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Exercise is associated with increased small HDL particle concentration and decreased vascular stiffness in rheumatoid arthritis

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Abstract

OBJECTIVE—Patients with rheumatoid arthritis (RA) have increased cardiovascular (CV) risk. In the general population, exercise improves several CV risk factors. In a cross-sectional study, we examined the hypothesis that more exercise is associated with protective traditional and non-traditional CV risk factor profile in patients with RA.

METHODS—Patient-reported exercise outside of daily activities was quantified by time and metabolic equivalents per week (METmin/week) and CV risk factors including blood pressure, standard lipid profiles, lipoprotein particle concentrations (NMR spectroscopy), and vascular indices were measured in 165 patients with RA. The relationship between exercise and CV risk factors was assessed according to whether patients exercised or not, and after adjustment for age, race and sex.

RESULTS—Over half (54%) of RA patients did not exercise. Among those who did exercise, median value for exercise duration was 113 minute/week [IQR: 60, 210], and exercise metabolic equivalent expenditure was 484 METmin/week [IQR: 258, 990]. Disease activity (measured by DAS28 score), C-reactive protein, waist-hip ratio, and prevalence of hypertension were lower in patients who exercised compared to those who did not (all P-values<0.05) but standard lipid profile and body mass index were not significantly different. Patients who exercised had significantly higher concentrations of HDL particles (P=0.004) and lower vascular stiffness as measured by pulse wave velocity (P=0.005).

CONCLUSIONS—More self-reported exercise in patients with RA was associated with a protective CV risk factor profile including lower waist-hip ratio, higher HDL particle concentration, lower vascular stiffness, and a lower prevalence of hypertension.

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Keywords

rheumatoid arthritis; HDL; cholesterol; exercise; cardiovascular diseases

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis disease associated with accelerated atherosclerosis and an increased prevalence of early cardiovascular (CV) events [1,2]. Studies suggest associations between RA and several CV risk factors, including sedentary lifestyle [3] and an increased prevalence of hypertension [4] and insulin resistance [5,6]. In patients with RA, standard lipid measurements are not substantially altered, but small HDL particle concentration is reduced and associated with the presence of coronary atherosclerosis [7].

In the general population, exercise is associated with improved CV health, in part through modification of several CV risk factors including systolic blood pressure, lipid levels, lipoprotein particle concentration, and HDL function [8–10]. Overall, RA patients exercise less than the general population, presumably due to physical limitations due to their disease, [3] but those patients who do exercise score higher on quality-of-life measures [11]. A growing body of literature has examined exercise's effects on CV risk factors in RA patients, but less is known about how exercise affects non-traditional CV risk factors in this population. Therefore, we examined the hypothesis that more exercise is associated with protective traditional and non-traditional CV risk factor profile in patients with RA.

METHODS

Study population

We performed a cross-sectional study including 165 patients with RA fulfilling ACR 1987 criteria [12]. Details of the recruitment procedures have been described previously [1,5,6,13]. All participants provided written informed consent prior to enrollment. The study was approved by the Vanderbilt University Institutional Review Board (IRB#000567).

Clinical variables

Patient assessment included clinical interview and physical examination as well as questions about the type, duration, frequency, and intensity of exercise performed. Exercise was defined as patient-reported dedicated exercise outside of activities of daily living. The 2011 Compendium of Physical Activities was used to convert patient responses into metabolic equivalents in minutes per week (METmin/week) [14].

The presence of hypertension was defined as the use of antihypertensive agents, or a systolic blood pressure of greater than or equal to 140 mmHg, or a diastolic pressure of greater than or equal to 90 mmHg [15]. Height, weight, and waist circumference measurements were obtained. Body mass index (BMI) was calculated as weight [kg]/height × height [m²]. RA disease activity was assessed by using the Disease Activity Score based on evaluation of 28 counted joints and erythrocyte sedimentation rate (DAS28) [16].

A fasting lipid profile, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides, as well as fasting

glucose concentrations, high sensitivity C-reactive protein (CRP) and erythrocyte sedimentation rate were measured by the Vanderbilt University Medical Center Clinical Laboratory. Plasma HDL particle concentration (HDL-P) and LDL particle concentration (LDL-P) were measured by nuclear magnetic resonance (Liposcience, Inc, Raleigh, NC) as previously reported [7].

Fasting plasma insulin concentrations were measured at the Vanderbilt Hormone Assay Core Laboratory by radioimmunoassay. Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) index and calculated as $[\text{serum insulin } (\mu\text{U/ml}) \times \text{glucose (mmol/l)}] / 22.5$ [17].

Net cholesterol efflux capacity was measured using an in vitro assay as previously reported [18], and was defined as the percent change in total cellular cholesterol content of cholesterol loaded macrophages exposed to medium only and to medium plus apolipoprotein B-depleted serum.

Augmentation index (AIx) is an indirect measure of arterial stiffness and is comprised of the ratio between the augmentation pressure and the pulse pressure, measured by radial artery tonometry. Increased AIx has been associated with adverse CV events as well as end organ damage [19]. Pulse wave velocity (PWV) is a direct measure of vascular stiffness, and measures the velocity of pulse wave reflection from one site to a more distal anatomical site. Carotid-femoral PWV was used as a measure of arterial stiffness. Carotid-femoral PWV and AIx normalized to a heart rate of 75 beats per minute were measured as described in detail previously [20]. Coronary calcium was measured by electron beam computed tomography and quantified by Agatston score as previously reported [1,21].

Statistical analysis

For continuous variables, data are presented as median with interquartile range [IQR]. Cardiovascular risk factors of interest were compared between patients who exercised and those who did not by Mann-Whitney U tests for continuous variables and chi-squared tests for categorical variables. We used linear, logistic, and proportional odds logistic regression models to determine the association between exercise status and CV risk factors with adjustment for age, race, sex and separately with adjustment for CRP and Framingham risk score. P values adjusted for age, race and sex are presented in the text for simplicity. Exploratory analyses were performed to examine the relationships with cardiovascular risk factors which were altered in exercisers versus non-exercisers and duration and intensity of exercise, adjusting for age, race, sex, and DAS28.

RESULTS

Baseline Characteristics Summary

A total of 165 patients with RA (88% Caucasian; 69% female) were studied. Their median age was 54 years, disease duration 3 years, and DAS28 3.90 units. Prevalent CV risk factors included current smoking (25%), diabetes mellitus type II (12%), and hypertension (52%). The median systolic and diastolic blood pressure was 135 mmHg and 75 mmHg, respectively. More than half of the patients (54%) reported no exercise outside of activities

of daily living. Among those who exercised, the median duration of exercise outside activities of daily living was 113 minutes/week [IQR: 60, 210 METmin/week], and metabolic equivalent expenditure was 484 METmin/week [IQR: 258, 990 METmin/week].

Relationship between patient-reported exercise and demographics and disease factors

Age, race, sex, and disease duration were not significantly different among patients who exercised and those who did not (all $p > 0.05$) (Table 1). Disease activity (DAS28 3.6 units [2.4, 4.4 units] vs 4.0 units [2.8, 5.2 units], $p = 0.01$) and CRP concentration (2.5 mg/dl [1.0, 9.0 mg/dl] vs. (5.0 mg/dl [2.0, 13.3 mg/dl], $p = 0.03$, Table 1) were lower in those who exercised compared to those who did not.

Traditional CV risk factors

The prevalence of hypertension was lower among patients who exercised (41%) compared to those who did not (60%, $p = 0.01$, Table 1). Systolic and diastolic blood pressure, prevalence of tobacco use and diabetes mellitus, and traditional lipid profiles were not significantly different among exercisers and non-exercisers (all $p > 0.05$, Table 1). Heart rate was lower in exercisers (68 beats per minute (bpm) [61, 75 bpm]) compared to non-exercisers (73 bpm [65, 80 bpm], $p = 0.05$).

Nontraditional CV risk factors

The following risk factors were lower in exercisers compared to non-exercisers: waist-hip ratio (0.85 [0.79, 0.93] vs 0.89 [0.82, 0.97], $p = 0.008$), and insulin resistance measured by HOMA (1.57 units [0.87, 3.02 units] vs. 2.47 units [1.27, 5.26 units], $p = 0.05$). The following protective factors were significantly different among exercisers: total HDL particle concentration (28.8 $\mu\text{mol/L}$ [26.4, 33.3 $\mu\text{mol/L}$] vs. 27.6 $\mu\text{mol/L}$ [24.9, 31.1 $\mu\text{mol/L}$], $p = 0.004$), and small HDL particle concentration (21.7 $\mu\text{mol/L}$ [18.5, 23.6 $\mu\text{mol/L}$] vs 20.0 $\mu\text{mol/L}$ [17.8, 22.0 $\mu\text{mol/L}$], $p = 0.003$, Table 2). There was no significant difference in net cholesterol efflux capacity of HDL enriched serum among exercisers compared to non-exercisers (36.1% [27.2, 43.4%] vs. 33.9% [28.2, 38.9%], $p = 0.57$). LDL particle concentrations were not significantly different between those who exercise and those who do not (Table 2).

Arterial PWV was significantly lower in exercisers compared to non-exercisers (8.48 m/s [7.15, 9.70 m/s] vs. 9.07 m/s [8.15, 10.03 m/s], $p = 0.005$, Table 2) and there was a non-significant decrease in AIx (28% [21, 35%], vs. 32% [25, 37%], $p = 0.10$) and median coronary artery calcium score (0 unit [0, 119] vs 3.3 [0, 240], $p = 0.06$) (Table 2).

These relationships persist in analyses with adjustment for CRP and Framingham risk score (Table 2).

Relationship between duration and intensity of exercise and CV risk factors

In exploratory analyses, we evaluated the relationship between duration and intensity of reported exercise and select CV risk factors among RA patients who exercised. Every 30 minutes of additional exercise were associated with 0.51 $\mu\text{mol/L}$ (95% confidence interval (CI), 0.09, 0.93 $\mu\text{mol/L}$) increase in total HDL particle concentration ($p = 0.02$, adjusted for

age, race, sex, and disease activity) and 0.55 $\mu\text{mol/L}$ (0.18, 0.92 $\mu\text{mol/L}$) increase in small HDL particle concentration ($p=0.006$, adjusted). However, there was no significant change in total or small HDL particle concentration with increase in METmin/week (all $p>0.05$). Waist-hip ratio and arterial pulse wave velocity did not vary significantly with increases in 30-minute increments of exercise or METmin/week (all $p>0.05$) (Table 3).

DISCUSSION

The study had three main findings. First, a large proportion of patients with RA report no exercise. Second, any amount of patient-reported exercise was associated with lower disease activity, lower inflammation, and some beneficial cardiovascular risk factors, specifically lower prevalence of hypertension, insulin resistance, waist-hip ratio, and vascular stiffness as measured by PWV. Third, we identified a direct relationship between exercise and plasma concentrations of total and small HDL particles.

Other studies have reported that patients with RA exercise less frequently and with lower intensity than control subjects. A large, cross-sectional study that included 5,235 patients with RA in 21 countries showed that >70% patients reported not engaging in regular physical activity (defined as questionnaire-reported moderate physical exercise 30 minutes with at least some shortness of breath and sweating) [3]. More recently, a cross-sectional study of 98 patients with RA that used accelerometry to obtain information about physical activity found that most patients are sedentary [22]. Our findings support these conclusions, as more than half of patients with RA reported no exercise.

We found that disease activity was lower in patients who exercised compared to those who did not. One explanation is that patients with more active RA are less likely to exercise because of the functional limitation resulting from active disease. Another possibility is that exercise improves disease activity in RA. There is evidence to support both interpretations of the finding. A recent, questionnaire-based longitudinal study evaluating the physical activity patterns of 573 patients with RA showed that disease activity was inversely associated with physical activity over a three year period [23]. On the other hand, a randomized, controlled trial found that an exercise intervention improved RA disease activity, particularly functional ability [24].

Our finding that some CV risk factors were more protective in RA patients who exercised strengthens the claim that dedicated exercise in patients with RA may positively impact their cardiovascular health. The inverse correlations between exercise and adverse cardiovascular risk factors such as hypertension, insulin resistance and waist-to-hip ratio all suggest that exercise may contribute positively to CV health in RA.

Studies thus far have generally focused on how lack of exercise negatively impacts CV health in RA patients [25]. A questionnaire-based study studying 65 patients with RA showed that physical inactivity is associated with higher blood pressure, higher LDL-cholesterol concentration, and higher total cholesterol concentrations [26]. Moreover, poor fitness defined by gold standard testing of maximal oxygen uptake during treadmill exercise ($\text{VO}_2 \text{ max}$) in a cross-sectional cohort of patients with RA was associated with worse CV

risk factors, including systolic blood pressure, HDL-cholesterol concentration, insulin resistance, BMI, and fat mass [27]. Light physical activity in patients with RA has been associated with improved CV risk factors, including lower BMI and blood pressure, higher HDL-cholesterol concentration, and better insulin sensitivity [22].

We found that exercise was associated with higher total HDL particle and small HDL particle concentrations while not affecting the standard measure of HDL cholesterol concentration. A recent study found similar results in a smaller group of 50 patients with RA. In that study, small HDL particle concentration increased significantly with increased exercise (measured by seven-day accelerometry) [28]. HDL particles have antiatherogenic functions mediated by antioxidant and anti-inflammatory properties and by their ability to drive reverse cholesterol transport [29–32,18]. Some of these functions may be altered in RA [10]. We found no significant difference in cholesterol efflux capacity, the first step of reverse cholesterol transport, comparing exercisers and non-exercisers, but other HDL functional assays could also prove useful in characterizing this relationship. While the clinical significance of HDL subfractions is mixed, it is accepted that small HDL particles demonstrate the most potent antioxidant function [33]. Moreover, in patients with RA, we previously found that lower concentrations of small HDL particles are associated with increased prevalence of coronary atherosclerosis [7]. Thus, increased small HDL particle concentration might be a possible mechanism by which exercise benefits patients with RA with respect to their CV risk. Replication studies and interventional trials should be performed to help further elucidate the relationship between exercise and HDL particle concentrations in patients with RA.

The study has several limitations. The cross sectional nature of the study does not allow us to draw conclusions about causality. Also, given the questionnaire-based approach to determining the amount and intensity of exercise, recall bias, and even social desirability bias, might cause overestimation of exercise. Nevertheless, the replication of a well-known physiological observation - lower heart rate in patients who exercise compared to those who did not - suggest that the patient-reported exercise measurement was credible.

CONCLUSION

In summary, in patients with RA more self-reported exercise was associated with a more beneficial cardiovascular risk profile including a lower prevalence of hypertension and insulin resistance, a lower waist-hip ratio, and higher HDL particle concentrations.

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Table 1

Relationship between patient characteristics and cardiovascular risk factors by exercise status.

	RA Exercisers (N = 63)	RA Non-exercisers (N= 102)	P	P Adjusted*
Patient Demographics				
Age, years	54 [44.0, 66.0]	54 [46, 61]	0.76	--
Sex, # (%) female	43 (68)	70 (69)	0.96	--
Race, # (%) Caucasian	57 (90)	88 (86)	0.37	--
DAS28, units	3.6 [2.4, 4.4]	4.0 [2.8, 5.2]	0.02	0.01
CRP, mg/dl	2.5 [1.0, 9.0]	5.0 [2.0, 13.3]	0.009	0.03
Disease duration, years	3.0 [2.0, 18.0]	4.25 [2.0, 19.0]	0.32	0.45
Cardiovascular Risk Factors				
Current smoker, # (%)	15 (24)	25 (25)	0.92	0.97
Diabetes Mellitus, # (%)	4 (6)	15 (15)	0.10	0.37
Hypertension, # (%)	26 (41)	59 (60)	0.03	0.01
Systolic BP, mm Hg	124 [115, 146]	136 [12, 147]	0.13	0.08
Diastolic BP, mm Hg	75 [67, 82]	74 [67, 83]	0.68	0.62
Heart rate, bpm	68 [61, 75]	73 [65, 80]	0.07	0.05
Total Cholesterol, mg/dl	184 [158, 210]	184 [154, 212]	0.86	0.60
LDL cholesterol, mg/dl	108 [90, 136]	114 [85, 135]	0.95	0.85
HDL cholesterol, mg/dl	43 [36, 55]	44 [38, 54]	0.63	0.75
Triglycerides, mg/dl	110 [79, 147]	110 [77, 173]	0.73	0.67
BMI, kg/m ²	27.9 [23.1, 31.3]	28.4 [24.2, 33.8]	0.12	0.11
Waist-hip ratio, units	0.85 [0.79, 0.93]	0.89 [0.82, 0.97]	0.03	0.008
HOMA, units	1.57 [0.87, 3.02]	2.47 [1.27, 5.26]	0.03	0.05

* P-value adjusted for age, race, and sex.

DAS28= disease activity based on 28 joint count and erythrocyte sedimentation rate, CRP= high sensitive C-reactive protein, BP= blood pressure, BPM, beats per minute, LDL= low density lipoprotein, HDL= high density lipoprotein, BMI= body mass index.

Table 2

Relationship between exercise status and lipoprotein particle concentration and function, and vascular studies.

	RA Exercisers (N = 63)	RA Non-exercisers (N= 102)	P-value with and without covariate adjustment			
			Unadjusted	Age, race, sex	Age, race sex, CRP	FRS, CRP
Lipoprotein Measures						
HDL particle, umol/L	28.9 [26.4, 33.3]	27.6 [24.9, 31.1]	0.04	0.004	0.02	0.01
HDL small particle, umol/L	21.7 [18.5, 23.6]	20.0 [17.8, 22.0]	0.005	0.003	0.01	0.003
HDL large particle, umol/L	6.1 [3.9, 8.2]	5.4 [3.4, 7.6]	0.29	0.38	0.45	0.30
LDL particle, umol/L	1154.1 [913.3, 1383.9]	1190.5 [983.3, 1397.9]	0.88	0.73	0.54	0.20
LDL small particle, umol/L	752.8 [571.9, 1015.4]	784.9 [551.4, 967.3]	0.30	0.29	0.21	0.11
LDL large particle, umol/L	308.1 [231.4, 427.7]	348.5 [197.6, 472.9]	0.18	0.18	0.20	0.39
Cholesterol efflux capacity, %	36.1 [27.2, 43.4]	33.9 [28.1, 38.9]	0.45	0.57	0.45	0.59
Vascular Indices						
Augmentation Index, %	28 [21,35]	32 [25, 37]	0.05	0.10	0.12	0.28
Pulse Wave Velocity, m/s	8.48 [7.15, 9.70]	9.07 [8.15, 10.03]	0.008	0.005	0.02	0.04
Agatston Score, units	0 [0, 119.2]	3.3 [0, 239.6]	0.40	0.06	0.12	0.62

CRP= high sensitivity C-reactive protein. FRS= Framingham Risk Score

Table 3
Relationship between intensity and duration of reported exercise and select CV risk factors among RA exercisers

N=63	Beta/OR [95% CI]	P-value*	P-value**
Intensity (per 100 METmin/week)			
log_ Waist-hip ratio	-1.218E-05 [-1.020E-03, 9.960E-04]	0.981	0.937
HDL particle, concentration, umol/L	0.063 [-0.086, 0.213]	0.398	0.422
HDL small particle, concentration, umol/L	0.120 [-0.009, 0.248]	0.068	0.077
Pulse wave velocity, m/s	0.013 [-0.025, 0.050]	0.506	0.566
Duration (30 minute increases in exercise)			
log_ Waist-hip ratio	-0.001 [-0.004, 0.002]	0.691	0.614
HDL particle, concentration, umol/L	0.509 [0.088, 0.930]	0.019	0.024
HDL small particle, concentration, umol/L	0.550 [0.183, 0.918]	0.004	0.006
Pulse wave velocity, m/s	0.020 [-0.092, 0.132]	0.719	0.890

* Adjusted for age, race, and sex.

** Adjusted for age, race, sex, DAS28.

HDL= high density lipoprotein. DAS28= disease activity based on 28 joint count and erythrocyte sedimentation rate.