tumors. Nat Genet 33: 49-54.
22. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, et al. (2001) The hormone resistin links obesity to diabetes. Nature 409: 307-312.
23. Dubé MP, Barker RA, Tebas P, Grinspoon SK, Zackin RA, et al. (2005) Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nefinavir or efavirenz plus dual nucleosides. AIDS 19: 1807-1818.
24. Robbins GK, De Gruttolta V, Shafer RW, Smeaton LM, Snyder SW, et al. (2003) Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 349: 2293–2303.
25. Arking DE, Pfeuffer A, Post W, Kao WH, Newton-Cheh C, et al. (2006) A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Nat Genet 38: 644-651.
26. Mallon PW, Miller J, Cooper DA, Carr A (2003) Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. AIDS 17: 971-979.
27. Parker RA, Flint OP, Mulvey R, Eloua C, Wang F, et al. (2005) Endoplasmic reticulum stress links dyslipidemia to inhibition of proteasome activity and glucose transport by HIV protease inhibitors. Mol Pharmacol 67: 1909–1919. Bibliographic Links.
28. International HapMap Consortium (2005) A haplotype map of the human genome. Nature 437: 1299-1320.
29. Botstein D, Risch N (2003) Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. Nat Genet (Suppl): 228–237.
30. Slomín N, Atwal GS, Tkacik G, Bialek W (2005) Information-based clustering. Proc Natl Acad Sci U S A 102: 18297-18302.
31. Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, et al. (2004) Regulation of fasting blood glucose by resistin. Science 303: 1195-1198.
32. Engert JC, Vohl MC, Williams SM, Lepage P, Loredo-Osti JC, et al. (2002) 5' flanking variants of resistin are associated with obesity. Diabetes 51: 1629-1634.
33. Wang H, Chu WS, Hemphill C, Elbein SC (2002) Human resistin gene: molecular scanning and evaluation of association with insulin sensitivity and type 2 diabetes in Caucasians. J Clin Endocrinol Metab 87: 2520-2524.
34. Pan W, Miller J, Cooper DA, Carr A (2003) Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. Nat Genet (Suppl): 228–237.
35. Slomín N, Atwal GS, Tkacik G, Bialek W (2005) Information-based clustering. Proc Natl Acad Sci U S A 102: 18297-18302.
36. Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, et al. (2004) Regulation of fasting blood glucose by resistin. Science 303: 1195-1198.
37. Engert JC, Vohl MC, Williams SM, Lepage P, Loredo-Osti JC, et al. (2002) 5' flanking variants of resistin are associated with obesity. Diabetes 51: 1629-1634.
38. Wang H, Chu WS, Hemphill C, Elbein SC (2002) Human resistin gene: molecular scanning and evaluation of association with insulin sensitivity and type 2 diabetes in Caucasians. J Clin Endocrinol Metab 87: 2520-2524.
39. Pan W, Miller J, Cooper DA, Carr A (2003) Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. Nat Genet (Suppl): 228–237.
40. Slomín N, Atwal GS, Tkacik G, Bialek W (2005) Information-based clustering. Proc Natl Acad Sci U S A 102: 18297-18302.
36. Osawa H, Yamada K, Onuma H, Murakami A, Ochi M, et al. (2004) The G/G genotype of resistin single-nucleotide polymorphism at -420 increases type 2 diabetes mellitus susceptibility by inducing promoter activity through specific binding of Sp1/3. Am J Hum Genet 75: 678–686.

37. Osawa H, Tabara Y, Kawamoto R, Ohashi J, Ochi M, et al. (2007) Plasma resistin, associated with single nucleotide polymorphism -420, is correlated with insulin resistance, lower HDL cholesterol, and high-sensitivity C-reactive protein in the Japanese general population. Diabetes Care 30: 1501–1506.

38. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, et al. (2008) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38: 320–323.

39. Ledru E, Christeff N, Patey O, de Truchis P, Melchior JC, et al. (2000) Alteration of tumor necrosis factor-a T cell homeostasis following potent antiretroviral therapy: contribution to the development of human immunodeficiency virus-associated lipodystrophy syndrome. Blood 95: 3519–3518.

40. Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ, et al. (2004) An inflammatory cascade leading to hyperresistinemia in humans. PLoS Med 1: e45.

41. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, et al. (2005) Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 111: 932-939.

42. Ene L, Goetghebuer T, Hainaut M, Peltier A, Toppet V, et al. (2007) Adipose tissue resistin expression is severely suppressed in obesity and type 2 diabetes mellitus. J Clin Endocrinol Metab 84: 4274-4277.

43. European Paediatric Lipodystrophy Group (2004) Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. AIDS 18: 1443-1451.

44. Paton NI, Yang Y, Tha NO, Sitoh YY (2003) Changes in facial fat in HIV-related lipoatrophy, wasting, and weight gain measured by magnetic resonance imaging. HIV Clin Trials 8: 227-234.

45. Viganò A, Mora S, Testolin G, Becchio S, Schneider L, et al. (2003) Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. J Clin Endocrinol Metab 88: 5452-5455.

46. Silha JV, Krsek M, Skrha JV, Sucharda P, Nyomba BL, et al. (2003) Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. J Clin Endocrinol Metab 88: 4848-4856.

47. Way JM, Gorgun CZ, Tong Q, Uysal KT, Brown KK, et al. (2004) Adipose tissue resistin expression is severely suppressed in obesity and stimulated by peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 279: 25651-25655.

48. Youn BS, Ky KK, Park HJ, Lee NS, Min SS, et al. (2004) Plasma resistin concentrations measured by enzyme-linked immunosorbent assay using a newly developed monoclonal antibody are elevated in individuals with type 2 diabetes mellitus. J Clin Endocrinol Metab 89: 150-156.

49. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW (2004) Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology 145: 2273-2282.

50. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 106: 1409-1421.

51. Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS (2003) The role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa. Lancet 366: 74-85.

52. Chan JL, Matarese G, Shetty GK, Raciti P, Kelesidis I, et al. (2006) Differential regulation of metabolic, neuroendocrine, and immune function by leptin in humans. Proc Natl Acad Sci U S A 103: 8481-8486.

Citation: Spagnuolo MI, Liguoro I, Guarino A (2014) Metabolic Disorders in HIV-infected Children Metabolic Disorders in HIV-infected Children. J Metabolic Synd 3: 169. doi:10.4172/2167-0943.1000169
74. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, et al. (2004) Recombinant human leptin in women with hypothalamic amenorrhea. N Engl J Med 351: 987-997.

75. Brennan AM, Mantzoros CS (2006) Drug Insight: the role of leptin in human physiology and pathophysiology—emerging clinical applications. Nat Clin Pract Endocrinol Metab 2: 318-327.

76. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, et al. (1996) Serum immuno-reactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 334: 292-295.

77. Martini G, Valenti R, Giovanacci C, Campagna S, Franci B, et al. (2001) Leptin and body composition in healthy postmenopausal women. Panminerva Med 43: 149-154.

78. Yarasheski KE, Zachwieja JJ, Horgan MM, Powderly WG, Santiago JV, et al. (2006) Leptin and body composition in healthy postmenopausal women. Panminerva Med 43: 149-154.

79. Lee JH, Chan JL, Sourlas E, Campagna S, Mantzoros CS (2006) Recombinant methionyl human leptin therapy in replacement doses improves insulin resistance and metabolic profile in patients with lipodystrophy and metabolic syndrome induced by the highly active antiretroviral therapy. J Clin Endocrinol Metab 91: 2605-2611.

80. Wunder D, Bersinger NA, Fux C, Weber R, Bernasconi E, et al. (2005) Leptin and body composition in healthy postmenopausal women. Panminerva Med 43: 149-154.

81. Koutkia P, Canavan B, Breu J, Johnson ML, Depaoli A, et al. (2004) Relation of leptin pulse dynamics to fat distribution in HIV-infected patients. Am J Clin Nutr 79: 1103-1109.

82. Harris RB (1998) Acute and chronic effects of leptin on glucose utilization in lean mice. Biochem Biophys Res Commun 242: 502-509.

83. Shibumura I, Hammer RE, Ikenoto S, Brown MS, Goldstein JL (1999) Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature 401: 73-75.

84. Petersen KE, Oral EA, Dufour S, Befroy D, Ariyan C, et al. (2002) Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 109: 1345-1350.

85. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, et al. (2002) Leptin-replacement therapy for lipodystrophy. N Engl J Med 346: 570-578.

86. Mandel MA, Mahmoud AA (1978) Impairment of cell-mediated immunity in mutation diabetic mice (db/db). J Immunol 120: 1375-1377.

87. Mantzoros CS, Moschos S, Mantzoros CS (2005) Leptin in immunology. J Immunol 174: 3137-3142.

88. Mancuso P, Gottschalk A, Phare SM, Peters-Golden M, Lukacs NW, et al. (1999) Leptin-deficient mice exhibit impaired host defense in Gram-negative pneumonia. J Immunol 168: 4018-4024.

89. Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, et al. (1998) Leptin regulates proinflammatory immune responses. FASEB J 12: 57-65.

90. Caldefie-Chezet F, Poulin A, Vasson MP (2003) Leptin regulates functional capacities of polymorphonuclear leukocytes. Free Radic Res 37: 143-151.

91. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, et al. (1998) Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 394: 897-901.

92. Baumann H, Morella KK, White DW, Dembski M, Bailon PS, et al. (1998) The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. Proc Natl Acad Sci U S A 93: 8374-8378.

93. Martin-Romero C, Sanchez-Margalet V (2001) Human leptin activates PI3K and MAPK pathways in human peripheral blood mononuclear cells: possible role of Sam68. Cell Immunol 212: 83-91.

94. Sanchez-Margalet V, Martin-Romero C (2001) Human leptin signaling in human peripheral blood mononuclear cells: activation of the JAK-STAT pathway. Cell Immunol 211: 30-36.

95. Howard JK, Lord GM, Matarese G, Vendetti S, Ghaezi MA, et al. (1999) Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. J Clin Invest 104: 1051-1059.

96. Ozata M, Ozdemir IC, Licinio J (1999) Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. J Clin Endocrinol Metab 84: 3686-3695.

97. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, et al. (2002) Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest 110: 1093-1103.

98. Chan JL, Stoyneva V, Kelesidis T, Raciti P, Mantzoros CS (2006) Peptide YY levels are decreased by fasting and elevated following caloric intake but are not regulated by leptin. Diabetologia 49: 169-173.

99. Canavan B, Salem RO, Schurgin S, Koutkia P, Lipinska I, et al. (2005) Effects of physiological leptin administration on markers of inflammation, platelet activation, and platelet aggregation during caloric deprivation. J Clin Endocrinol Metab 90: 5779-5785.

100. Mantzoros CS, Flier JS, Rogol AD (1997) A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. J Clin Endocrinol Metab 82: 1066-1070.

101. Licinio J, Caglayan S, Ozata M, Yildiz BO, de Miranda PB, et al. (2004) Phenotypic effects of leptin replacement on morbidity, obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proc Nail Acad Sci U S A 101: 4531-4536.

102. Musso C, Cochran E, Javor E, Young J, Depaoli AM, et al. (2005) The long-term effect of recombinant methionyl human leptin therapy on hyperandrogenism and menstrual function in female and pituitary function in male and female hypoleptinemic lipodystrophic patients. Metabolism 54: 255-263.

103. Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, et al. (1998) A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 392: 398-401.

104. LaPaglia N, Steiner J, Kirsteins V, Emanuele M, Emanuele N (1998) Recombinant methionyl human leptin therapy for lipodystrophy. N Engl J Med 338: 112-118.

105. Krause JC, Toye MP, Stechenberg BW, Reiter EO, Allen HF (2005) HIV-associated lipodystrophy. Pediatr Endocrinol Rev 3: 45-51.
113. Vigano A, Giacomini V (2005) Nucleoside analogues toxicities related to mitochondrial dysfunction: focus on HIV-infected children. In: Proceedings from the 1st Meeting on mitochondrial toxicity & HIV infection: understanding the pathogenesis for a therapeutic approach. 10 Suppl 2: M53-64.

114. Fredriks AM, van Buuren S, Fekkes M, Verloove-Vanhorick SP, Wit JM (2005) Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? Eur J Pediatr 164: 216-222.

115. Scherer R, Shen W, Bacchetti P, Kotler D, Lewis CE, et al. (2008) Comparison of dual-energy X-ray absorptiometry and magnetic resonance imaging-measured adipose tissue deposits in HIV-infected and control subjects. Am J Clin Nutr 88: 1088-1096.

116. Jansen I, Kutzmannz R, Ross R (2002) Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med 162: 2074-2079.

117. Fernandez JR, Redden DT, Pietrobelli A, Allison DB (2004) Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. J Pediatr 145: 439-444.

118. Yoon C, Gulick RM, Hoover DR, Vaamonde CM, Gleesby MJ (2004) Case-control study of diabetes mellitus in HIV-infected patients. J Acquir Immune Defic Syndr 37: 1464-1469.

119. Jerico C, Knobel H, Montero M, Ordonez-Llanos J, Guelar A, et al. (2012) Metabolic consequences and therapeutic options in HIV-infected children. J Metabolic Synd 3: 169.

120. Jacobson DL, Tang AM, Spiegelman D, Thomas AM, Skinner S, et al. (2005) Incidence of metabolic syndrome in a cohort of HIV-infected adults and prevalence relative to the US population (National Health and Nutrition Examination Survey). J Acquir Immune Defic Syndr 43: 458-466.

121. Lainka E, Oezbek S, Falck M, Ndagijimana J, Niehues T (2002) Marked dyslipidemia in human immunodeficiency virus-infected children on protease inhibitor-containing antiretroviral therapy. Pediatrics 100: e56.

122. Salehian B, Bilas J, Bazargan M, Abbasi M (2005) Prevalence and incidence of diabetes in HIV-infected minority patients on protease inhibitors. J Natl Med Assoc 97: 1088-1092.

123. Amorosa V, Synnestvedt M, Gross R, Friedman H, MacGregor RR, et al. (2005) A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia. J Acquir Immune Defic Syndr 39: 537-541.

124. Howard AA, Floris-Moore M, Arnsten JH, Santoro N, Fleischer N, et al. (2005) Disorders of glucose metabolism among HIV-infected women. Clin Infect Dis 40: 1492-1499.

125. Justman JE, Benning L, Danoff A, Minkoff H, Levine A, et al. (2003) Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women. J Acquir Immune Defic Syndr 32: 298-302.

126. Tien PC, Schneider MF, Cole SR, Levine AM, Cohen M, et al. (2007) Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study. AIDS 21: 1739-1745.

127. Yacizciglo GP, Istan F, Alunbas H, Suleymanlar I, Ozdogan M, et al. (2004) Insulin resistance in chronic hepatitis C. Int J Clin Pract 58: 1020-1022.

128. Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, et al. (2007) Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. Clin Infect Dis 45: 111-119.

129. Grinspoon S, Carr A (2005) Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 352: 48-62.

130. Panz VR, Joffe BI (1999) Impact of HIV infection and AIDS on prevalence of type 2 diabetes in South Africa in 2010. BMJ 318: 1351A.

131. Levitt NS, Bradshaw D (2006) The impact of HIV/AIDS on Type 2 diabetes prevalence and diabetes healthcare needs in South Africa: projections for 2010. Diabet Med 23: 103-104.

132. Grundy SM, Brewer B, Cleeman JI, Smith SC, Lenfant C (2004) Definition of metabolic syndrome. Report of the National Heart, Lung, and Blood Institute/ American Heart Association Conference on Scientific Issues related to definition. Circulation 109: 433-438.

133. Alberti KG, Zimmet P, Shaw J (2005) The metabolic syndrome--a new worldwide definition. Lancet 366: 1059-1062.

134. Alam N, Cortina-Borja M, Goetgebuer T, Marcynska M, Vigano A, et al. (2012) for the European Paediatric HIV and Lipodystrophy Study Group in EuroCoord. Body Fat Abnormality in HIV-Infected Children and Adolescents Living in Europe: Prevalence and Risk Factors. J Acquir Immune Defic Syndr 59: 314-24.

135. Bockhorst JL, Kseiriy I, Toye M, Chipkin SR, Stechenberg BW, et al. (2003) Evidence of human immunodeficiency virus-associated lipodystrophy syndrome in children treated with protease inhibitors. Pediatr Infect Dis J 22: 463-465.

136. Arpadi S, Shaik S, v.d. Rijn D, Martens L, Patel F, et al. (2013) Metabolic abnormalities and body composition of HIV-infected children on Lopinavir or Nelfinavir-based antiretroviral therapy. Arch Dis Child 98: 258-264.

137. Morén C, Nogueira-Julian A, Rovira N, Corrales E, Garrabou G, et al. (2011) Mitochondrial impact of human immunodeficiency virus and antiretrovirals on infected pediatric patients with or without lipodystrophy. Pediatr Infect Dis J 30: 992-995.

138. Blumer RM, van Vonderen MG, Sutinen J, Hassink E, Ackermans M, et al. (2008) Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. AIDS 22: 227-236.

139. Argini M, van der Nederpel M, Sutinen J, Hassink E, ACKERMANS M, et al. (2008) Zidovudine/lamivudine contributes to insulin resistance within 3 months of starting combination antiretroviral therapy. AIDS 22: 227-236.

140. Arpadi S, Shaik S, v.d. Rijn D, Martens L, Patel F, et al. (2013) Metabolic abnormalities and body composition of HIV-infected children on Lopinavir or Nelfinavir-based antiretroviral therapy. Pediatr Infect Dis J 31: 384-388.

141. Kamin D, Hadigan C, Lehrke M, Maaza S, Lazar MA, et al. (2005) Resistin levels in human immunodeficiency virus-infected patients with lipodystrophy decrease in response to resoliglitzazone. J Clin Endocrinol Metab 90: 3423-3426.

142. Barb D, Wadhwa SG, Kratzsch J, Gavrila A, Chan JL, et al. (2005) Circulating resistin levels are not associated with fat redistribution, insulin resistance, or metabolic profile in patients with the highly active antiretroviral therapy-induced metabolic syndrome. J Clin Endocrinol Metab 90: 5324-5328.

143. Garg A (2004) Acquired and inherited lipodystrophies. N Engl J Med 350: 1220-1234.
Citation: Spagnuolo MI, Liguoro I, Guarino A (2014) Metabolic Disorders in HIV-infected Children Metabolic Disorders in HIV-infected Children. J Metabolic Synd 3: 169. doi:10.4172/2167-0943.1000169

Page 9 of 10

150. Miller KK, Daly PA, Sentochnik D, Doweiko J, Samore M, et al. (1998) Human immunodeficiency virus type 1-related lipatrophy and lipo hypertrophy are associated with serum concentrations of leptin. Clin Infect Dis 36: 795-802.

151. Miller KK, Daly PA, Sentoczynk D, Dowdico J, Samore M, et al. (1998) Pseudo-Cushing's syndrome in human immunodeficiency virus-infected patients. Clin Infect Dis 27: 68-72.

152. Carter VM, Hoy I, Bailey M, Colman PG, Nyulasi I, et al. (2001) The prevalence of lipodystrophy in an ambulant HIV-infected population: it all depends on the definition. HIV Med 2: 174-180.

153. Santos CP, Felipe YX, Braga PE, Ramos D, Lima RO, et al. (2005) Self-perception of body changes in persons living with HIV/AIDS: prevalence and associated factors. AIDS 19 Suppl 4:S14-21.

154. Lichtenstein KA, Ward DJ, Moorman AC, Delaney KM, Young B, et al. (2001) Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. AIDS 15: 1389-1398.

155. Thebaud R, Daoust V, Mercie P, Ekouevi DK, Malay D, et al. (2000) Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. Groupe d'Épidémiologie Clinique du Syndrome d’Immunodeficience Acquise en Aquitaine. Clin Infect Dis 31: 1482-1487.

156. Ranganathan S, Kern PA (2002) The HIV protease inhibitor saquinavir impairs lipids metabolism and glucose transport in cultured adipocytes. J Endocrinol 172: 155-162.

157. Imami N, Antonopoulos C, Hardy GA, Gazzard B, Gotch FM (1999) Assessment of type 1 and type 2 cytokines in HIV type 1 infected individuals: impact of highly active antiretroviral therapy. AIDS Res Hum Retroviruses 15: 1499-1508.

158. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, et al. (1996) cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). Biochem Biophys Res Commun 221: 286-289.

159. Fitch KV, Anderson EJ, Hubbard JL, Carpenter SJ, Waddell WR, et al. (2006) A lifestyle modification program in HIV-infected patients with the metabolic syndrome. AIDS 20: 1843-1850.

160. Turcinov D, Stanley C, Canchola JA, Rutherford GW, Novotny TE, et al. (2009) Dyslipidemia and adherence to the Mediterranean diet in Croatian HIV-infected patients during the first year of highly active antiretroviral therapy. Coll Antropol 33: 423-430.

161. Lazzaretti RK, Kuhmmer R, Sprinz E, Polanczyk CA, Ribeiro JP (2012) Dietary Intervention Prevents Dyslipidemia Associated With Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus Type 1–Infected Individuals. A Randomized Trial. JACC 59: 979–88.

162. Chantry CJ, Hughes MD, Alvero C, Cervia JS, Meyer WA 3rd, et al. (2001) Clinical assessment of HIV-associated lipodystrophy in an ambulant HIV-infected population. AIDS 15: 1389-1398.

163. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Increased risk of mortality in a community-based cohort of HIV-infected persons treated with protease inhibitors. J Infect Dis 188: 1184-1190.

164. Bitnun A, Sochett E, Dick PT, To T, Jefferies C, et al. (2005) Insulin sensitivity and beta-cell function in protease inhibitor-treated and -naive human immunodeficiency virus-infected children. J Clin Endocrinol Metab 90: 168-174.

165. Biton A, Sochent E, Dick PT, To T, Jefferies C, et al. (2005) Insulin sensitivity and beta-cell function in protease inhibitor-treated and -naive human immunodeficiency virus-infected children. J Clin Endocrinol Metab 90: 168-174.

166. van der Valk M, Gisolf EH, Reiss P, Wit FW, Japour A, et al. (2001) and the Prometheus Study Group. Increased risk of lipodystrophy when

167. Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, et al. (2003) Adult AIDS Clinical Trials Group Cardiovascular Subcommittee; HIV Medical Association of the Infectious Disease Society of America. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 37: 613–27.

168. Tassiopoulos K, Williams P, George R, Marilyn c, James O, John F, et al. (1999) Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 338: 1650-1656.

169. Thöm GI, Fedou C, Brun JF, Fabre J, Renard E, et al. (2002) Reduction of fat accumulation and lipid disorders by individualized light aerobic training in human immunodeficiency virus infected patients with lipodystrophy and/or dyslipidemia. Diabetes Metab 28: 397-404.

170. Terry L, Sprinz E, Stein R, Medeiros NB, Oliveira J, et al. (2006) Exercise training in HIV-1-infected individuals with dyslipidemia and lipodystrophy. Med Sci Sports Exerc 38: 411-417.

171. Imami N, Antonopoulos C, Hardy GA, Gazzard B, Gotch FM (1999) Assessment of type 1 and type 2 cytokines in HIV type 1 infected individuals: impact of highly active antiretroviral therapy. AIDS Res Hum Retroviruses 15: 1499-1508.

172. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA (2003) Increased risk of mortality in a community-based cohort of HIV-infected persons treated with protease inhibitors. J Infect Dis 188: 1184-1190.
nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. AIDS 15: 847–855.

185. Dolan SE, Hadigan C, Killilea KM, Sullivan MP, Hemphill L, et al. (2005) Increased cardiovascular disease risk indices in HIV-infected women. J Acquir Immune Defic Syndr 39: 44-54.

186. Mora S, Sala N, Bricalli D, Zuin G, Chiumello G, et al. (2001) Bone mineral loss through increased bone turnover in HIV-infected children treated with highly active antiretroviral therapy. AIDS 15: 1823-1829.

187. Mora S, Zamproni I, Beccio S, Bianchi R, Giacomet V, et al. (2004) Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. J Clin Endocrinol Metab 89: 24–28.

188. Jacobson DL, Spiegelman D, Duggan C, Weinberg GA, Bechard L, et al. (2005) Predictors of bone mineral density in human immunodeficiency virus-1 infected children. J Pediatr Gastroenterol Nutr 41: 339-346.

189. Castillo AB, Tarantal AF, Watnik MR, Martin RB (2002) Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (Macaca mulatta). J Orthop Res 20: 1185-1189.

190. O’Brien KO, Razavi M, Henderson RA, Caballero B, Ellis KJ (2001) Bone mineral content in girls perinatally infected with HIV. Am J Clin Nutr 73: 821-826.

191. Zamboni G, Antoniazzi F, Bertoldo F, Lauriola S, Antozzi L, et al. (2003) Altered bone metabolism in children infected with human immunodeficiency virus. Acta Paediatr 92: 12-16.

192. Stagi S, Bindi G, Galluzzi F, Galli L, Salti L, et al. (2004) Changed bone status in human immunodeficiency virus type 1 (HIV-1) perinatally infected children is related to low serum free IGF-I. Clin Endocrinol 61: 692-699.

193. Mora S, Zamproni I, Giacomet V, Cafarelli L, Figini C, et al. (2005) Analysis of bone mineral content in horizontally HIV-infected children naive to antiretroviral treatment. Calcif Tissue Int 76: 336-340.