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Insulin Resistance in South African Youth Living with Perinatally Acquired HIV Receiving Antiretroviral Therapy

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Abstract

To investigate the prevalence of and risk factors for insulin resistance (IR) in a cohort of youth living with perinatally acquired HIV (YLPHIV) receiving antiretroviral treatment (ART). A cross-sectional analysis of IR in YLPHIV and age-matched HIV-uninfected youth enrolled in the Cape Town Adolescent Antiretroviral Cohort. South African youth ages 9–14 years, with perinatally acquired HIV who were on ART for >6 months and age-matched HIV-uninfected adolescents, were eligible. The homeostatic model assessment of insulin resistance (HOMA-IR), calculated from fasting insulin and glucose measurements at enrollment, was used to assess IR. Multiple linear regression was used to examine adjusted associations between HOMA and HIV-related and traditional cardiovascular risk factors. Of 448 adolescents, 385 (85.9%) were YLPHIV; median age was 12.1 years [interquartile range (IQR): 10.8–13.5], and 50.4% were female. Median duration on ART was 7.5 (IQR: 4.5–9.2) years. The prevalence of IR in YLPHIV was 18%. Among YLPHIV, waist circumference ($\beta = 0.01$, $p = .01$), hypertriglyceridemia ($\beta = 0.07$, $p = .01$), CD4 count >500 cells/mm^3 ($\beta = 0.08$, $p = .02$), or prior use of abacavir ($\beta = 0.06$, $p = .04$) were associated with increased HOMA, after adjusting for age, sex, body mass index, and Tanner stage. In a South African cohort of YLPHIV on ART, IR was not significantly different from uninfected adolescents. YLPHIV with traditional cardiovascular risk factors or abacavir exposure may be at higher risk for IR.

Keywords: insulin resistance, metabolic syndrome, youth living with perinatally acquired HIV, sub-Saharan Africa

Introduction

Metabolic complications, including insulin resistance (IR), are increasingly reported in youth living with perinatally acquired HIV (YLPHIV). Widely variable rates of IR have been reported in children and adolescents on antiretroviral therapy (ART) ranging from 0.0% to 52.0%,[1–4] which may reflect variations in age, Tanner staging, ethnic and genetic differences, small sample sizes, and differing methods of measuring IR. Reports from middle-income countries, Latin America and Thailand, show rates of 6.8% and 6.5% in YLPHIV on ART.[5,6] There are relatively little data from Africa: two Ugandan studies; one reporting no hyperglycemia (insulin was not measured)[4]; the other, done in younger children, found an increase in homeostatic model assessment of insulin resistance (HOMA-IR) 1 year after ART initiation and higher HOMA-IR in children on abacavir.[7] Two South African studies done in younger children found an IR prevalence of 1.9%–10%.[8–10] Both South African studies, however, had a relatively small sample size of 100–156 children and used different definitions of IR.

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Common risk factors for the development of IR are puberty, increased body mass index (BMI), and a family history of diabetes.[10] A study of children and YLPHIV reported an IR prevalence of 15.2% that was more closely linked to obesity than any other HIV-related variable.[1] A longitudinal study of the same cohort showed that female sex, waist circumference (WC), and BMI were associated with incident or resolved IR as in HIV-negative youth.[11]

Development of IR in patients with HIV is thought to be multifactorial and includes factors related to HIV and ART. Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) can cause IR by direct inhibition of the insulin-responsive facilitative glucose transporter isoform (GLUT4).[12,13]

IR precedes the development of metabolic syndrome. Metabolic syndrome is defined as hypertension, low high-density lipoprotein (HDL) cholesterol levels, hypertriglyceridemia, and abdominal obesity.[14] Metabolic syndrome is an independent risk factor for cardiovascular disease (CVD). The prevalence of metabolic syndrome in a cohort of Spanish HIV-infected children was 1.97% using the International Diabetes Federation (IDF) criteria.[15] The prevalence of metabolic syndrome in YLPHIV in Africa is unknown.

The primary objective of this study was to investigate the prevalence of and risk factors for IR in a stable cohort of African YLPHIV on ART. A secondary objective was to investigate the prevalence of metabolic syndrome.

Materials and Methods

Study population

The Cape Town Adolescent Antiretroviral Cohort (CTAAC) is a longitudinal cohort study that enrolled 515 YLPHIV ages 9–14 years on ART for more than 6 months from seven sites in Cape Town, South Africa, and 110 age-matched HIV-uninfected youth of similar ethnicity from July 2013 to March 2015. There were no other exclusion criteria, and participants did not have to be virally suppressed at enrollment. Ethical approval was given by the Faculty of Health Sciences, University of Cape Town, and Stellenbosch University, Human Research Ethics Committee (051/2013).[16] Parents gave informed consent and assent was obtained from all adolescents. All YLPHIV knew that their HIV status was a prerequisite to study enrollment.

Primary outcome

The primary outcome was IR at enrollment visit. HOMA (defined as fasting insulin [mIU/L] × fasting glucose [mmol/L] divided by 22.5)[17] was used to assess IR. IR was defined as a HOMA >2.5 in Tanner stage 1 patients or >4.0 in Tanner stage ≥2 based on previous thresholds in the literature.[18] Participants were fasting for ∼12 h. Glucose and insulin were measured on stored frozen samples.

Secondary outcome

The prevalence of metabolic syndrome was a secondary outcome, defined according to the recent IDF consensus definition: abdominal obesity (WC >90th percentile) plus >2 criteria (hypertriglyceridemia, low HDL, hypertension, increased plasma glucose).[14]

Covariates

Routine sociodemographic data were collected at enrollment and the participant's clinical record was reviewed at the primary treatment facility.

A physical examination, including Tanner staging, World Health Organization (WHO) HIV staging, blood pressure (BP), and anthropometry, was performed at enrollment. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). BMI was classified according to the WHO reference standards.[19] BP was measured using an electronic sphygmomanometer (Spot Vital Signs, Welch Allyn). WC was measured in centimeters midway between the superior border of the iliac crest and the lowermost margin of the ribs at the end of normal expiration. Median thigh circumference and median upper arm circumference were measured in centimeters using standard techniques.[20] All anthropometric measures were performed by one of two trained study nurses to ensure standardization of measures.

Laboratory measures performed at enrollment included HIV viral load (Roche Cobas AmpliPrep/TaqMan) and CD4 count in HIV-infected and fasting lipid subfractions, including total cholesterol (TC), triglycerides (TG), HDL, and low-density lipoprotein (LDL) cholesterol.

Abnormal TC, HDL, and LDL were defined as >5.18, <1.03, and >3.37 mmol/L, respectively. Abnormal TG were defined as >2.85 mmol/L if age <10 years or >3.89 mmol/L if age ≥10 years at enrollment visit.[21] Insulin was measured using an electrochemiluminescence immunoassay (Cobas 6000; Roche Diagnostics USA, Indianapolis, IN) and glucose using the enzymatic method (Cobas 6000; Roche Diagnostics USA).

Statistical analysis

Baseline variables were compared between groups using *t*-tests, Wilcoxon, and chi-square tests as appropriate. HOMA was log transformed to approximate a normal distribution. Rates of IR between YLPHIV and HIV-uninfected participants were compared using chi-square tests in univariate analysis, and logistic regression modeling was used to assess the association between HIV infection and IR adjusting for confounders. Among YLPHIV, multivariable linear regression modeling was performed to evaluate factors associated with increased HOMA while adjusting for age, gender, BMI, and Tanner stage. Covariates considered for associations with HOMA included anthropometry (BMI and WC), HIV laboratory parameters, metabolic parameters, and duration and type of ART. Statistical analysis was performed using Stata version 14.1 (StataCorp, Inc., College Station, TX).

Results

Among the 625 adolescents enrolled in CTAAC, 448 (71.7%) had samples available for HOMA (385 YLPHIV and 63 HIV uninfected). One child with diabetes (defined as a fasting glucose of >6.9 mmol/L) was excluded from this analysis. Median age, sex, and family history of diabetes were similar between YLPHIV and HIV-uninfected adolescents (Table 1). Only three participants smoked tobacco at enrollment.

Median BMI was lower in YLPHIV (17.2 vs. 18.1 kg/m^2, $p = .01$). Sixteen (4%) YLPHIV were obese versus 7 (11%)

Table 1. Baseline Characteristics of Youth Living with Perinatally Acquired HIV and HIV-Uninfected Adolescents

	YLPHIV (n = 385)	*HIV uninfected (n = 63)*	p
Demographics			
Age (years)	12.1 (10.8–13.5)	11.9 (10.0–13.4)	.16
Female	194 (50.4)	29 (46.0)	.52
Black African	354 (92.0)	63 (100)	.02
Family history of diabetes			
Yes	80 (20.89)	13 (20.63)	
BP (mm Hg)			
Systolic (mean ± SD)	105.0 (11.5)	109.5 (10.5)	<.01
Diastolic (mean ± SD)	67.0 (9.1)	68.2 (9.4)	.32
Growth measures			
BMI (kg/m^2)	17.2 (16.0–19.1)	18.1(16.5–20.4)	.01
WC (cm)	61 (58–66)	64 (57–70)	.21
Midthigh circumference (cm)	39 (37–44)	42 (38–46)	<.01
Midupper arm circumference (cm)	20.5 (19–22)	21 (19–23.5)	.07
Tanner stage			
1	190 (50.1)	21 (33.9)	.07
2	85 (22.4)	18 (29.0)	
3	53 (14.0)	8 (12.9)	
4	30 (7.9)	10 (16.1)	
5	21 (5.5)	5 (8.1)	
Puberty			
Prepubertal (Tanner stage 1)	190 (50.1)	21 (33.9)	.02
Pubertal (Tanner stages 2–5)	189 (49.9)	41 (66.1)	
Laboratory measures			
TG	0.9 (0.7–1.1)	0.6 (0.5–0.8)	.00
Hypertriglyceridemia	32 (8.3)	1 (1.6)	.07
TC	4.1 (3.6–4.6)	3.8 (3.4–4.2)	<.01
Hypercholesterolemia	44 (11.6)	2 (3.2)	.04
LDL-C	2.2 (1.8–2.6)	2 (1.5–2.4)	
HDL-C	1.5 (1.2–1.7)	1.5 (1.3–1.7)	.60
Insulin (mIU/L)	9.6 (6.6–14.3)	9.7 (6.1–19.4)	.57
Log insulin	0.99 (0.25)	1.0 (0.38)	.32
Glucose/insulin ratio	8.6 (4.2–13.3)	8.9 (6.2–12.7)	.21
Glucose (mg/dL)	86.8 (9.0)	83.4 (9.0)	.01
HOMA	2.1 (1.4–3.2)	1.9 (1.2–3.7)	.98
Log HOMA	0.3 (0.3)	0.3 (0.4)	.62
Viral load (copies/mL)			
<50	289 (75.06)	—	—
50–1,000	44 (11.43)	—	—
1,001–10,000	28 (7.27)	—	—
>10,000	24 (6.23)	—	—
CD4 count (cells/mm^3)			
<200	7 (1.83)	—	—
200–499	58 (15.14)	—	—
500–1,000	248 (64.75)	—	—
>1,000	70 (18.28)	—	—
WHO HIV staging		—	—
Stage I	24 (6.49)	—	—
Stage II	43 (11.62)	—	—
Stage III	217 (58.65)	—	—
Stage IV	86 (23.24)	—	—
Missing value	15	—	—
Age at initiation of ART (years)			
Median age	4.6 (2.12–7.72)	—	—
0–2	126 (33.4)	—	—
3–5	108 (28.65)	—	—
6–14	143 (37.93)	—	—
Missing values	8	—	—

(*continued*)

TABLE 1. (CONTINUED)

	YLPHIV (n = 385)	*HIV uninfected (n = 63)*	p
Duration on ART before enrollment (years)	7.46 (4.48–9.23)	—	—
Current ART regimen			
2 X NRTI + NNRTI	226 (58.7)	—	—
2 X NRTI + PI	142 (36.88)	—	—
Other	9 (2.34)	—	—
Unknown	8 (2.08)	—	—
Currently on D4T	35 (9.1)	—	—
Currently on DDI	7 (1.82)	—	—
Currently on ABC	280 (72.7)	—	—
Currently on AZT	60 (15.58)	—	—
Ever on D4T	261 (67.79)	—	—
Ever on DDI	34 (8.83)	—	—
Ever on ABC	305 (79.22)	—	—

All continuous variables expressed as median (interquartile range) or mean (SD) and categorical variables as number (%).

ABC, abacavir; ART, antiretroviral treatment; AZT, zidovudine; BMI, body mass index; BP, blood pressure; D4T, stavudine; DDI, didanosine; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment; LDL-C, low-density lipoprotein cholesterol; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; TC, total cholesterol; TG, triglycerides; WHO, World Health Organization; YLPHIV, youth living with perinatally acquired HIV; WC, waist circumference.

HIV-uninfected adolescents ($p = .02$). YLPHIV were more likely to be Tanner stage 1 (prepubertal) than uninfected adolescents (50.1% vs. 33.9%, $p = .02$). Mean midthigh circumference was lower in YLPHIV compared with uninfected youth (39 vs. 44 cm, $p = .01$). Systolic BP was also lower (105 vs. 109 mm Hg, $p < .01$). Median fasting glucose (86.8 vs. 83.4 mg/dL, $p = .01$), TG (0.9 mmol/L vs. 0.6 mmol/L, $p < .01$), TC (4.1 mmol/L vs. 3.8 mmol/L, $p < .01$), and rates of hypercholesterolemia (11.6% vs. 3.2%, $p = .04$) were higher in YLPHIV (Table 1).

Among YLPHIV participants, median duration on ART was 7.46 (4.48–9.23) years, and median age at ART initiation was 4.6 (2.12–7.72) years. Approximately 58.7% were receiving an efavirenz-based ART with the remainder (36.9%) receiving a lopinavir/ritonavir-based ART. Seventy-two percent received an abacavir-containing ART. Median duration of abacavir was 2.8 years. Eighteen percent had CD4 cell counts >1,000 cells/mm^3 and 75.1% had a viral load <50 copies/mL at enrollment. Nadir CD4 cell count was poorly documented at enrollment sites.

YLPHIV had an IR rate of 18.0% but this did not differ from uninfected youth (18% vs. 20%, $p = .17$). This relationship remained unchanged after adjustment for age, sex, family history of diabetes, BMI z-score, Tanner stage, and WC (adjusted odds ratio: 0.86, $p = .70$).

In subgroup analysis of YLPHIV participants, WC ($\beta = 0.01$, $p = .01$), hypertriglyceridemia ($\beta = 0.07$, $p = .01$), CD4 count >500 cells/mm^3 ($\beta = 0.08$, $p = .02$), and "ever" (previous or current) use of abacavir ($\beta = 0.06$, $p = .04$) were associated with increased HOMA, after adjusting for age, sex, BMI, and Tanner stage (Table 2). There was no association between being on a PI regimen and IR.

One female YLPHIV and one HIV-uninfected youth met criteria for metabolic syndrome.

Discussion

We found an 18.5% prevalence of IR in this cohort of YLPHIV, with similar rates in YLPHIV and uninfected youth. Recognition of IR is important as it represents a low-level inflammatory state that can lead to early CVD in children.[22] Subclinical atherosclerosis has been shown in HIV-infected children on ART for >6 months.[23–25] YLPHIV may be at further risk of CVD due to their lifelong exposure to both HIV and ART.

In children without HIV, rates of IR have been reported as 3% in young nonobese children and up to 40% in obese children and adolescents.[18] The fact that black South Africans may have an increased genetic predisposition to type 2 diabetes[26] may explain the finding of high prevalence of IR in this cohort. In addition, an increasingly urban high-fat diet may be contributing to high rates of IR in South Africa.[27] The median value of 1.9 was higher than in an HIV-uninfected cohort of European prepubertal adolescents between 10.5 years and 11 years who had a median HOMA between 1.7 (girls) and 1.4 (boys).[28]

The IR prevalence of 20% in our study is similar to the 15.2% prevalence reported in earlier cohorts of U.S. children

TABLE 2. LINEAR REGRESSION MODELS FOR KEY PREDICTORS OF HOMEOSTATIC MODEL ASSESSMENT AMONG YOUTH LIVING WITH PERINATALLY ACQUIRED HIV IN CTAAC

Model	*β coefficient*	p
WC[a]	0.01	.01
Midupper arm circumference[a]	0.02	.02
Systolic BP[a]	0.00	.18
TG[a]	0.07	.01
CD4 count		
≤499	Ref	
≥500	0.08	.02
Ever on abacavir		
Not exposed	Ref	
Exposed	0.06	.03

All models adjusted for age, sex, BMI, and Tanner stage.

[a]Continuous variable.

on ART and YLPHIV in the Pediatric HIV/AIDS Cohort Study (PHACS), adolescent master protocol study. In the PHACS cohort, HOMA was associated with higher alanine transferase, BMI, nadir CD4%, Tanner stage 5, and ever having received amprenavir. (1) Another smaller U.S. cohort reported a 33% prevalence, similar to that in adults living with HIV. (2) The IR rate in our cohort was above 6.8% and 6.5% described in more recent Latin American and Thai cohorts.[5,6] Differences in rates of IR between our South African cohort and the Thai cohort are most likely explained by different criteria used to define IR. The Thai study used a threshold of ≥3.16, which did not take into account the pubertal stage. However, the PHACS and Latin American cohort studies used the same HOMA thresholds to define IR as our study (>2.5 for prepubertal and >4 for pubertal individuals). Of note, the median HOMA in our cohort of YLPHIV was higher than in the PHACS cohort (2.1 vs. 1.0). In a large U.S. study, a 1 U rise in HOMA has been found to be associated with increased mortality in adults without diabetes.[29] The only other study done in 100 South African children living with HIV showed a prevalence of 10%, which may be explained by the lower age of this cohort of 6.5 years.[9]

Among YLPHIV in our cohort, traditional risk factors for IR such as WC and hypertriglyceridemia were associated with increased HOMA. WC was associated with incident IR in a longitudinal study of HOMA-IR in the United States.[11] A Spanish cohort also found WC but not hypertriglyceridemia as associations with increased HOMA.[30] Hypertriglyceridemia is associated with IR in adults on PIs. With regard to lipid abnormalities in children and youth, other cohorts have suggested a higher rate of hypertriglyceridemia from 33.6% (5) with a median age at start of ART of 7.1 years and a median duration of ART of 5.6 years. The rate of hypertriglyceridemia in our cohort was 8.3% in YLPHIV. This is surprising as lipid abnormalities may have been expected to be more pronounced, given the longer duration of ART use. Those adolescents on a PI regimen had a higher rate of hypertriglyceridemia than those on a non-NRTI regimen (65.6% vs. 34.4%, $p = .00$). This rate was not significantly different to HIV-uninfected adolescents in our cohort but this may be due to a small sample size.

In addition, in subgroup analysis of YLPHIV, abacavir use was associated with higher HOMA. While there are no studies on abacavir and cardiometabolic outcomes in youth, in adults living with HIV, abacavir has been shown to increase the risk of CVD, a known potential sequela of IR.[31] In YLPHIV, a higher prevalence of risk factors for subclinical vascular disease, including a higher Pathobiological Determinants of Atherosclerosis (PDAY) score, has been documented.[32–34] In YLPHIV with a high PDAY score, a switch from an abacavir-containing regimen score may be warranted.

The finding that a higher CD4 count was associated with IR may reflect the fact that healthier YLPHIV are likely to have more fat reserves, potentially resulting in increased rates of IR. Unlike in other studies,[1,8,13] we found no association between PI usage and increased HOMA-IR in our cohort. This may be because we were unable to assess total duration on a PI regimen. Another South African study assessing HOMA-IR in a younger cohort of children also found no association between type of ART and IR.[9]

Only two participants had metabolic syndrome according to the IDF definition. Metabolic syndrome has been described in other adolescent HIV cohorts.[15] A recent Spanish study found a metabolic syndrome prevalence of 1.97%, but when a different classification was used (National Cholesterol Education Program Adult treatment Panel III NCEP-ATP III), a prevalence of 5.92% was found.[15] This difference was thought to be attributable to the WC that is crucial for the IDF classification. In our cohort, three adolescents had a WC meeting the criteria for central obesity. IR in the Spanish cohort was observed in 17 patients (11.18%) and associated with metabolic syndrome if the NCEP-ATP III criteria were used. The low prevalence of metabolic syndrome in our cohort may be due to the low rate of hypertension as well as the fact that metabolic syndrome is thought to be more common in late puberty (Tanner stage 5) and half of YLPHIV in our study were prepubertal.[35]

This study was limited by the small size and lack of rigorous Tanner stage and BMI matching of the comparison group. However, it was one of the largest in sub-Saharan Africa to characterize metabolic parameters among YLPHIV. In addition, the cross-sectional study design precluded our ability to draw causal inferences, but future studies in our longitudinal cohort will allow us to further explore our current findings, especially the association between abacavir and IR. Glucose and insulin were measured using previously stored frozen samples and this could have resulted in lower HOMA values as insulin may be underestimated in frozen samples.

Conclusions

In a South African cohort of YLPHIV, although a high prevalence of IR was found, it did not differ from that in uninfected age-matched adolescents. In addition to traditional risk factors such as WC and hypertriglyceridemia, abacavir exposure may be associated with increased HOMA. This finding needs further exploration. Longitudinal follow-up is needed to assess which adolescents develop IR and what factors are associated with this.

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Authors' Contributions

L.J.F. did data quality and statistical analyses, and wrote the article. J.J. was involved in initial idea conception and wrote the article. S.M. collected data and did data quality and statistical analysis. N.A.A.A. collected data and data quality analysis. M.F.C. was involved in the overall cohort design and obtained funding. L.M. was involved in initial idea conception, overall cohort design, and obtained funding. H.J.Z. was involved in oversight of the study, and obtained funding.

Author Disclosure Statement

No competing financial interests exist.

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