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Insulin Resistance and Glucose and Lipid Concentrations in a Cohort of Perinatally HIV-Infected Latin American Children

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Abstract

We measured glucose, insulin, and lipids in 249 perinatally HIV-infected Latin American children. Only one subject had impaired fasting glucose; 6.8% had insulin resistance. Abnormalities in total, LDL and HDL cholesterol, and triglycerides were reported for 13%, 13%, 21%, and 34%, respectively. Continued follow up of this populationis necessary to characterize the evolution and clinical consequences of these findings.

As the perinatally HIV-infected population in the United States and Europe enters the third decade of life, they face high rates of traditional risk factors for cardiovascular disease, such as obesity, dyslipidemia, and insulin resistance, though they are still too young to have experienced clinical events (1). Earlier studies in HIV-infected children reported rates of insulin resistance of 8-52% based upon different thresholds (2-4). More recent studies have used fasting insulin and glucose measurements to calculate the homeostatic model assessment of insulin resistance (HOMA-IR), with rates of insulin resistance ranging from 6.5% in Thai children receiving effective antiretroviral therapy (ART) for 2 years (5) to 33% in an older American cohort predominantly treated with protease inhibitor (PI)-containing ART (6). The largest study to date, from the Pediatric HIV/AIDS Cohort Study (PHACS), found insulin resistance in 15% of 401 perinatally HIV-infected American children (7).

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Given these varying results and differences across geographic regions, which may reflect varied dietary habits and genetic susceptibility, we examined fasting insulin, glucose, and lipid results in a cohort of perinatally HIV-infected children followed in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) International Site Development Initiative [NISDI] Pediatric Latin American Countries Epidemiologic Study [PLACES].

Methods

PLACES is a prospective cohort study that enrolled perinatally HIV-infected children younger than 6 years of age in 2008-2011 at 14 clinical sites (12 in Brazil, 1 each in Peru and Mexico). This study also enrolled subjects for continued follow-up that were younger than 6 years of age at the time of enrollment to the earlier version of the NISDI pediatric protocol (2002-2007) (8).The protocol was approved by the ethical review boards of each clinical site; the sponsoring institution (NICHD); the data management and statistical center (Westat); and the Brazilian National Ethics Committee (CONEP). Informed consent was obtained from the parents or guardians.

A description of the earlier version of the protocol and the cohort has been published elsewhere(8). In brief, demographic, laboratory, and clinical data were collected at enrollment and every 6 months. Growth Z-scores were determined using World Health Organization (WHO) standards (http://www.who.int/childgrowth/standards/en/). In addition to CD4+ T cell phenotyping and HIV-1RNA concentration (viral load, VL), fasting insulin, glucose, and lipidswere obtained once a year in those ≥ 5 years of age. Specimens for insulin and glucose were stored locally and shipped to a central laboratory (Quest Diagnostics, Baltimore) every 6 months for testing. Other measurementswere performed at local laboratories. The first glucose, insulin, and lipid results obtained after study enrollment from all eligible subjects were included in the analysis.

HOMA-IR (fasting insulin [mcIU/mL] times fasting glucose [mg/dL], divided by 405) was used to evaluate insulin and glucose results. Abnormal values were based upon those used in prior studies: insulin resistance was defined as HOMA-IR>2.5 in those with Tanner stage 1 or as HOMA-IR>4.0 in those with Tanner stage >1. A glucose level ≥110 mg/dL was used to identify impaired fasting glucose (IFG). Abnormal total, HDL and LDL cholesterol were defined as >200, <35, and >130 mg/dL, respectively. Abnormal triglycerides were defined as >110 mg/dL if age <10 years or >150 mg/dL if age ≥10 years at time of specimen collection.

The type of antiretroviral (ARV) regimen received at the time of specimen collection was classifiedinto one of the following four categories according to ARV class: 1) receiving PI-containing therapy, with or without a non-nucleoside reverse transcriptase inhibitor (NNRTI); 2) receiving an NNRTI-containing regimen, without a PI; 3) receiving mono-or dual-nucleoside reverse transcriptase inhibitor (NRTI) therapy; or 4) not receiving any ARVs at the time of specimen collection.

Statistical Analyses

Bivariate associations of covariates with abnormalities in metabolic measures and type of ARV regimen received were examined using Fisher's exact test for categorical covariates and nonparametric procedures (Kruskal-Wallis test) for continuous scaled covariates. Covariates associated with metabolic measures or type of ARV received at the alpha 0.2 level or lower were considered as candidates for multivariable modeling. Logistic regression was used to fit covariate-adjusted models for assessing the relationship of ARV use with indicators of metabolic abnormalities and linear regression was used for continuous-scaled

metabolic measures. All analyses were performed using SAS, Version 9.0, with p-values below alpha 0.05 defining statistical significance.

Results

Among the 500 participants enrolled in the PLACES protocol as of December 31, 2009, 233 were younger than 5 years of age at enrollment and during available follow-up and therefore ineligible for fasting insulin or glucose testing per protocol specifications. Of the 267 subjects eligible for testing, 18 were excluded from the analysis because they did not have available results to calculate the HOMA-IR (4 had glucose results only, all in the normal range [76-98 mg/dL]), leaving 249 with their first available HOMA-IR result for this analysis.

The majority of subjects (80.3%) were enrolled at sites in Brazil. The mean (± standard deviation [SD]) age at time of specimen collection was 7.5 (±2.1) years; 53% were female. Mean (±SD) Z-scores for height, weight, and BMI were -0.8 (±1.0), -0.6 (±1.2), and -0.2 (±1.2), respectively. At the time of specimen collection, 36.1% (n=90) were receiving a PI-containing regimen, 14.1% (n=35) were receiving an NNRTI-containing regimen, 15.3% (n=38) were receiving either mono or dual NRTI therapy, and 34.5% (n=86) of participants were not receiving any ARVs. Median duration of use of current ARV was 1.2 years and of lifetime ARV use was 5.6 years. Fifty-two percent had a VL <400 copies/mL and mean (±SD) CD4 absolute count and percentage were 912.6 (±447.2) cells/mm^3 and 30.1% (±9.1). None of the subjects had a diagnosis of diabetes.

The mean (±SD) fasting glucose, total, HDL, and LDL cholesterols, and triglycerides were 79.1 (±9.6), 163 (±36), 45 (±13), 96 (±32) and 109 (±62) mg/dL, respectively.

As shown in the Table, overall, 17 (6.8%) of participants had an abnormal HOMA-IR. Althoughtype of ARV regimen was not associated with abnormal HOMA-IR, the abnormal rate ranged from 2.9% for those receiving NNRTI-based ARV to 8.1% for those not on ARVs. Abnormal HOMA-IR was not associated with age, ARV duration, HIV VL, CD4 count, or growth parameters (data not shown) but was associated with gender (10.7% of females [n=14] and 2.5% of males [n=3)] had abnormal values, p=.01). When examined as a continuous outcome, $\log_{10}$ transformed HOMA-IR was also not associated with type of ARV in either the unadjusted (p=.12) or adjusted model (p=.26).

Only 1 participant had an abnormal fasting glucose (134 mg/dL); this child also had the highest HOMA-IR of 11.9 but was not on ARVs. Insulin concentrations (log transformed) differed among ARV groups (p=.04), with the highest levels reported in those on PIs and mono or dual NRTIs in a model that adjusted for gender, BMI Z-score, age, and CDC classification at time of specimen collection (data not shown).

With respect to lipid measures, the percentage with abnormal results for total cholesterol, HDL and LDL cholesterol, and triglycerides was 12.7%, 21.4%, 13.0%, and 33.6%, respectively (Table). Type of ARV was significantly associated with total cholesterol (p=.02) and HDL cholesterol (p<.001); those on a PI-based ARV regimen and mono or dual NRTIs had the highest rates of abnormal total cholesterol, while those not receiving ARVs had the highest rates of abnormal HDL. However, these associations did not persist with adjustment for potential confounders (p=.19 and .14 for total and HDL cholesterol, respectively); when the continuous-scaled lipid measures were investigated there were no differences after adjustment for covariates, except for triglycerides (p=.04), where higher levels were observed among those on PIs (data not shown).

Discussion

Although ART has been linked with the whole range of abnormalities of glucose metabolism, from insulin resistance to hyperglycemia and diabetes mellitus, impaired fasting glucose was detected in only one child (0.4%) in this cohort of perinatally HIV-infected Latin American children. Studies from the United States have shown rates as high as 4-7% (9, 10). Insulin resistance, as determined by HOMA-IR, was found in 6.8% of the children in this study, comparable to the results from studies of HIV-infected children of similar ages in both the United States and Thailand (5, 10). Studies of older perinatally HIV-infected youth in the United States have shown higher rates of insulin resistance (6, 7), suggesting that abnormalities of glucose metabolism develop as children enter adolescence. Similar to the findings in those studies, the few cases of abnormal glucose metabolism we found seemed to be more related to factors other than ART. In contrast, rates of lipid abnormalities were similar to those reported from several US and European cohorts (1).

The strengths of this study include a well characterized, large cohort with fasting specimens and detailed laboratory assessments, including centralized insulin and glucose measurements. These findings provide important data from a part of the world that has not been represented in previous reports of glucose metabolism. Limitations include the lack of metabolic data from a comparable HIV-uninfected populationand small numbers of abnormalities that limit power to detect differences among ARV treatment groups. Longer term follow up of this perinatally HIV-infected population in Latin America will be necessary to assess evolution of the findings described and their eventual clinical consequences.

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Table

Abnormalities in metabolic measures overall and according to type of ARV received at the time of specimen collection

Metabolic measure	Overall (n=249)	Type of Antiretroviral Received at the Time of Specimen Collection				P-value	
		PI-containing regimen (n=90)	NNRTI-containing regimen (n=35)	Other ARVs (n=38)	No ARVs (n=86)	Unadjusted[1]	Adjusted[2]
Fasting glucose: (mg/dL)							
<110 (normal)	248 (99.6)	90 (100)	35 (100)	38 (100)	85 (98.8)	.64	NA
≥110 to <126 (impaired)	--	--	--	--	--		
≥126 (diabetic)	1 (0.4)	--	--	--	1 (1.2)		
HOMA-IR:							
Abnormal[3]	17 (6.8)	6 (6.7)	1 (2.9)	3 (7.9)	7 (8.1)	.78	.71
Normal	232 (93.2)	84 (93.3)	34 (97.1)	35 (92.1)	79 (91.9)		
Total cholesterol: (mg/dL)							
>200 (abnormal)	31 (12.7)	16 (17.8)	1 (3.0)	9 (23.7)	5 (6.0)	.015	.19
≤200 (normal)	213 (87.3)	74 (82.2)	32 (97.0)	29 (76.3)	78 (94.0)		
HDL cholesterol: (mg/dL)							
<35 (abnormal)	51 (21.4)	13 (15.5)	3 (9.1)	3 (7.9)	32 (38.6)	<.001	.14
≥35 (normal)	187 (78.6)	71 (84.5)	30 (90.9)	35 (92.1)	51 (61.4)		
LDL cholesterol: (mg/dL)							
>130 (abnormal)	31 (13.0)	14 (16.7)	4 (12.1)	8 (21.1)	5 (6.0)	.10	.82
≤130 (normal)	207 (87.0)	70 (83.3)	29 (87.9)	30 (78.9)	78 (94.0)		
Triglycerides: (mg/dL)							
Abnormal[4]	82 (33.6)	39 (43.3)	9 (27.3)	13 (34.2)	21 (25.3)	.08	.10
Normal	162 (66.4)	51 (56.7)	24 (72.7)	25 (65.8)	62 (74.7)		

[1]The p-value for assessing the association between ARV therapy and fasting glucose was obtained using Fisher's exact test since the logistic regression model failed to converge to an answer; all other unadjusted p-values were obtained using logistic regression.

[2]Logistic regression was used to fit covariate-adjusted models for assessing the relationship of ARV use with metabolic abnormalities; the p-value for type of ARV received is presented. All models adjusted for age at time of specimen collection, gender and BMI z-score; total cholesterol and LDL cholesterol additionally adjusted for $\log_{10}$ peak viral load and HDL cholesterol adjusted for $\log_{10}$ peak viral load and CD4 count at time of testing in addition to the common elements.

[3] HOMA-IR >2.5 in children (Tanner stage <2) or >4.0 in adolescents (Tanner stage ≥2).

[4] Triglycerides >110 mg/dL for age <10 or >150 mg/dL for age ≥10.

ARV indicates antiretrovirals; PI, protease inhibitor; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor; NA, not available; HOMA-IR, homeostatic model assessment of insulin resistance; BMI, body mass index