Physical Activity and Its Association with Insulin Resistance in Multicenter AIDS Cohort Study Men

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Abstract

The association between physical activity (PA), degree of insulin resistance (IR), and HIV infection is unclear. We hypothesized that PA might differentially affect the degree of IR through the direct and indirect influences of HIV, antiretroviral medications, and sociodemographic characteristics. The International Physical Activity Questionnaire (IPAQ) was administered to Multicenter AIDS Cohort Study (MACS) participants from 4/2010 to 3/2011 to generate metabolic equivalents (METs) total score and PA category. We determined the concurrent homeostatic model assessment IR (mmol/liter) (HOMA-IR) value from fasting glucose and insulin. We examined the HIV-PA relationship using quantile regression and the HIV-PA-HOMA-IR value relationship using linear regression. Among the 1,281 men, the proportions of men in the low (25% in HIV⁺ vs. 23% in HIV⁻), moderate (26% vs. 27%), and high (49% vs. 49%) PA categories were similar by HIV status. The HOMA-IR value was higher among the HIV⁺ men ($p < 0.001$), and both HIV infection and low PA were associated with a higher degree of IR ($p < 0.0001$ and $p = 0.0007$). However, the PA-HOMA-IR value interaction was not different by HIV status. The HOMA-IR value was higher among HIV⁺ men although the PA was similar. It is unknown if more exercise will overcome the metabolic derangements associated with HIV and its treatment.

Introduction

PHYSICAL ACTIVITY (PA) may improve the quality of life¹ and brain function² and can lower insulin resistance (IR) in adults.³ Lower insulin resistance decreases the risk of other adverse health consequences such as diabetes mellitus. Additionally, some data show that PA may counteract the adverse effects of HIV and improve related comorbid conditions: PA decreases the frequency of side effects associated with highly active antiretroviral therapy (ART), enhances immunity through higher CD4⁺ T cell counts, and improves glucose uptake through higher expression of glucose-metabolism signaling proteins in skeletal muscle.⁴

HIV-infected adults show higher fasting glucose measurements and impaired glucose tolerance, suggesting a greater degree of insulin resistance that may result from direct or indirect effects of highly active antiretroviral therapy

(HAART) and chronic systemic inflammation caused by persistent HIV infection.⁵⁻⁹ Various interventions have been tested to decrease IR among HIV-infected individuals. One potential intervention is PA, as even low levels of PA improve glucose uptake by the increased expression of signaling proteins involved with glucose metabolism in skeletal muscle.^{3,10}

PA frequency and intensity among HIV-infected adults are characterized by several studies, and in comparison to general population estimates, HIV-infected adults do not achieve the recommended levels of physical activity.^{11,12} Although disability may limit PA, there are no specific PA recommendations for those infected with HIV and it is unclear whether those with HIV should adhere to the general PA recommendations for adults. For example, lower levels of PA, adjusted for effects of disability, may be warranted for HIV-infected adults. However, some might suggest that high

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levels of PA may be more beneficial for HIV-infected adults in order to counter the effects of chronic inflammation and metabolic abnormalities related to long-term HAART use.

To explore the association between HIV infection, PA, and homeostatic model assessment (HOMA)-IR value, we evaluated data for 1,281 HIV-infected and HIV-uninfected gay, bisexual, and other men who have sex with men (MSM) participating in the Multicenter AIDS Cohort Study (MACS). We hypothesized that a higher PA would improve the HOMA-IR value, and that the effects would vary for HIV-infected and HIV-uninfected men.

Materials and Methods

Patient population

The MACS has been described extensively elsewhere.¹³ Briefly, 6,973 MSM were enrolled over three separate time periods beginning in 1984 at one of four sites: Baltimore/Washington, DC, Chicago, Los Angeles, and Pittsburgh. In 1984–1985, 1,813 HIV-infected and 3,141 HIV-uninfected men entered follow-up, with 425 HIV-infected and 243-uninfected men enrolled between 1987 and 1990 and 705 HIV-infected and 646 HIV-uninfected men enrolled in 2001–2003. The protocol is approved by the Institutional Review Board at each site and each study participant signed an informed consent.

Self-report PA data were collected using the International Physical Activity Questionnaire (IPAQ), and IR was calculated from fasting insulin and glucose test results within 6 months of the IPAQ. Although 1,713 men completed a study visit during which an IPAQ was administered, data from 284 men were excluded from the analyses due to missing or incomplete IPAQ data, and another 148 men were excluded due to a greater than 6 month gap between the IPAQ and the laboratory assessment, leaving a sample of 1,281 for analysis.

Physical activity

The short form of the IPAQ assesses physical activity undertaken across a comprehensive set of domains including leisure time physical activity, domestic and gardening (yard) activities, work-related physical activity, and transport-related physical activity.¹⁴ The questionnaire captures three specific types of activity (walking, moderate-intensity, vigorous-intensity activity) in the four domains. Data from the first self-administered IPAQ that could be scored were used to generate a metabolic equivalents (METs) total score (continuous variable), calculated by adding MET-min/week for all activity performed.

The summary IPAQ score was evaluated as a continuous variable. However, the IPAQ data were also categorized as low, moderate, and high levels of PA reported over the course of a week. Categorical scores (low, moderate, and high) were assigned as follows: (1) High: Vigorous activity on at least 3 days and accumulating at least 1,500 MET-min/week *or* 7 or more days of any combination of walking, moderate, or vigorous activity accumulating at least 3000 MET-min/week. (2) Moderate: 3 or more days of vigorous activity of at least 20 min/day *or* 5 or more days of moderate activity and/or walking of at least 30 min/day *or* 5 or more days of any combination of walking, moderate activity, or vigorous activity achieving a minimum of at least 600 METs. (3) Low: either no

activity reported or activity does not meet the criteria for moderate or high activity. IPAQ scoring strategies and scale characteristics are available at www.ipaq.ki.se/ipaq.htm.

Insulin resistance

Venous blood specimens were gathered and tested using a standard protocol within 6 months of the IPAQ administration. HOMA-IR value, the outcome of interest, was calculated from fasting blood glucose and fasting insulin using a homeostatic model assessment (HOMA-IR): glucose [mmol/liter] $\times$ insulin [μ U/ml]/22.5.¹⁵ Radioimmunoassay (RIA) was used to quantify fasting insulin.

Additional covariates

HIV infection is evaluated using ELISA and confirmed with Western blot at every semiannual visit until HIV is detected. Once confirmed, diagnostic HIV testing is discontinued and HIV RNA (viral load) is measured semiannually. CD4 T-lymphocyte count (cells/mm³), HIV viral load (RNA copies/ml), and presence of chronic hepatitis C virus (HCV) infection were evaluated using standard laboratory protocols. Body mass index (BMI) was calculated from weight and height measured at the index visit. Self-reported age (analyzed as the effect of each 10 years), race, education, smoking (classified as current, former, or never), history of AIDS-defining conditions, ART medications, and diagnosis of diabetes mellitus were evaluated.

Statistical methods

To evaluate the association between HIV status and PA, we performed adjusted quantile regression modeling. The quantiles included the lowest 10%, the 10–25% group, the 25–50% group, the 50–75% group, the 75–90% group, and the top 10%. To evaluate the association between HIV status, physical activity (low, medium, high), and IR, we used adjusted linear regression. The association between PA and IR in HIV-infected men was adjusted for CD4 cell count and HAART. As appropriate, interaction terms of PA with HIV status were also tested.

SAS versions 9.2 and 9.3 (Cary, NC) were used for the analysis

Results

Cohort characteristics

Table 1 presents the distribution of relevant demographic and clinical characteristics according to HIV status. Of the 1,281 men included, 596 (47%) were HIV infected and 685 (53%) were HIV uninfected. On average, HIV-infected men were younger, more often reported African American and Hispanic race and ethnicity, more often had diabetes and hepatitis C, and showed lower BMI. Most (85%) HIV-infected men reported current use of HAART and were virally suppressed (441/596, 74%). The median CD4 cell count was 591 cells/mm³. Among the diabetic patients, HIV-uninfected men were more likely to be on diabetes medication, and there was no difference by HIV status in insulin use. There was no significant difference between the number of diabetes medications used by HIV-infected and HIV-uninfected men, although more HIV-infected men used no

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE

	<i>HIV infected</i> (n = 596)	<i>HIV uninfected</i> (n = 685)	p-value
Age (years)	51 (46, 57)	55 (48, 62)	< 0.001
Race			< 0.001
White (%)	54	73	
African American (%)	17	9	
Hispanic/other (%)	29	17	
Education			< 0.001
High school or less (%)	24	13	
College (%)	51	50	
Grad school (%)	24	37	
Smoking			< 0.001
Never (%)	22	28	
Current (%)	30	19	
Former (%)	48	53	
Chronic hepatitis C infection (%)	8	3	< 0.001
Body mass index (kg/m ²)	25.3 (23.1, 28.1)	26.4 (23.8, 29.9)	< 0.001
Diabetes (%)	13	8	0.010
Diabetic patient on diabetes medication	50 (65%)	48 (83%)	0.02
Diabetic patient on metformin	21 (27%)	32 (55%)	0.56
Diabetic patient on insulin	18 (23%)	15 (26%)	0.75
Number of diabetes medications for diabetic patients			0.05
0	24 (31%)	9 (16%)	
1	31 (40%)	27 (47%)	
2	17 (22%)	13 (22%)	
3+	2 (3%)	7 (12%)	
Employment status			< 0.001
Disabled	108 (18%)	42 (6%)	
Unemployed	61 (10%)	51 (7%)	
Retired	54 (9%)	107 (16%)	
Student	9 (2%)	3 (0%)	
Part time	45 (8%)	44 (6%)	
Self-employed	43 (7%)	61 (9%)	
Full time	240 (40%)	343 (50%)	
Dyslipidemia	471 (79%)	505 (74%)	0.03
Hypercholesterolemia	184 (31%)	281 (41%)	0.003
On lipid-lowering agent	208 (35%)	195 (28%)	0.013
Hypertension	252 (42%)	292 (43%)	0.99
On antihypertensive medication	209 (35%)	204 (30%)	0.09
Depression	439 (74%)	443 (65%)	< 0.001
On antidepressant	173 (29%)	126 (18%)	< 0.001
HIV RNA <200 copies/ml (%)	74	—	—
CD4 ⁺ cell count (cells/mm ³)	591 (405–742)	—	—
CD4 ⁺ cell count nadir (cells/mm ³)	247 (144–349)	—	—
Duration of HAART (years)	8.8 (5.4, 12)	—	—
History of clinical AIDS (%)	12	—	—
PI-based HAART (%)	43	—	—
PI- and EFV-based HAART (%)	2	—	—
EFV-based HAART (%)	40	—	—
Other HAART (%)	34	—	—
No HAART (%)	15	—	—

HAART, highly active antiretroviral therapy; PI, protease inhibitor; EFV, efavirenz.

medications and fewer HIV-infected men used three or more medications. HIV-infected men were more likely to be disabled and less likely to be working full time.

Physical activity measures and degree of insulin resistance by HIV status

HIV-infected men reported overall METs per week similar to HIV-uninfected men (Table 2). The IPAQ category was

similar by HIV status, with most men falling into the moderate or high activity categories: 26% vs. 27% of HIV-infected and HIV-uninfected men, respectively, reported moderate activity and 49% of both groups reported high activity (Table 2). The median HOMA-IR value (3.0) was the same in both groups. Norms indicate that HOMA-IR > 2.6 is suggestive of being insulin resistant.¹⁶ The interquartile ratio (IQR) for this sample spanned 2.0 to 5.0 for HIV-infected men and 2.0 to 4.0 for HIV-uninfected men ($p < 0.0001$).

TABLE 2. PHYSICAL ACTIVITY AND INSULIN RESISTANCE BY HIV STATUS

	<i>HIV infected (n=596)</i>	<i>HIV uninfected (n=685)</i>	<i>p-value</i>
Walking METs per week	693 (198, 1,386)	594 (198, 1,386)	0.08
Moderate METs per week	360 (0, 1,680)	480 (0, 1,200)	0.54
Vigorous METs per week	480 (0, 1,920)	480 (0, 2,400)	0.43
Sum of METs per week	2,369 (739, 5,428)	2,316 (792, 4,782)	0.61
IPAQ category			
Low	150 (25%)	158 (23%)	0.74
Moderate	153 (26%)	188 (27%)	
High	293 (49%)	339 (49%)	
HOMA-IR	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	<0.001

METs, metabolic equivalents.

Factors associated with physical activity

Quantile regression was used to examine the associations between our covariates of interest and PA examined as a continuous variable, allowing us to identify particular associations between our covariates and PA among groups of men with varying activity levels, as shown in Table 3. At all physical activity levels, BMI was inversely associated with PA. Among men in the highest physical activity level (90th percentile), the association between HIV-infected status and more physical activity approached statistical significance ($p=0.07$).

Factors associated with degree of insulin resistance, all men

HIV, HCV, BMI, and age were all associated with higher HOMA-IR value (Table 4). High PA category vs. low PA category was inversely associated with the degree of insulin resistance ($\beta = -0.19$, $p=0.0007$); however, moderate PA category vs. low PA category was not associated with IR ($p=0.13$). The HIV-PA interaction term was not associated with the degree of insulin resistance (data not shown). When men with diabetes on diabetic medication were removed from the analysis, as diabetic medication may affect the degree of insulin resistance, the point estimates did not vary greatly (data not shown).

Factors associated with degree of insulin resistance, HIV-infected men only

Among HIV-infected men alone, data showed that high activity and moderate activity were associated with a lower degree of insulin resistance than was low activity reported by participants ($\beta = -0.30$, $p<0.0001$ for high; $\beta = -0.22$, $p=0.006$ for moderate, Table 5). Current regimen type [protease inhibitor (PI)-based, efavirenz (EFV)-based, or PI- and EFV-based regimens] was not associated with a higher degree of insulin resistance, and cumulative years of HAART exposure was borderline significantly associated with degree of insulin resistance ($\beta = 0.01$, $p=0.07$).

Discussion

Among HIV-infected and HIV-uninfected men in the MACS, many individuals achieved moderate or high PA levels, and there was no difference in PA category by HIV status. Despite similar PA levels, HIV-infected men had a higher degree of insulin resistance than the HIV-uninfected

men. Contrary to our hypothesis, we did not observe a difference in the benefit of PA on degree of insulin resistance by HIV status.

HIV and physical activity

Our results showed that many MACS participants achieved moderate or high PA levels. Prior investigations from the MACS showed lower physical function among HIV-infected vs. HIV-uninfected men; however, a different measure of physical function was used.¹⁷ Compared with a 2003 study examining exercise habits of individuals with HIV in two outpatient settings in the Great Lakes region of the United States, our estimates of PA were higher. In that study, patients' preferred PA was walking. Only 28.2% of the total sample met the CDC's recommendations for moderate PA.¹⁸ Our results were similar to a study by Fillipas *et al.* in 2008¹⁹ examining the exercise habits of 261 attendees (191 HIV infected) of an infectious disease clinic in Melbourne, Australia.

Similar to our study, the investigators used the IPAQ and found that about a quarter of HIV-infected and a third of HIV-uninfected respondents fell into the low PA category. Finally, a recent study by Stein *et al.*²⁰ examined the exercise habits of 124 HIV-infected men and 159 HIV-uninfected men, mostly (88%) MSM, with a median age of 35 years. The proportion of patients performing any PA was significantly lower ($p=0.028$) within the HIV-infected group (61.3%) than within the HIV-uninfected group (74.2%). This difference remained significant after accounting for possible confounders such as age, gender, and injecting drug use.²⁰ A systematic review in 2012 reported sedentary lifestyle prevalence ranging from 19% to 73% depending on the method of assessment, but noted that there were few high-quality assessments of exercise prevalence in HIV-infected individuals.²¹ Our exercise prevalence may be higher than those reported in earlier studies due to the unique composition of the MACS cohort, a group of long-term survivors who are generally motivated and engaged in improving health behaviors.

In addition to cross-sectional studies examining PA prevalence such as those described above, trials have been conducted to examine the fitness and metabolic effects of PA in people with HIV. A 2010 systematic review and meta-analysis⁴ evaluated randomized controlled trials of aerobic exercise interventions for HIV-infected adults and showed clinically meaningful and statistically significant improved $\text{VO}_2 \text{ max}$, decreased body fat, and increased leg muscle area

TABLE 3. QUANTILE REGRESSION—FACTORS ASSOCIATED WITH PHYSICAL ACTIVITY

	Quantile	β	p-value
Intercept	0.10	1103.24	
BMI		−15.83	<0.0001
HIV infected		−78.86	0.10
Age (per 10 years)		−105.75	0.003
Race			
White		Ref	
Black		−120.24	0.04
Hispanic/other		−38.07	0.72
Education			
High school		Ref	
Some college		171.16	0.0002
Postgrad		303.61	<0.0001
Intercept	0.25	1486.21	
BMI		−35.02	<0.0001
HIV infected		−37.76	0.70
Age (per 10 years)		−46.65	0.38
Race			
White		Ref	
Black		−69.68	0.59
Hispanic/other		440.42	0.09
Education			
High school		Ref	
Some college		496.09	<0.0001
Postgrad		634.64	<0.0001
Intercept	0.50	5,760.77	
BMI		−105.50	<0.0001
HIV infected		−101.90	0.64
Age (per 10 years)		−200.76	0.09
Race			
White		Ref	
Black		−133.36	0.60
Hispanic/other		770.55	0.02
Education			
High school		Ref	
Some college		856.81	0.01
Postgrad		486.17	0.18
Intercept	0.75	9,838.67	
BMI		−171.52	<0.0001
HIV infected		337.55	0.34
Age (per 10 years)		−268.18	0.12
Race			
White		Ref	
Black		530.05	0.27
Hispanic/other		1,361.49	0.03
Education			
High school		Ref	
Some college		899.80	0.06
Postgrad		508.23	0.41
Intercept	0.90	11,585.72	
BMI		−192.829	0.001
HIV infected		1,051.413	0.07
Age (per 10 years)		125.5168	0.65
Race			
White		Ref	
Black		1,078.775	0.11
Hispanic/other		2,332.981	0.03
Education			
High school		Ref	
Some college		698.6334	0.49
Postgrad		−768.145	0.47

Factors also adjusted for smoking status.
BMI, body mass index (kg/m^2).

TABLE 4. FACTORS ASSOCIATED WITH INSULIN RESISTANCE

	β	p-value
Age (q 10 years)	0.07	0.0001
Physical activity		
Low	REF	—
Moderate	−0.10	0.13
High	−0.19	0.0007
HIV	0.27	<0.0001
BMI	0.05	<0.0001
HCV	0.22	0.004

Factors adjusted for education, smoking status, race, and HIV $\times$ physical activity interaction.

associated with aerobic exercise. Another systematic review of 17 studies ($n=332$ HIV-infected adults) exploring the effects of progressive resistive exercise²² showed that weight training and isotonic and isometric strengthening exercises increased body weight, increased arm and thigh girth, and increased health-related quality of life and that submaximum heart rate and exercise time were also improved.

A third review including data from 494 HIV-infected participants in nine studies revealed that aerobic exercise decreased adiposity and may improve certain lipid subsets. Two of the nine studies measured lipids: one showed that reductions in total cholesterol and insulin following aerobic exercise with small effect sizes and reductions in glucose and triglycerides with moderate effect sizes were reported. The other found no effect on any metabolic parameter with aerobic exercise.²³ In our study, a higher PA was associated with a lower HOMA-IR value; however, there was no difference in the effect of PA on IR by HIV status as we expected.

HIV and IR

Insulin resistance is common in people with HIV,²⁴ with various factors associated with the degree of insulin resistance including HAART, increasing waist circumference,

TABLE 5. FACTORS ASSOCIATED WITH INSULIN RESISTANCE (HIV-INFECTED MEN ONLY)

	β	p-value
Age (q 10 years)	0.13	0.002
Physical activity		
Low	REF	—
Moderate	−0.22	0.006
High	−0.30	<0.0001
Body mass index	0.05	<0.0001
Chronic hepatitis C virus infection	0.17	0.13
Cumulative years HAART exposure	0.01	0.07
History of AIDS	−0.02	0.84
Undetectable HIV RNA	0.05	0.59
Current efavirenz-based HAART	−0.15	0.16
Current PI-based HAART	−0.02	0.78
Current efavirenz- and PI-based HAART	−0.03	0.87

Factors adjusted for education, smoking status, race, and current CD4.

HAART, highly active antiretroviral therapy; PI, protease inhibitor.

increasing triglycerides, and older age.²⁵ Herein we examined the hypothesis that HIV differentially influences the protective influence PA has on the degree of insulin resistance. Some studies show that exercise improves peripheral insulin sensitivity within the context of HIV. For example, Yarasheski *et al.*²⁶ studied the metabolic effect of pioglitazone treatment with or without supervised, progressive aerobic and resistance training (1.5–2 h/session, three times per week). They found that 4 months of exercise training augmented the peripheral insulin-sensitizing benefits of pioglitazone in HIV-infected adults with insulin resistance and central adiposity.²⁶ In our analysis including only HIV-infected men, we did demonstrate that a higher PA was associated with a lower degree of insulin resistance; however, we did not find an effect of cumulative HAART exposure or current HAART on HOMA-IR value.

Study limitations

Limitations of our study include the cross-sectional nature of the data and the potential inaccuracy of PA collected by the IPAQ due to overreporting. In a 2010 study by Fillipas and colleagues²⁷ comparing accelerometry with the IPAQ among HIV-infected subjects, the IPAQ correlated with accelerometry, but substantial overreporting occurred. The authors concluded that the tool may be useful in screening PA but should not be used to determine precise levels. A recent review by Lee and colleagues²⁸ emphasized that although the IPAQ's reliability has been demonstrated through multiple studies, the validity has been less thoroughly studied. In their review, they included studies that compared the IPAQ to either an objective measuring device (e.g., an accelerometer) or a fitness/anthropometric measure ($\text{VO}_{2\text{ max}}$ or body fat). Most of the validation studies did not show a correlation with objective measures of PA. The exceptions were walking and vigorous activity, for which the IPAQ showed acceptable correlations with objective data.

Another potential limitation is that we do not have physical activity data from men who did not complete the IPAQ. The IPAQ questionnaire from that visit was part of the standard questionnaire battery, which should limit selection bias caused by less active/sedentary men choosing not to complete the questionnaire.

Future research directions

One potential future research direction is to determine the level of PA needed to prevent factors that predispose individuals with HIV to insulin resistance including ART and HIV-related inflammation. This research could inform HIV-specific PA guidelines.

Summary

These analyses show that many HIV-infected and HIV-uninfected men achieved the recommended level of PA, with no real differences between them. Nonetheless, despite similar PA levels, HIV-infected men showed a greater degree of insulin resistance. Contrary to our hypothesis, we found that HIV did not differentially influence the measured benefits of exercise on the degree of insulin resistance. It is unknown to what extent exercise can overcome the metabolic derangements associated with HIV and its treatment.

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