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Factors Associated with Insulin Resistance among Children and Adolescents Perinatally Infected with HIV-1 in the Pediatric HIV/AIDS Cohort Study

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Key Words
Insulin resistance · HIV · Highly active antiretroviral therapy · Homeostatic model assessment of insulin resistance

Abstract
Background/Aims: Because of prior inconsistent findings, we studied a large cohort of HIV-infected children to determine: (1) prevalence of insulin resistance (IR); (2) anthropometric and clinical correlates of IR, and (3) concomitant abnormalities of glucose tolerance. ***Methods:*** The study population consisted of 451 children from the Pediatric HIV/AIDS Cohort Study. The outcome of interest was HOMA-IR. Covariates included demographic, metabolic, growth, body composition, HIV laboratory tests, and treatment characteristics. Children meeting triggers for IR underwent oral glucose tolerance tests and hemoglobin A1c (HbA1c) measurements. ***Results:*** Among 402 children with glucose and insulin measurements, 15.2% had IR of whom 79% were pubertal. IR was associated with higher alanine aminotransferase, body mass index, and nadir CD4%, Tanner stage 5, and ever having received amprenavir. Of those with IR, three had impaired fasting glucose (IFG), three impaired glucose tolerance (IGT), one IFG and IGT, none diabetic glucose tolerance, and three HbA1c between 6.1 and 6.5%. ***Conclusion:*** In our cohort of HIV-infected adolescents, we observed a 15.2% prevalence of IR more closely linked to obesity than any other variable. This finding mirrors the high prevalence of obesity-mediated IR in American youth. However, associations with CD4 count and use of protease inhibitors may indicate some effect of HIV and/or its treatment.

Introduction

Insulin resistance (IR) has a reported prevalence of 25–33% in human HIV-infected adults [1]. In a much smaller percentage of infected adults, IR has progressed to disturbances in glucose tolerance and even overt dia-

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betes in 5–10% [2]. The relationship to highly active antiretroviral therapy (HAART) is supported by reversal of IR in drug-switch studies [3] and by induction of IR after short-term administration of HAART components to normal volunteers [4].

Reported prevalence of IR in children with HIV infection ranges from 6.5% to as high as 52% [5, 6], with variability potentially related to ethnic/racial differences, small sample sizes, and variable methodologies for quantification of IR. Generic and interrelated risk factors for IR to which populations at risk for HIV are preferentially exposed include overweight related to poor nutrition and inadequate exercise, minority background, low educational level, and lower socio-economic stratum [7].

The exact pathogenesis of IR in HIV-infected subjects is not known, but is likely to be multifactorial. IR has been attributed to HIV itself and/or, more likely, to the use of HAART, especially protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) [8]. It has also been associated with unfavorable changes in body composition (lipodystrophy), which may occur de novo in untreated HIV-infected patients, but is more often seen in those receiving PIs. The accompanying increase in visceral fat is likely to contribute to IR, perhaps mediated by heightened production of resistin [9] and/or reduced production of adiponectin [10] by adipose tissue. Several studies have now established that direct inhibition of the insulin-responsive facilitative glucose transporter isoform 4 (GLUT4) is a primary mechanism by which PIs and NRTIs acutely alter peripheral glucose disposal [8]. As an additional mechanism underlying IR, mitochondrial DNA and function can be altered by NRTI treatment and/or by HIV infection [10].

Because of these relatively limited and somewhat inconsistent findings in HIV-infected pediatric populations, we sought to study a large cohort of well-characterized children with perinatally acquired HIV infection with the specific goals of: (1) estimating the prevalence of IR; (2) identifying anthropometric and clinical correlates of IR, and (3) quantifying any concomitant abnormalities of glucose tolerance.

Methodology

The source population for this study comprised 451 HIV-infected children enrolled in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective cohort study designed to evaluate the impact of HIV infection and HAART on multiple domains in preadolescents and adolescents with perinatal HIV infection. Between March 2007 and December 2009, HIV-infected children from 15 study sites in the US, including Puerto Rico, were eligible for enrollment into AMP if they were born to HIV-infected mothers, were between 7 and 16 years of age, and were previously enrolled in another protocol team-approved longitudinal cohort study. These studies include the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) protocols 219 and 219C (which were earlier prospective studies designed to evaluate the long-term effects of HIV infection and in utero and postnatal exposure to HAART) and the Women and Infants Transmission Study (WITS) (a longitudinal study of HIV-infected pregnant women and their infants). Children with a complete medical history since birth, including details of HAART use, HIV RNA concentrations, and lymphocyte subsets, were also eligible for enrollment. The AMP protocol was approved by the institutional review board at each participating site and by that of the Harvard School of Public Health. Written informed consent was obtained from each child's parent or legal guardian, and assent was obtained from child participants according to local institutional review board guidelines.

This is a cross-sectional analysis of fasting (≥8 h) laboratory data [including plasma glucose, serum insulin, lipids, alanine aminotransferase (ALT), and hemoglobin A1c (HbA1c)], along with blood pressure (BP), and anthropometrics [height, weight, and body mass index (BMI), and dual-energy X-ray absorptiometry (DXA) measurements for body composition] collected at study entry. Laboratory tests were assayed at the clinical sites. Elevated total cholesterol was defined as >11.1 mmol/l, elevated low-density lipoprotein (LDL) cholesterol as >7.2 mmol/l, reduced high-density lipoprotein (HDL) cholesterol as <1.9 mmol/l, and elevated triglycerides as >1.2 mmol/l (age <10 years) or >1.7 mmol/l (age ≥10 years) [11]. Local normal ranges for other analytes were employed.

BP was measured using an automated, noninvasive monitor with subjects in the sitting position. The average of at least two readings was standardized for sex, age, and height using methods outlined in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf). Heights were measured using wall-mounted stadiometers, weights using electronic scales, and BMI was calculated by dividing weight in kilograms by the square of the height in meters. For our analyses, lean was defined as ≤85th percentile, overweight as >85th to ≤97th percentile, moderately obese as >97th to ≤99th percentile, and severely obese as >99th percentile. Total body DXA scans were performed on either a Lunar (General Electric Healthcare, UK) or Hologic (Hologic Inc., Bedford, Mass., USA) scanner and the results were sent to the Body Composition Analysis Center at Tufts University School of Medicine for analysis and standardization across sites. A phantom was circulated and scanned at each clinical site to cross-calibrate DXA scanners. Tanner staging was assessed by the site pediatric medical practitioners who routinely evaluate growth and development in children and received standardized training from the same pediatric endocrinologist (M.E.G.). Tanner stage was ascertained by inspection of breasts and pubic hair for females and of genitalia and pubic hair for males at semi-annual visits until Tanner stage 5 was reached. For boys and girls, the more advanced stage of the two respective pubertal components was used for classification if there were discordances between sites.

The outcome of interest was IR at entry defined as a calculated homeostatic model assessment of IR or HOMA-IR [fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5] >2.5 in prepubertal (Tanner stage 1) or >4.0 in pubertal aged children (Tanner stage >1) [12]. Those children meeting these triggers for IR were further characterized based on results of a 2-hour oral glucose tolerance test (OGTT) and simultaneous HbA1c measurement. Abnormal glucose tolerance was defined according to American Diabetes Association (ADA) criteria: impaired fasting glucose (IFG) = fasting glucose >5.5 mmol/l, but <6.9 mmol/l; impaired glucose tolerance (IGT) = 2-hour glucose (post-glucose load) between 7.7 and 11.0 mmol/l; diabetes mellitus = fasting plasma glucose ≥6.9 mmol/l, 2-hour glucose (post-glucose load) ≥11.0 mmol/l, or HbA1c ≥6.5%. Children with known diabetes were excluded from this analysis.

Covariates considered for associations with IR included demographic, metabolic, growth, body composition, laboratory, and antiretroviral treatment (ART) characteristics, non-ART medications associated with hyperglycemia (http://www.globalrph.com/glycemia.htm), and clinical history of diagnoses, ART use, lymphocyte subsets, HIV viral loads, and HIV disease progression as measured by the Centers for Disease Control clinical classification which were abstracted from medical charts and obtained from available databases of prior studies. Ever-use of individual ART medications assessed for their association with IR included those known to be associated with hyperglycemia: amprenavir/fosamprenavir (APV), lopinavir (LPV), abacavir, stavudine, didanosine, indinavir, nelfinavir, ritonavir, and saquinavir [13, 14], and those ever used by at least 10% of the source population.

Univariable associations between covariates and IR were assessed using Kruskal-Wallis tests for continuous parameters and χ^2 or Fisher exact tests for categorical parameters as appropriate based on sample size. To identify independent factors associated with IR, covariates associated with IR in univariable analyses at $p < 0.10$ were entered into a multivariable logistic regression model. Among collinear univariable predictors, one was chosen to be included in multivariable analyses based on univariable effect sizes. In a secondary analysis, calculations were rerun excluding children with other diagnoses associated with hyperglycemia (http://www.globalrph.com/glycemia.htm). All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, N.C., USA).

Results

Among the 451 HIV-infected children in AMP, 448 had an entry visit as of October 1, 2010. Two of these children had a prevalent diagnosis of type 2 diabetes and one other was on metformin prior to entry. These three children and an additional 43 children with missing fasting insulin and glucose results were excluded from this analysis. Of the remaining 402 children, 61 (15.2%) had IR at entry, including 13/104 (12.5%) at Tanner stage 1 (prepubertal) and 47/296 (15.9%) at greater than Tanner stage 1. Among those at Tanner stage 1, the median HOMA was 1.0 (interquartile range: 0.4–1.8). As expected, the median HOMA among the children at Tanner stage >1 was significantly higher (median: 1.8, interquartile range: 1.1–3.2; $p < 0.0001$).

Comparisons of the children with IR to those without IR (n = 341) at entry, including demographic, metabolic, growth, body composition, laboratory, and ART characteristics, are shown in online supplementary table 1 (for all online supplementary materials, see www.karger.com/doi/10.1159/000332957). There were no differences between groups in terms of age, sex, or race/ethnicity. As expected, compared to children without IR, those with IR had significantly higher fasting insulin concentrations (252 ± 235 pmol/l vs. 61.2 ± 35.6 pmol/l, $p < 0.0001$). In addition, higher fasting glucose concentrations (4.9 ± 0.51 mmol/l vs. 4.4 ± 0.5 mmol/l, $p < 0.0001$) were observed in those with IR. Greater percentages of those with IR compared to those without had hypertriglyceridemia (36 vs. 22%, p = 0.03) and elevated ALT concentrations (21 vs. 6%, $p < 0.0001$, with mean values of 27.9 vs. 21.1 U/l, respectively). There were no significant differences between groups in terms of total, LDL, and HDL cholesterol, BP, or use of medications associated with hyperglycemia. Those with IR had significantly more advanced pubertal staging overall and greater BMI, along with significantly higher weight z-score, waist circumference, and waist-to-hip ratio compared to those without IR. In addition, those with IR had a significantly greater percentage of total body and trunk fat, and trunk-to-limb fat ratio compared to those without IR. Compared to those without IR, a significantly greater proportion of those with IR had lipodystrophy as well. With regard to HIV-specific laboratory parameters, children with IR had higher nadir CD4% measurements (absolute and percent) compared to children without IR, but no difference in duration of HAART exposure (mean ± SD): 9.2 ± 3.1 years in the group with IR and 8.6 ± 3.1 years in the group without IR (p = 0.15). No significant differences between the groups were observed by viral load. Ever having received specific classes of ART did not differ between those with and without IR. However, children with IR were more likely to have ever used APV (15 vs. 6%, p = 0.04) and less likely to have ever used LPV (39 vs. 54%, p = 0.03) compared to children without IR.

In multivariable analysis (online suppl. table 2), the characteristics found to be significantly associated with IR included elevated ALT, Tanner stage 5, higher BMI, higher nadir CD4%, and ever having received APV. Due to collinearity with BMI, weight z-score, waist circumference, and waist-to-hip ratio were not included in the

multivariable model even though they were associated with IR in univariable analyses. Similarly, the other DEXA measures of body fat were not included in the multivariable model due to collinearity with trunk-to-limb fat ratio. Children with elevated ALT were 4 times more likely to have IR at entry compared to children with normal ALT [adjusted odds ratio (aOR): 4.24, 95% confidence interval (CI): 1.54–11.69, p = 0.005]. Children at Tanner stage 5 were also 4 times more likely to have IR compared to children at Tanner stages 1–4 (aOR: 3.97, 95% CI: 1.66–9.47, p = 0.002). Children at Tanner stage 5 were compared to those at Tanner stages 1–4 because there was no difference in the effects of Tanner stages 1–4 on IR. Children classified as obese were >10 times more likely to have IR compared to lean children (aOR: 10.20, 95% CI: 3.68–28.22, $p < 0.0001$). Ever having received APV was also independently associated with a fourfold greater odds of IR compared to never use of APV (aOR: 4.67, 95% CI: 1.40–15.59, p = 0.01). Results excluding those from subjects with conditions potentially associated with hyperglycemia (four children with hepatitis C, one with Cushing's syndrome, and one with chronic renal failure) were similar, as were those with exclusion of subjects using medications associated with hyperglycemia.

Of the 61 subjects noted to have IR, 45 (74%) had a follow-up OGTT test and 43 (70%) had a HbA1c measurement. Three of 45 (6.7%) had IFG only, three (6.7%) IGT only, and one other (2.2%) both IFG and IGT. Three of 43 (7.0%) children had a HbA1c >6.0%, but none had >6.5%. Compared to the 16 subjects who did not undergo OGTTs, these subjects were more likely to be Hispanic, less likely to be Caucasian, had higher HOMA-IR, were taller and heavier, and had more unfavorable body composition (all $p < 0.05$), i.e., they had more significant IR and its associated phenotype.

Conclusions

In a cohort of both prepubertal and pubertal children with HIV infection, using the HOMA-IR method for quantifying insulin sensitivity, the prevalence of IR was 15.2%. As expected, compared to subjects without IR, those with IR had significantly higher fasting insulin. They also had significantly higher glucose concentrations, but minimal disturbances in glucose tolerance (6.7% IFG, 6.7% IGT, and 15.6% with prediabetes, defined as IFG and/or IGT). This contrasts to the unadjusted prevalences of IFG, IGT, and prediabetes of 13.1, 3.4, and 16.1%, respectively, in NHANES (2005–2006), which includes data from approximately 2,500 adolescents aged 12–19 years with oversampling of low-income individuals, African Americans, and Mexican Americans [15].

Compared to our HIV group without IR, those with IR had more frequent hypertriglyceridemia and higher (although not above normal) mean serum ALT concentrations, biochemical manifestations also known to accompany IR in those with exogenous obesity [16]. No differences between groups were seen for any cholesterol component or BP. The prevalence of the full metabolic syndrome cluster (typically including abdominal obesity, atherogenic dyslipidemia, hypertension, IR/glucose intolerance, prothrombotic state, and proinflammatory state) could not be determined in our groups because, in young children, the definition of metabolic syndrome is poorly defined [17] with limited availability of complete sets of normative data.

As a group, those with IR in our HIV cohort, compared to those without IR, had significantly more advanced pubertal staging and higher BMI, weight z-score, waist circumference, and waist-to-hip ratio, all known risk factors for IR in non-HIV populations. Our findings regarding a relationship of IR to advancing puberty mimic the physiological reduction in insulin sensitivity of adolescence [7] which is at least partially related to increased secretion of growth hormone, an anti-insulin hormone. In addition, as suggested by their higher BMI, our subjects with IR had a significantly greater percentage of total body and trunk fat by DXA than those without IR. The only HIV-specific laboratory difference between the groups was that nadir CD4% measurements in the IR group were significantly higher than those in the group without IR, with no difference in duration of HAART (data not shown). Analysis of ever-use of particular classes of ART drugs or particular ART agents only found higher use of amprenavir in those with IR. Previous studies have shown that IR is a frequent and early finding in HIV-infected patients treated with PIs and can occur even in the absence of changes in body fat distribution or hyperlipidemia [8]. Whereas all currently available PIs have been linked to IR, the frequency of patients affected and the degree of reduction in insulin sensitivity differ between them. Of note, in adults with HIV infection, amprenavir, contrary to our findings, has only a modest effect [18]. Proposed general mechanisms for IR in HIV-infected subjects have focused on direct effects of the virus and, more likely, those of HAART, most notably PIs and NRTIs, on fat redistribution (lipodystrophy), periph-

eral glucose transport/utilization, and/or on mitochondrial function [8]. The ability of amprenavir to induce IR has been linked to inhibition of in vitro glucose transport and GLUT4 expression [10].

Previous cross-sectional in vivo studies of IR in HIV-infected children have shown variable results (online suppl. table 3), with a low prevalence of IR at best and even rarer occurrences of disturbed glucose metabolism. Differences in results between studies are potentially explicable on the basis of varying and often small cohort size, age/pubertal status, method of assessment of IR, and ART regimen [13, 14, 19–21]. Longitudinal studies of IR in HIV-infected children are relatively limited, of small size and short duration, and have reported no change over time [5] or improvement [22]. Most contemporary metabolic studies of HIV-infected adults have reported resistance to insulin and hyperlipidemia which is sometimes associated with increased abdominal fat and/or loss of peripheral fat. These changes are most commonly seen in those receiving HAART and most commonly with use of PIs, but may occasionally be present prior to treatment. Individuals who experience these effects appear to be at increased risk for partial or complete metabolic syndrome and cardiovascular disease [23].

The main strength in our study design is the use of a large, well-characterized HIV cohort of perinatally infected children. This includes use of predetermined triggers for the HOMA-IR adjusted for pubertal status followed by performance of OGTTs and HbA1c measurements in those meeting the appropriate trigger. The cross-sectional nature of the current analysis, however, is a limitation. While we have identified factors associated with IR, the temporality of the observed associations is unclear since the exact time of development of IR is unknown. The results of this study, however, provide us with hypotheses for incident analyses of follow-up data that are currently being collected. Another limitation was the use of local laboratories to assess basic analytes. Although not considered as valid as the euglycemic-hyperinsulinemic clamp or the frequently sampled intravenous glucose tolerance test, HOMA-IR (and/or fasting serum insulin) is well-accepted as a reasonable predictor of insulin sensitivity in large cohort studies of children with normal glucose tolerance [7]. Although HbA1c measurements have been reported to underestimate mean glycemia in adult HIV patients with type 2 diabetes [24], this finding has not been replicated in HIV-infected children, most of whom have normal glucose tolerance.

In summary, our 15.2% prevalence of IR in a mostly peripubertal and pubertal cohort of HIV-infected adolescents, most tightly linked to obesity than any other variable (anthropometric, biochemical, radiological, or HIV-specific), may merely reflect the existing high prevalence of obesity-linked IR found in today's youth and, thus, not indicate any exaggerated relationship because of HIV and/or its treatment. Historically, the overall prevalence of BMI ≥99th percentile has increased by more than 300% since NHANES II (1976) and over 70% since NHANES III (1994) in children aged 2–19 years, with a possible plateauing observed in the most recent analysis in 2010 [25]. Since minimal longitudinal data regarding IR and glucose metabolism currently exist in pediatric HIV populations [5, 22], it is imperative to follow this large cohort of HIV-infected children (and a contemporary tracked, uninfected, but HIV-exposed, control group) to determine the number of incident cases and overall prevalence of IR and disturbances of glucose metabolism. Such data will allow elucidation of the roles of HIV infection and/or particular ART therapies versus general societal socio-demographics in contributing to observed rates over time.

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