Lower Insulin, Acylcarnitines, and Branched-Chain Amino Acids in HIV-exposed Infants

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BACKGROUND

In utero **HIV/antiretroviral (ARV) and postnatal ARV treatment are known to perturb energy metabolism and provide a model of early environmental exposure that could have permanent effects on future metabolic health. Few studies have evaluated fetal/postnatal ARV exposures and both infant insulin and intermediary metabolites.**

OBJECTIVES

To assess the association between *in utero* HIV/ARV exposure and pre-prandial insulin levels at 6 weeks of life and differences in intermediary metabolites between HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants in relation to insulin.

METHODS

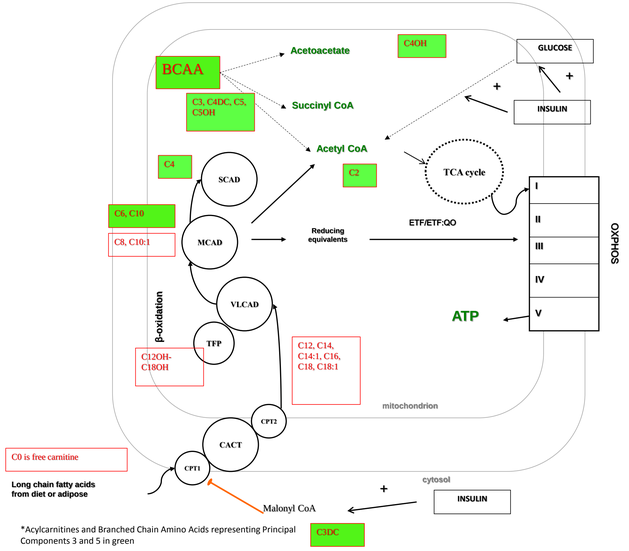
DESIGN: Prospective cohort study of maternal-infant dyads
EXCLUSION CRITERIA: HIV-infected infants and twin gestations
PRIMARY OUTCOME: Pre-prandial insulin at 6 wk of age measured from dried blood spots (DBS) via direct sandwich ELISA ~~technique~~
SECONDARY OUTCOME: HOMA-IR
EXPOSURE OF INTEREST: *In utero* and postnatal HIV/ARV
PREDICTOR VARIABLES: Maternal socio-demographics, pre-term birth [<37 weeks' gestational age (GA)], and maternal HIV history
***Physiologic measurements*: Maternal blood pressure and anthropometrics, and infant anthropometrics**
***Biochemical measurements*: Acylcarnitines (AC) and branched-chain amino acids (BCAA) from DBS via tandem mass spectrometry**
STATISTICAL ANALYSIS: Characteristics of pregnant women and their infants were compared between groups using Kruskal Wallis, chi-square, or Fisher exact tests as appropriate. Insulin and HOMA-IR were quarter-root transformed to approximate a normal distribution. Principal component analysis (PCA) using an orthogonal rotation was performed to consolidate the ACs and BCAAs into 5 uncorrelated domains. Linear regression models were used to assess the association of *in utero* HIV/ARV exposure and infant insulin while adjusting for confounders and PCA-derived AC/BCAA component scores.

TABLE 1. CHARACTERISTICS OF WOMEN AND INFANTS

	HIV-exposed uninfected (n=155)	HIV-unexposed uninfected (n=209)	p value
MOTHERS			
Age of Mother, years	30 (27-33)	28 (24-31)	<0.001
Gravida	3 (2-4)	3 (2-4)	0.008
Marital Status			
Single	36 (22.9)	26 (12.3)	0.018
Living with partner	5 (3.2)	12 (5.7)	
Married	116 (73.9)	173 (82.0)	
Highest Level of Education			
Primary school or lower	76 (48.4)	83 (39.3)	0.035
Secondary school	29 (18.5)	28 (13.3)	
High school or vocational school	28 (17.8)	62 (29.4)	
University of higher	24 (15.3)	38 (18.0)	
Gainful Employment	35 (25.6)	50 (24.4)	0.808
Water Source			
Tap water in the home	25 (15.9)	43 (20.4)	0.276
Community water	132 (84.1)	168 (79.6)	
Gestational Diabetes	9 (5.7)	11 (5.2)	0.828
Systolic Blood Pressure, mm Hg	105 (98-113)	104.0 (98-111)	0.668
Diastolic Blood Pressure, mm Hg	65 (61-69)	64 (60-70)	0.659
Maternal BMI, 6 weeks postpartum, kg/m²	25.8 (23.3-28.5)	25.3 (23.1-29.3)	0.963
C-section delivery	21 (13.7)	34 (16.5)	0.469
INFANTS			
Female Infant	76 (49)	110 (52)	0.527
Preterm (<37 weeks GA)	21 (13.4)	30 (14.2)	0.817
Infant Birth Weight, g	3250 (3000-3500)	3300 (3100-3600)	0.181
Infant LBW (<2500 g)	9 (5.7)	8 (3.8)	0.380
Infant Birth Weight z score	-0.07 (-0.73, +0.57)	0.11 (-0.32, +0.70)	0.141
Infant Insulin at 6-week visit, µU/mL	3.6 (2.2-5.7)	4.9 (3.5-6.7)	<0.001
Infant Glucose/Insulin Ratio at 6-week visit	26.5 (17.5-45.0)	19.6 (14.4-28)	<0.001
Infant Glucose, mg/dL	97.2 (89-107)	97.0 (89-106)	0.491
Infant HOMA-IR at 6-week visit	0.87 (0.53-1.40)	1.12 (0.83-1.7)	<0.001
Infant HOMA-B at 6-week visit	47.3 (34.9-75.9)	58.6 (43.8-79.0)	0.002
Infant Weight at 6-week visit, g	5000 (4650-5500)	5055 (4658-5500)	0.386
Infant WAZ at 6-week visit	0.15 (-0.48, +0.85)	0.35 (-0.38, +0.91)	0.180
Infant LAZ at 6-week visit	0.42 (-0.48, 1.44)	0.91 (-0.12, 1.73)	0.050
Infant HCAZ at 6-week visit	0.30 (-0.46, +1.26)	0.75 (-0.27, +1.77)	0.010
Infant WFLZ at 6-week visit	-0.35 (-1.68, +0.84)	-0.63 (-1.55, +0.51)	0.559

All continuous variables shown as Median (IQR) and categorical variables as No. (%).
BMI = Body Mass Index; GA = Gestational Age; HCAZ = Head Circumference for age z score; HOMA-IR= Homeostatic Model Assessment of Insulin Resistance; HOMA-B = Homeostatic Model Assessment Beta cell function; IQR = Interquartile Range; LAZ = Length for age z score; LBW=Low Birth Weight;; WAZ = Weight for age z score; and WFLZ = Weight for length z score

FIGURE. ACYLCARNITINES AND BRANCHED-CHAIN AMINO ACIDS ASSOCIATED WITH INFANT INSULIN



*Acylcarnitines and Branched Chain Amino Acids representing Principal Components 3 and 5 in green

RESULTS

- **Median insulin levels and HOMA-IR scores were lower in HEU infants (3.6 vs. 4.9 µU/mL, $p<0.01$ and 0.87 vs. 1.12, $p<0.01$ respectively).**
- **Two PCA components differed significantly between groups: Component 3 comprised of AC C2, C3, C4, C5, C6, C4OH, C5OH, C3DC, C4DC, C5DC, and C10 ($p=<0.01$) and Component 5 comprised of BCAA (leucine, isoleucine, and valine, $p=0.04$).**
- **In multivariate modeling, HEU status remained associated with lower infant pre-prandial insulin [β=(-0.06), $p=0.04$].**
- **Furthermore, infant WAZ (β=0.04, $p<0.01$), Component 3 (β=0.06, $p<0.01$), and Component 5 (β=0.03, $p=0.02$) were associated with higher insulin levels.**

TABLE 2. LINEAR REGRESSION MODEL FOR INFANT PRE-PRANDIAL INSULIN AT 6 WEEKS

Risk Factor	Coefficient	p value
Maternal HIV Status		
HIV-exposed uninfected	-0.058	0.041
HIV-unexposed uninfected	0	
Maternal Age, per year	-0.001	0.761
Highest Level of Education		
Secondary School or lower	-0.026	0.326
High School or higher	0	
Maternal Gestational Diabetes Status		
Gestational diabetes	0.061	0.280
No gestational diabetes	0	
Infant Gender		
Female	-0.004	0.873
Male	0	
Low Birth Weight (<1500 g)	0.036	0.614
Preterm Birth (<37 weeks)	0.009	0.817
Infant Weight-for-Age z score at 6 weeks	0.043	<0.001
Long-Chain Hydroxyl ACs – PC 1	-0.005	0.713
Long-Chain ACs – PC 2	-0.006	0.696
Short-Chain ACs – PC 3	0.059	<0.001
Medium- and Long-Chain ACs – PC 4	0.013	0.325
BCAAs (Leucine, Isoleucine, Valine) – PC 5	0.031	0.019

AC= Acylcarnitines; BCAA= Branched-Chain Amino Acids; PC = Principal Component

CONCLUSIONS

- **Compared to HUU, HEU infants have lower pre-prandial insulin levels at 6 weeks of life.**
- **Distinguishing clusters of short-chain ACs and BCAAs were also associated with infant insulin levels.**
- **Future studies should determine the significance of these early metabolic changes on later health and morbidity.**

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