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Acute Hyperinsulinemia Effects on Systemic Markers of Immune Activation in HIV

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Summary

The well-treated HIV population remains at risk for insulin resistance and chronic immune activation. We tested the effects of acute hyperinsulinemia on inflammation in HIV. Twenty HIV-infected and 10 non-HIV-infected individuals well-matched for BMI underwent oral glucose tolerance testing to stimulate insulin secretion and assess for changes in circulating sCD163, sCD14, and MCP-1. sCD14 decreased significantly after stimulation of hyperinsulinemia and no significant changes in sCD163 or MCP-1 were demonstrated in HIV-infected and non-HIV-infected groups.

Keywords

HIV; Oral Glucose Tolerance Testing; Hyperinsulinemia; Immune Activation; sCD163; sCD14; MCP-1

Introduction

Shifts towards an increasing monocyte population in chronic well-treated HIV infection[1] are correlated with insulin resistance(IR). While a pathologic link between IR and inflammation has been reported, the exact directionality and causality of this relationship remains unclear. As systemic hyperinsulinemia evolves in a state of IR, we took advantage of standardized oral glucose tolerance testing(OGTT) to physiologically stimulate endogenous insulin secretion and assess for parallel changes in systemic soluble CD163(sCD163), soluble CD14(sCD14), and monocyte chemoattract protein 1(MCP-1) among HIV-infected and non-HIV infected groups. We hypothesized that excess insulin would enhance macrophage-driven inflammation in HIV, an important question to address,

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as such data could direct treatment towards insulin-sensitizing strategies to dampen inflammatory-mediated metabolic sequelae in HIV.

Methods

Participants

Twenty HIV-infected and 10 non-HIV-infected individuals were recruited to be of similar age (18–65 years), sex, and waist circumference. Individuals with known diabetes, cardiovascular disease or pregnancy were excluded. All individuals provided IRB-approved informed consent to participate.

Oral Glucose Tolerance Testing

A standard 75g OGTT was performed in the morning following a 12 hour fast. Measurements of plasma glucose and serum insulin were obtained at 0 and 120 minutes.

Markers of Monocyte and Macrophage Activation

EDTA plasma was collected at 0 and 120 minutes during the OGTT. ELISA was performed to quantify sCD163(Trillium Diagnostics, Bangor, ME), sCD14 and MCP-1(R&D Systems, Minneapolis, MN), key immune markers in HIV well-recognized for their relevance to IR and metabolic dysregulation[2–6].

Statistical Analysis

Data are presented as mean±standard error of the mean if normally distributed or median[interquartile range] if non-normally distributed. Paired within-group(HIV or non-HIV) or between-group comparisons of the absolute change in glycemic and immune parameters at baseline and 120 minutes of the OGTT were assessed using the appropriate test(Student's t-test or Wilcoxon).

Results

Characteristics

HIV-infected and non-HIV-infected groups were of similar age and sex. Individuals with HIV had a chronic history of infection(18 ± 1 years) and ART use(11 ± 1 years) and demonstrated good immunological control($CD4\ 571\pm 73$ cells/ μ L). Body composition, including BMI(26 ± 1 vs. 25 ± 1 kg/ m^2 , $P=0.65$, HIV vs. non-HIV), and other metabolic parameters did not differ based on serostatus(Supplemental Table 1).

Glycemic Parameters During OGTT

Fasting glucose(84 ± 1 vs. 87 ± 1 mg/dL, $P=0.08$) and insulin($4[3,9]$ vs. $3[2,7]$ uIU/mL, $P=0.14$) were comparable between both HIV-infected and non-HIV-infected groups. At 120 minutes, glucose levels rose to similar levels within each group(129 ± 8 vs. 114 ± 11 mg/dL, change glucose $P\ 0.0001$ and $P=0.04$, HIV and non-HIV). Insulin levels at 120 minutes($49(39,73)$ vs. $19(8,46)$ uIU/mL) were higher in HIV-infected vs. non-HIV-infected groups($P=0.03$). The absolute change in insulin during the OGTT was significantly increased within-group(change insulin $P\ 0.0001$ and $P=0.002$, HIV and non-HIV) and between-

group($P=0.03$), while the absolute glucose change was similar between-groups($P=0.21$) (Table 1).

Systemic Immune Markers During OGTT

Soluble CD14 levels at baseline[1927(1433,2172) vs. 1360(1288,1521)pg/mL, $P=0.005$] and 120 minutes[1756(1473,2059) vs. 1333(1177,1502)pg/mL, $P=0.002$] were significantly higher in HIV-infected vs. non-HIV-infected individuals. sCD14 significantly decreased within both the HIV-infected($P=0.04$) and non-HIV-infected($P=0.049$) groups during the OGTT, while there was no significant between-group change. Baseline MCP-1 and sCD163 were similar regardless of serostatus, and there was no considerable change noted within-group or between-group during the OGTT for sCD163 and MCP-1(all $P>0.05$)(Table 1).

Discussion

The current study utilizing the OGTT assessed for the first time effects of acute hyperinsulinemia on immune markers among HIV-infected and non-HIV-infected groups. Our testing demonstrated an expected overall increase in glucose and insulin levels among all subjects after 120 minutes. The significantly greater rise in insulin levels during the OGTT among HIV-infected vs. non-HIV-infected individuals reflects known physiology among the HIV population whom demonstrate an increased risk of IR compared to the age- and BMI-matched non-HIV population[7]. In contrast to changes in glycemic parameters, there was a significant decrease in sCD14 after stimulation of hyperinsulinemia through glucose loading in both the HIV-infected and non-HIV-infected groups. In addition, sCD163 appeared to decrease in both groups during the OGTT, though not to a significant degree.

Similar studies investigating inflammation during OGTT in the obese and diabetes populations have generated mixed results, with hyperinsulinemia having decreased, increased or neutral effects on markers of generalized inflammation and immune activation[8, 9]. As some evidence suggests IR is monocyte and macrophage-mediated through inhibition of insulin signaling pathways or impaired GLUT4 translocation[10], we may have anticipated neutral effects of insulin on immune markers during the OGTT if this were an exclusive and unidirectional relationship. Other data demonstrate that insulin may fuel monocyte and macrophage activation in the adipose depot, evidenced by increases in circulating immune markers[11, 12]. Contrary to this and our hypothesis, we did not see a significant increase in immune markers, but rather a decrease in sCD14 and possibly sCD163. The similar change among both HIV-infected and non-HIV-infected individuals suggests this phenomenon occurs regardless of serostatus. Greater differences within and between serostatus groups may have resulted had we enrolled individuals with severe IR.

In support of our findings demonstrating reduced sCD14 during a state of hyperinsulinemia, insulin is reported to have direct anti-inflammatory actions by decreasing NF κ B or inhibiting toll-like receptor expression[13]. Insulin also indirectly exerts anti-inflammatory effects on metabolic disease by lowering glucose and inhibiting lipolysis-generated fatty free acids. Taken together, these evidence build upon a novel biologic concept, such that hyperinsulinemia may have salutary effects, acting to dampen chronic inflammation in the well-treated HIV population whom remain at dual risk for inflammation and IR.

A limitation of the study includes the small sample size. The focus of our investigation was evaluating acute rather than chronic effects of hyperinsulinemia on immune activation. In addition, changes in immune activation should be evaluated for effects on IR. To that end, a more sophisticated biologic crosstalk may exist, such that insulin and monocyte/macrophage-derived inflammation feedback (whether negative or positive) on one another during HIV infection.

The main strength of this study was our ability to further investigate the directionality and causality of a correlative relationship, using a physiologic intervention to stimulate endogenous insulin secretion and evaluate for changes in markers of immune activation. In summary, these novel findings, though paradoxical to our hypothesis, provide unique insight into the complex metabolic interrelationship between inflammation and IR in HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Principal contributions of the authors are project conception/design (SKG, SS), subject recruitment and implementation of the original study protocol (KVF,SS), data acquisition and analysis and database management (TKO, JAR, THB, KVF, SS), statistical analysis and interpretation (TKO, SKG, SS), drafting of the manuscript (TKO, SS), and critical revision of the manuscript (TKO, JAR, THB, KVF, SKG, SS).

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Table 1

Comparison of Glycemic Parameters and Immune Markers during Oral Glucose Tolerance Testing Among HIV-infected and Non-HIV-Infected Groups

	Baseline	120 Minutes	Change Between 120 Minutes and Baseline	Within-Group Change P Value ^a	Between-Group Change P Value ^b
Glucose (mg/dL)					
HIV-Infected	84 ± 1	129 ± 8	46 ± 8	<0.0001	0.21
Non-HIV-Infected	87 ± 1	114 ± 11	28 ± 11	0.04	
Insulin (uIU/mL)					
HIV-Infected	4 (3, 9)	49 (39, 73) ^c	44 (31, 69)	<0.0001	0.03
Non-HIV-Infected	3 (2, 7)	19 (8, 46)	16 (6, 38)	0.002	
sCD163 (ng/mL)					
HIV-Infected	817 (647, 1187)	781 (588, 1022)	-26 (-112, 37)	0.25	0.50
Non-HIV-Infected	770 (569, 880)	662 (509, 804)	-48 (-99, -3)	0.13	
sCD14 (ng/mL)					
HIV-Infected	1927 (1433, 2172) ^c	1756 (1473, 2059) ^c	-84 (-165, 25)	0.04	0.88
Non-HIV-Infected	1360 (1288, 1521)	1333 (1177, 1502)	-89 (-170, -22)	0.049	
MCP-1 (pg/mL)					
HIV-Infected	358 (229, 431)	333 (217, 436)	8 (-24, 40)	0.99	0.91
Non-HIV-Infected	277 (189, 343)	272 (210, 333)	2 (-23, 19)	1.00	

Data reported as mean±standard error of the mean or median (interquartile range).

^aP value obtained by Student's Matched T-Test or Wilcoxon signed-rank test.^bP value obtained by Student's T-Test or Wilcoxon rank sums.^cP value <0.05 HIV-infected vs. non-HIV-infected

Abbreviations: sCD163, soluble CD163; sCD14, soluble CD14; MCP-1, monocyte chemoattractant protein-1