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Insulin-like Growth Factor 1 Inversely Relates to Monocyte/Macrophage Activation Markers in HIV

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Abstract

Objective—Monocyte/macrophage activation is increased among people with HIV, and may contribute to the heightened risk of atherosclerosis and neurocognitive dysfunction in this population. Insulin-like growth factor 1 (IGF-1) has been shown to attenuate the innate immune response in animal models of atherosclerosis and inflammatory bowel disease. We investigated for the first time relationships of circulating IGF-1 with monocyte/macrophage-specific indices among HIV-infected individuals and uninfected controls.

Design—Observational.

Methods—131 HIV-infected subjects and 65 well-matched controls without known cardiac disease or viral hepatitis were recruited previously. IGF-1, expressed as a z-score relative to the age- and sex-adjusted population mean, was related to log-transformed inflammatory markers within HIV and non-HIV groups.

Results—In HIV, IGF-1 inversely related to sCD163 ($r = -0.28$, $P = 0.002$), sCD14 ($r = -0.29$, $P = 0.002$), and high-sensitivity IL-6 ($r = -0.27$, $P = 0.006$). There was no association of IGF-1 with high-sensitivity CRP, MCP-1, IL-18, or LPS in HIV, or between IGF-1 and any inflammatory marker in controls. Relationships of IGF-1 with sCD163 and sCD14 remained significant in HIV after controlling for age, sex, smoking, body mass index, visceral fat, statin use, viral load, and

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antiretroviral therapy. For every 1-unit decline in IGF-1 z-score, sCD163 and sCD14 increased by 14% (95% CI, 0.23%, 29%) and 29% (95% CI, 1.4%, 63%), respectively.

Conclusions—Low IGF-1 was robustly associated with high sCD163 and sCD14 in HIV. Prospective studies are needed to investigate augmentation of IGF-1 as a novel strategy to reduce monocyte/macrophage activation in this population.

Keywords

Monocytes; Immunity; innate; Immune markers; Insulin-like growth factor 1; HIV

Introduction

Despite a reduction in AIDS-defining illnesses in the modern era of antiretroviral therapy (ART), individuals with HIV remain at heightened susceptibility to cardiovascular disease, cancer, and neurocognitive dysfunction [1]. Evidence has emerged that chronic innate immune activation may contribute to the increased risk of serious non-AIDS events among HIV-infected patients [1]. Biomarkers associated with monocyte and macrophage activation including interleukin-6 (IL-6) [2], soluble CD163 (sCD163) [3], and soluble CD14 (sCD14) [4] are increased in people living with HIV, irrespective of ART treatment status. Furthermore, in this population, these indices have been shown to relate directly to cardiovascular disease [5–7] and neurocognitive impairment [8–10], and to predict mortality [11–13]. Accordingly, identifying mechanisms of monocyte/macrophage activation and developing strategies for immune modulation are critical aspects of the HIV research agenda [1].

Insulin-like growth factor 1 (IGF-1) is a peptide that acts in an endocrine and autocrine/paracrine manner to regulate growth, differentiation, and cell survival. While circulating IGF-1 levels primarily reflect hepatic synthesis and secretion in response to pituitary-derived growth hormone (GH) [14], multiple tissues produce IGF-1 including monocytes and macrophages [15]. Monocytes and macrophages also express the IGF-1 receptor (IGF1R), and IGF-1 has been shown to exert anti-inflammatory effects on these cell populations [16–18]. In mice fed a high-fat diet, myeloid-specific ablation of the IGF1R led to an increase in adipose tissue macrophages, which were polarized away from an M2 (anti-inflammatory) phenotype [16]. Additionally, a study of atherosclerosis-prone apoE-deficient mice found that infusion of IGF-1 decreased atherosclerotic plaque progression and macrophage accumulation within plaque lesions [17]. In a mouse model of colitis, the adoptive transfer of IGF-1-primed monocytes but not naïve monocytes was shown to reduce intestinal inflammation [18].

Since IGF-1 has immunosuppressive effects on monocytes and macrophages, perturbed IGF-1 signaling may potentiate chronic innate immune activation in HIV. Here, for the first time, we investigated relationships between systemic levels of IGF-1 and inflammatory markers in HIV, focusing on those associated with monocyte/macrophage activation. Given the anti-inflammatory properties of IGF-1, we postulated that HIV-infected subjects with the lowest IGF-1 levels would have the highest monocyte/macrophage-specific indices. An

association between IGF-1 and inflammatory markers in HIV may implicate low IGF-1 as a novel driver of chronic immune activation among this patient population.

Subjects and Methods

Study design

In this observational study, we utilized data from a well-characterized sample of HIV-infected individuals and uninfected controls [6, 19, 20] to explore relationships between IGF-1 and monocyte/macrophage activation markers. IGF-1 has never before been examined in these subjects.

HIV-infected and uninfected men and women without known cardiac disease were prospectively recruited from the Boston area. Body composition and metabolic factors were not criteria for enrollment. Participants on ART were required to be on a stable regimen for over 3 months. Individuals who were taking growth hormone, glucocorticoids, or anti-inflammatory medications or who had an acute infection were excluded. Since we postulated that viral hepatitis might alter hepatic IGF-1 production and systemic inflammatory markers, participants with a history of hepatitis B or C infection also were excluded from the current report. All subjects provided informed consent to participate. The study was approved by the Institutional Review Boards of Massachusetts General Hospital and Massachusetts Institute of Technology.

Study procedures

All participants underwent a detailed history and physical examination. Weight and height were measured in a fasting state to calculate body mass index (BMI). Body composition was further characterized through assessment of visceral (VAT) and subcutaneous adipose tissue (SAT) areas using a single slice abdominal computed tomography (CT) scan at the level of the L4 pedicle [21]. High sensitivity C-reactive protein (hs CRP), monocyte chemoattractant protein-1 (MCP-1), high sensitivity IL-6 (hs IL-6), sCD163, sCD14, and interleukin-18 (IL-18) were measured by enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions (Labcorp [hs CRP], R&D Systems [MCP-1, hs IL-6, sCD14, and IL-18], Trillium Diagnostics [sCD163]). The endpoint *Limulus* Amebocyte Lysate assay (Associates of Cape Cod) was used to quantify plasma lipopolysaccharide (LPS). The anti-inflammatory markers adiponectin and interleukin-10 (IL-10) also were ascertained by ELISA using standard protocols (R&D Systems [adiponectin], Invitrogen [IL-10]). Serum IGF-1 was determined by liquid chromatography/mass spectrometry (Quest Diagnostics). IGF-1 results were expressed as a z-score that denotes the number of standard deviations a value is above or below the population mean adjusted for age and sex.

Statistical analysis

Demographic, metabolic, and immunologic parameters were compared between the HIV and non-HIV groups using a two-tailed *t*-test for continuous variables that were normally distributed, Wilcoxon rank-sum test for continuous variables that were not normally distributed, and chi-square test for categorical variables. To test for a relationship between IGF-1 z-score and monocyte/macrophage activation, IGF-1 z-score was related to

logarithmically transformed inflammatory markers using Pearson correlation coefficient among participants with or without HIV. Markers that significantly related to IGF-1 z-score were tested in multivariable models that controlled for factors postulated to affect inflammation. Within each group, inflammatory markers also were compared between subjects dichotomized by IGF-1 z-score < 0 or ≥ 0 using Wilcoxon rank-sum test.

In an exploratory analysis, select anti-inflammatory markers were compared between HIV and non-HIV groups using Wilcoxon rank-sum test. Within the HIV and non-HIV groups, these markers were further compared between subjects dichotomized by IGF-1 z-score < 0 or ≥ 0 using Wilcoxon rank-sum test.

Variables with a normal distribution were expressed as mean $\pm$ standard deviation, whereas those not normally distributed were denoted as median [interquartile range]. A critical value of $P < 0.05$ was used to designate statistical significance. All statistical analyses were performed using JMP Pro 12.0.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Characteristics of participants

A total of 131 HIV-infected individuals (46.7 ± 8.2 years old, 67% men) and 65 uninfected controls (45.4 ± 7.1 years old, 62% men) were analyzed. Demographic, metabolic, and immunologic characteristics of study participants are summarized in Supplemental Table 1. There was no difference in age, sex, race, smoking status, BMI, or VAT between groups. Statin use was more prevalent in participants with HIV compared to controls (17% vs. 5%, $P = 0.02$). HIV-infected subjects had long-standing disease (time since diagnosis 14.4 ± 6.9 years) that was immunologically controlled ($CD4^+$ count 556 [392,816] cells/mm³, 75% with viral load undetectable) with ART use in 81%.

IGF-1 z-score did not differ between HIV and non-HIV groups (-0.09 ± 0.8 vs. -0.3 ± 0.7 , $P = 0.11$). MCP-1 (261 [179,359] vs. 223 [166,271] pg/mL, $P = 0.01$), sCD163 (1081 [711,1564] vs. 820 [591,1054] ng/mL, $P = 0.0002$), and IL-18 (247 [181,319] vs. 197 [142,246] pg/mL, $P = 0.0002$) were higher in the HIV-infected participants compared to controls. hs IL-6, sCD14, and LPS also tended to be greater in HIV, though these differences did not achieve statistical significance. hs-CRP was similar between groups.

Relationships of IGF-1 with inflammatory markers

We next tested the univariate association of IGF-1 z-score with logarithmically transformed inflammatory markers among HIV and non-HIV groups (Supplemental Table 2). As hypothesized, in individuals with HIV, IGF-1 inversely correlated with sCD163 ($r = -0.28$, $P = 0.002$), sCD14 ($r = -0.29$, $P = 0.002$), and hs IL-6 ($r = -0.27$, $P = 0.006$). Moreover, HIV-infected patients with IGF-1 z-score < 0 had higher sCD163 (1196 [928,2070] vs. 882 [674,1416] ng/mL, $P = 0.004$), sCD14 (1250 [383,1928] vs. 323 [153,477] ng/mL, $P = 0.0001$), and hs IL-6 (1.4 [1.0,2.1] vs. 1.0 [0.6,1.5] pg/mL, $P = 0.009$) than those with IGF-1 z-score ≥ 0 (Figure 1). There was no relationship of IGF-1 with hs-CRP, MCP-1, IL-18, or LPS in the HIV group, or between IGF-1 and any inflammatory marker in the controls.

We then examined whether the significant correlations of IGF-1 with sCD163, sCD14, and hs IL-6 in HIV would persist in multivariable models that controlled for covariates that may alter inflammation (Table 1). The relationships of IGF-1 with sCD163 and sCD14 remained significant among individuals with HIV when accounting for age, sex, smoking status, BMI, VAT, statin use, viral load, and ART regimen. For every 1-unit decline in IGF-1 z-score, sCD163 and sCD14 increased by 14% (95%CI 0.23%, 29%) and 29% (95%CI 1.4%, 63%), respectively. On the other hand, the association of IGF-1 with hs IL-6 in HIV was no longer significant when controlling for these factors. There also was no relationship of IGF-1 with sCD163, sCD14, or hs IL-6 in multivariable models among controls.

Of note, in these models, male sex was associated with lower sCD163 in HIV, and lower sCD14 and hs IL-6 in both HIV and non-HIV. This observation is consistent with a previous report by our group demonstrating heightened immune activation in women compared to men irrespective of HIV status [20].

Exploratory analysis of anti-inflammatory markers

In an exploratory analysis, we examined relationships between IGF-1 and the anti-inflammatory markers adiponectin and IL-10. Adiponectin was comparable between individuals with HIV and healthy controls (4051 [2517,8982] vs. 4347 [3283,7155] ng/mL, $P=0.80$), and did not relate to IGF-1. Similarly, IL-10 did not differ between HIV-infected and uninfected participants (0 [0, 0] vs. 0 [0, 21] pg/mL, $P=0.17$), although the highest levels were seen among uninfected individuals. In contrast to the inverse relationship between IGF-1 and monocyte/macrophage activation markers in HIV, IL-10 was not higher among HIV-infected subjects with low IGF-1 (Supplemental Figure 1).

Discussion

In this observational study, we showed for the first time an inverse association between IGF-1 and monocyte/macrophage activation markers among individuals with HIV. While IGF-1 did not differ between HIV and non-HIV groups, HIV-infected patients with IGF-1 below the population mean adjusted for age and sex had higher hs IL-6, sCD163, and sCD14 than those with IGF-1 at or above the mean. Relationships of IGF-1 with sCD163 and sCD14 were independent of multiple factors that may alter the inflammatory milieu including age, sex, visceral fat, active smoking, statin use, and viral load. IL-6 is a pro-inflammatory cytokine produced predominantly but not exclusively by monocytes and macrophages [22], whereas sCD163 and sCD14 are solubilized receptors shed specifically by monocytes and macrophages in response to activation [23, 24].

While this is the first report to relate IGF-1 to chronic innate immune activation in HIV, low IGF-1 has been described in other inflammatory processes including nonalcoholic steatohepatitis [25, 26] and inflammatory bowel disease (IBD) [27, 28]. Since treatment of IBD has been shown to restore IGF-1 toward the normal range [29], the inflammatory milieu itself may contribute to the low IGF-1 observed in the setting of inflammation [30]. Indeed, IL-6 was found to directly mediate hepatic GH resistance *in vitro* [31], consistent with our finding of an inverse correlation between IGF-1 and hs IL-6 in HIV.

Conversely, in data from animal models, IGF-1 has been shown to play a critical role in the regulation of the monocyte/macrophage inflammatory response. In atherosclerosis-prone apoE-deficient mice, monocyte/macrophage-specific knockout of the IGF1R (IGF1R-KO) led to increased plaque burden and a less stable plaque phenotype as evidenced by increased macrophage infiltration and a thin fibrous cap. Moreover, macrophages isolated from these IGF1R-KO animals were found to have enhanced production of pro-inflammatory cytokines and reduced cholesterol efflux capacity [32]. In another study of apoE-deficient mice, IGF-1 infusion decreased the extent of overall atherosclerotic plaque as well as macrophage infiltration within plaque lesions, further demonstrating the anti-inflammatory effects of IGF-1 on monocyte/macrophage function [17].

Though low IGF-1 has been described in a variety of inflammatory states, to our knowledge, this is the first study to relate IGF-1 to monocyte/macrophage-specific indices in any population of patients. Given evidence that IGF-1 suppresses monocyte and macrophage activity [16–18], our findings that IGF-1 inversely relates to sCD163 and sCD14 in HIV raise several important questions. First, does low IGF-1 exacerbate chronic innate immune activation in HIV? The relationship of IGF-1 with monocyte/macrophage-specific markers in HIV suggests that IGF-1 may be an important modulator of monocyte/macrophage activity among this patient population. Specifically, low IGF-1 may shift monocytes/macrophages toward a pro-inflammatory state among individuals who as a group are primed for immune activation. In contrast, higher IGF-1 may have opposite effects to reduce monocyte/macrophage activity and to increase anti-inflammatory cytokines. Of note, while IGF-1 may contribute to significant within-group differences in inflammation among individuals with HIV, it is unlikely to underlie the heightened immune response that characterizes HIV-infected patients compared to healthy controls. IGF-1 levels were comparable between the HIV and non-HIV groups in the current study, as is consistent with previous reports [33, 34].

Second, given that low IGF-1 may exacerbate chronic innate immune activation in HIV, would restoration of normal IGF-1 signaling blunt the monocyte/macrophage inflammatory response among this patient population? There has been intense interest in IGF-1 as a potential therapeutic agent in inflammatory states including IBD [35], atherosclerosis [17], and thermal injuries [36]. Though data in humans are limited, in a randomized controlled study of severely burned children, infusion of IGF-1 with IGF binding protein-3 (IGFBP-3) attenuated the acute phase response [36]. The growth hormone-releasing hormone (GHRH) analogue tesamorelin, approved to treat abdominal fat accumulation in HIV, has been shown in Phase III trials to augment IGF-1 levels by an average of 84% [37]. While the effect of tesamorelin on monocyte/macrophage activation in HIV has not been previously explored, our current findings provide a rationale for such an interventional study.

A strength of this report is our detailed phenotyping of subjects, which has allowed us to examine relationships between IGF-1 and inflammatory markers while controlling for a host of factors. An important limitation of our analysis is its cross-sectional design from which we cannot ascertain causality. Prospective studies, as detailed above, are needed to further delineate the interplay between IGF-1 and monocyte/macrophage activation in HIV. Additionally, our examination of IGF-1 in relation to circulating monocyte/macrophage-

specific markers should be extended to include monocyte/macrophage subsets in future work. As another study limitation, the relatively smaller number of controls compared to HIV-infected subjects may have restricted our power to detect associations within this group.

In conclusion, we show for the first time an inverse association between IGF-1 and monocyte/macrophage activation markers among people living with HIV. Since IGF-1 attenuates the pro-inflammatory response of monocytes and macrophages, low IGF-1 may promote immune activation and related sequelae in this population. Further studies are needed to evaluate the IGF-1 system as a novel target for immune modulation among HIV-infected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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L.T.F. and S.K.G. designed analyses, interpreted results, and drafted the initial manuscript. L.T.F., N.C., and S.D.S. performed the statistical analyses. T.H.B., K.C.W., K.V.F., and J.L. participated in data acquisition and database management. K.V.F. and J.L. completed subject recruitment and implementation of the original study protocol. All authors edited and provided substantial input to the manuscript.

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Figure 1. Low IGF-1 Standard Deviation Z-score Was Associated with Higher Monocyte/Macrophage Activation Markers in HIV
 sCD163, sCD14, and hs IL-6 were compared among HIV-infected subjects with IGF-1 below the age- and sex-adjusted population mean (z-score < 0) to those with IGF-1 greater than or equal to the population mean (z-score ≥ 0). Boxes span the 25th to 75th percentiles, whereas whiskers designate the 10th to 90th percentiles. *P*-values were determined using Wilcoxon rank-sum test.

Table 1
Multivariable Models Relating IGF-1 Z-score to Inflammatory Markers in HIV-Infected Participants and Uninfected Controls

Parameter	log sCD163 (ng/mL)			log sCD14 (ng/mL)			log hs IL-6 (pg/mL)		
	HIV (n = 94)		Non-HIV (n = 58)		HIV (n = 92)		HIV (n = 85)		Non-HIV (n = 49)
	β	P-value	β	P-value	β	P-value	β	P-value	P-value
IGF-1 z-score	-0.06	0.046	-0.04	0.29	-0.11	0.04	-0.06	0.19	-0.07
Age (y)	0.001	0.70	0.0001	0.98	-0.01	0.08	-0.006	0.35	-0.01
Male sex	-0.09	0.001	-0.03	0.46	-0.35	<0.0001	-0.11	0.02	-0.14
Current smoker	-0.005	0.84	-0.002	0.95	0.03	0.55	-0.02	0.56	0.04
BMI (kg/m ²)	-0.001	0.81	0.00003	1.0	0.004	0.70	0.005	0.56	0.94
VAT (cm ²)	0.0004	0.16	0.0004	0.39	0.00002	0.98	0.0007	0.19	0.0007
Statin use	-0.02	0.55	0.03	0.68	0.11	0.08	-0.03	0.62	-0.09
log VL (copies/mL)	-0.006	0.73	—	—	-0.04	0.19	0.009	0.74	—
NNRTI use	-0.13	0.0005	—	—	-0.06	0.32	-0.06	0.35	—
NNRTI use	-0.009	0.75	—	—	-0.08	0.13	-0.08	0.09	—
PI use	0.01	0.60	—	—	-0.01	0.78	0.0003	0.99	—

Multivariable models are shown with β -coefficient and P-value for each parameter. Bold text denotes statistical significance with $P < 0.05$.

IGF-1, insulin-like growth factor 1; BMI, body mass index; VAT, visceral adipose tissue area; VL, viral load; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.