Poster 745

Rainbow Babies & Children's Hospital

SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY

The Effect of Physical Activity on Cardiometabolic Health and Inflammation in HIV

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BACKGROUND

Regular physical activity lowers all-cause mortality by protecting against atherosclerosis and insulin resistance. However, the long term benefits of physical activity, including preventing diseases associated with chronic inflammation (e.g., type 2 diabetes, atherosclerosis, and rheumatoid arthritis) may be associated an anti-inflammatory effect.

In healthy adults, increased physical activity is associated with reduced inflammation independent of cardiovascular disease risk factors. In HIV-infected adults, little is known about the effect of physical activity on inflammatory markers and cardiometabolic health. The aim of this study was to examine the effects of physical activity and statin use on markers of cardiometabolic health and inflammation over 96 weeks.

MATERIALS & METHODS

Study design: Secondary analysis from a double blind placebo controlled trial

Subjects: SATURN trial criteria: HIV-infected subjects ≥ 18 years of age who were undergoing successful ART and had normal low-density lipoprotein (LDL) cholesterol levels (<130 mg/dl), but who had elevated levels of inflammation and immune activation. All were randomized to receive rosuvastatin (10 mg daily) or placebo.

Physical activity:
Assessed using the NIAID ACTG Physical Activity Assessment. This measures reports the number of times subjects participated in one of 27 activities in the past two weeks and on average, how many minutes each activity bout was. The total activity amount was summed and divided by two to indicate, the amount of physical activity each subject engaged in over the past week.

Inflammation and soluble immune activation markers:
- CD4+ and CD8+ T-cell activation (CD38 and HLA-DR expression)
- Inflammatory (CD14+CD16+) and patrolling (CD14dimCD16+) monocytes.
- Plasma markers of monocyte activation: Soluble CD163 (sCD163) and CD14 (sCD14),
- Plasma biomarkers of inflammation and endothelial activation

Measures of Cardiovascular Risk:
- Mean-max common carotid artery intima-media thickness (CCA-IMT): the maximum IMT of the distal 1cm of the CCA far wall was measured at 3 separate angles bilaterally (anterior, lateral, and posterior; 6 total measurements). The mean of the 6 maximum measurements was used for analyses.
- Carotid distensibility was calculated using the same formula [(2*(Ds-Dd)/Dd)/PP] used in the Women's Interagency Health Study (WIHS) and the Multicenter AIDS Cohort Study (MACS). Ds, systolic diameter; Dd, diastolic diameter; PP, pulse pressure.
- Flow-mediated dilation (FMD) and hyperemic velocity (VTI) of the brachial artery was measured by ultrasound with
semi-automated edge detection software pre- and post- reactive hyperemia using the forearm occlusion method and 5 minute occlusion time.
- Peircardial fat was quantified from a non-contrast CT scan of the chest.

Analyses: Descriptive statistics were used to describe the sample. Median regression were used to explore baseline cross-sectional relationships between exercise and our inflammatory and cardiometabolic variables of interest; median regression were also used to examine the effects of physical activity and statin use on inflammatory and cardiometabolic longitudinal outcomes. For analyzing longitudinal outcomes, we used bootstrap procedure for correcting the standard errors of the estimates.

RESULTS SUMMARY

Table 1: CHARACTERISTICS OF THE SUBJECTS, BY TREATMENT GROUP

	Rosuvastatin (*n*=72)	Placebo (*n*=75)
Demographics		
Age (mean)	45 (41,51)	47 (39,53)
Male sex	81%	76%
African American	69%	67%
HIV parameters		
HIV duration (years)	11 (6-17)	12 (6-19)
Current CD4+ count	608 (440-848)	627 (398-853)
Nadir CD4+ count	173 (84-312)	190 (89-281)
Undetectable viral load (<50 copies/ml)	78%	77%
ART duration (years)	5.2 (3.1-9.9)	5.9(3.3-9.6)
Current Protease Inhibitor use	50%	48%
Current TDF use	89%	88%
Metabolic and cardiovascular risk factors		
Body Mass Index (kg/m^2)	27 (22,30)	27 (23,30)
Systolic Blood Pressure (mm Hg)	122 (112,136)	120(110,132)
Diastolic Blood Pressure, mm Hg	79 (73-85)	80 (72-83)
HDL cholesterol (mg/dL)	47 (38-58)	46 (37-57)
LDL cholesterol (mg/dL)	96 (76-107)	97 (77-121)
Homeostatic Model Assessment of Insulin resistance (HOMA-IR) ≥2.5	1.7 (1-2.81)	1.95 (1.13-4.45)
Smoking current	43 (60)	50 (67)
Physical exercise		
Mean Overall Physical Activity (minutes per week)	155.1(0,150)	216 (0-150)

TABLE 2: BASELINE PHYSICAL ACTIVITY WAS ASSOCIATED WITH CARDIOMETABOLIC AND INFLAMMATORY MARKERS

	Univariate analysis estimate by Physical Activity Intensity					
	Moderate Intensity	*p*-value	Moderate-High Intensity	*p*-value	Overall Activity	*p*-value
Metabolic Factors						
Body Mass Index (kg/m^2)	-0.039	0.52	-0.17	0.04	-0.14	0.09
HDL	-0.19	0.02	-0.01	0.87	-0.15	0.08
LDL	-0.05	0.56	-0.09	0.27	-0.04	0.62
Triglycerides	-0.01	0.93	-0.06	0.48	-0.04	0.65
HOMA-IR	0.04	0.64	-0.18	0.03	-0.11	0.21
Leptin	-0.10	0.22	-0.34	<0.001	-0.28	0.00
Inflammation and Immune activation						
Interleukin 6	-0.19	0.02	-0.14	0.09	-0.23	<0.001
hsCRP	-0.20	0.02	-0.13	0.12	-0.20	0.02
TNFα- receptor I	0.01	0.95	-0.05	0.52	-0.04	0.62
TNFα- receptor II	-0.08	0.35	0.00	1.0	-0.05	0.44
CD4+CD38+HLADR+ T-cells	0.11	0.18	0.07	0.38	0.07	0.39
CD8+CD38+HLADR+ T-cells	0.18	0.03	0.07	0.44	0.11	0.17
sCD163 (ng/ml)	0.05	0.53	-0.00	0.98	-0.03	0.75
sCD14 (ng/ml)	-0.16	0.06	0.08	0.34	-0.02	0.79
CD14+ CD16+ monocytes	-0.05	0.59	-0.13	0.12	-0.15	0.07
CD14dimCD16+ monocytes	-0.12	0.16	0.02	0.83	-0.06	0.47
Cardiovascular measures						
Hyperemic VTI (cm)	0.11	0.18	0.18	0.03	0.19	0.02
CCA IMT (mm)	-0.00	0.94	0.03	0.74	0.00	0.91
Carotid Bulb IMT (mm)	-0.02	0.80	-0.01	0.84	-0.05	0.60
Pericardial Fat	-0.06	0.44	-0.16	0.05	-0.12	0.14
Carotid Distensibility (10^{-6}*$Newtons^{-1}$*m^2)	0.10	0.22	-0.00	0.99	0.08	0.32

TABLE 3 THERE WERE CHANGES IN WEEKLY PHSYICAL ACTIVITY BETWEEN TREATMENT GROUPS

	Statin	Placebo	P value
Baseline mean (IQR) minutes of exercise per week	155.1(0, 150)	216.6 (0,150)	0.084
Week 24 mean (IQR) minutes of exercise per week	195 (15, 225)	91.5 (0, 105)	0.026
Week 48 mean (IQR) minutes of exercise per week	217.2 (22.5, 300)	224.4 (0, 180)	0.155
Week 96 mean (IQR) minutes of exercise per week	239.1 (0, 270)	160.5 (0, 180)	0.393

TABLE 4: BASELINE PHYSICAL ACTIVITY WAS ASSOCIATED WITH HOMA-IR AND CAROTID IMT

	HOMA IR		Carotid Bulb IMT	
	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value
Physical Activity	0.033	<0.001	-0.002	<0.001
Age	0.004	0.818	0.01	<0.001
sex	1.19	0.002	-0.067	0.041
Race	0.25	0.219	-0.039	0.023
CD4 Nadir	-0.0002	0.817	-0.000	0.077
ARV duration	-0.66	0.526	-0.000	0.115

TABLE 5: PHYSICAL ACTIVITY WAS ASSOCIATED WITH MARKERS OF VASCULAR HEALTH OVER ALL TIME POINTS

	Carotid IMT (mean bulb)		Carotid Distensibility		FMD (hyperemic VTI)	
	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value
Physical Activity	-0.001	<0.0001	0.839	<0.0001	0.001	<0.001
Age	0.010	<0.0001	-0.552	<0.0001	-0.005	<0.001
sex	-0.001	0.99	3.819	<0.0001	0.014	0.545
Race	-0.026	0.326	-2.039	0.019	-0.590	0.003
CD4 Nadir	<0.0001	0.110	0.001	0.247	<-0.0001	<0.001
ARV duration	-0.001	<0.0001	-0.008	0.020	<-0.0001	0.076
STATIN Group						
	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value	Multivariable analysis estimate	p- value
Physical Activity	-0.001	<0.0001	0.0836	<0.0001	0.001	0.460
Age	0.011	<0.0001	-.0567	<0.0001	-0.005	<0.0001
sex	-0.001	0.943	4.078	<0.0001	0.013	0.788
Race	-0.231	0.413	-1.881	0.021	-0.050	<0.0001
CD4 Nadir	-0.001	0.228	0.001	0.606	-0.001	0.001
ARV duration	-0.001	<0.0001	-0.008	0.065	-0.001	0.304
statin	0.403	<0.0001	0.527	0.269	0.038	0.444

CONCLUSIONS

- At baseline, in this HIV+ subjects on ART, self reported physical activity was independently associated with insulin resistance and with several markers of markers of cardiovascular disease
- In addition, over the 96 week study period, exercise was associated with multiple measures of subclinical vascular disease, suggesting that exercise in HIV-infected patients may improve vascular structure as well as function
- This association was evident, even when accounting for statin use
- At baseline, exercise was associated with several markers of inflammation, however these relationships were not evident during the study period
- Prospective studies assessing the effect of exercise on inflammation markers and cardiovascular health are needed in HIV

LIMITATIONS

- Secondary analysis using a self-report recall measure to assess physical activity; data were negatively skewed owing to many subjects reporting no physical activity
- Further analyses are planned to better explore the effect of changes in physical activity on changes in inflammation and cardiometabolic outcome