Relationships between metabolic and lipoprotein measures with cardiometabolic risk factors and clinical outcomes in rheumatoid arthritis

Grace Kim, Leanna M. Ross, Alyssa M. Sudnick, Johanna L. Johnson, Margery A. Connelly, William E. Kraus, Brian J. Andonian, and Kim M. Huffman

This project was funded by the Lisa S. Krivickas Clinician/Scholar Award from the American College of Sports Medicine and the Third Year Dean's Award from the Duke University School of Medicine.

Background. Persons with rheumatoid arthritis (RA) have increased risk of cardiometabolic disease. The Supervised Weight loss and Exercise Training for Rheumatoid Arthritis (SWET-RA) trial demonstrated improved RA cardiometabolic risk with a weight loss and exercise intervention. This study aims to understand underlying effects of the intervention on RA cardiometabolic risk and clinical outcomes using mass spectroscopy (MS) and nuclear magnetic resonance (NMR) metabolites and lipoproteins.

Methods. Older adults with RA and overweight/obesity (n=20) underwent 16 weeks of SWET (hypocaloric diet and aerobic and resistance training) or lifestyle counseling. Baseline MS and NMR measures were logarithmically transformed. "Change" scores were calculated. Principal components analysis (PCA) reduced MS baseline measures and change scores into respective factors (**Table 1**). Spearman's rank correlations assessed baseline and change associations with cardiometabolic risk and RA clinical outcomes. T-tests and linear regression models compared group differences for MS change factors and NMR change scores, respectively.

Results. Greater PCA Baseline Factor 2 (large neutral amino acids) associated with greater peak and average knee extension torque, grip strength, and fasting insulin (ρ=0.57, p=0.01; ρ=0.50, p=0.04; ρ=0.52, p=0.03; ρ=0.56, p=0.02; ρ=0.53, p=0.02) (**Table 2**). Increases in PCA Change Factor 1 (short- and medium-chain acylcarnitines) associated with triglyceride (TG) and fatigue improvements (ρ=-0.50, p=0.03; ρ=-0.69, p<0.001) (**Table 3**). Increases in ketone bodies associated with metabolic syndrome score improvements (ρ=-0.45, p=0.049) (**Table 4**). Reductions in total high-density lipoprotein (HDL) particle and apolipoprotein A1 associated with fat mass reductions (ρ=-0.52, p=0.02; ρ=-0.47, p=0.04) (**Table 4**).

Conclusions. Exercise may help mitigate fatigue through enhanced whole-body metabolism and β-oxidation. Caloric restriction induces ketone body production, which may improve lipid handling. Decreased HDL may be a favorable outcome affected by dietary composition. Lifestyle interventions may have the potential to target specific metabolic pathways and improve RA health.

Table 1. MS Metabolite Factors

Baseline Factors	
Factor 1	Medium-chain acylcarnitines (ACs), C4OH
Factor 2	Large neutral amino acids
Factor 3	Non-esterified fatty acids, long-chain ACs, C2
Factor 4	Amino acids
Change Factors	
Factor 1	Short and medium-chain ACs
Factor 2	Branched-chain amino acids (BCAA), long-chain ACs
Factor 3	Medium-chain ACs
Factor 4	Amino acids

Table 2. MS Metabolite Baseline Correlations

Variable	Fasting insulin (pg/mL)	Peak knee extension torque (Nm)	Average knee extension torque (Nm)	Right grip strength (kg)
Factor 1	-0.04	0.13	0.19	0.11
Factor 2	0.53*	0.57*	0.50*	0.52**
Factor 3	0.55*	-0.22	-0.21	0.18
Factor 4	0.20	-0.03	-0.08	0.30

Table 3. MS Metabolite Change Correlations

Variable	TGs (mg/dl)	Fasting insulin (pg/mL)	Patient-reported cognitive function	Patient-reported fatigue
Factor 1	-0.69***	0.01	0.21	-0.50*
Factor 2	-0.12	0.49*	-0.48*	-0.07
Factor 3	-0.23	-0.43	0.34	0.08
Factor 4	-0.24	0.22	0.02	0.13

Table 4. NMR Lipoprotein and Metabolite Change Correlations

Variable	MSSc	Fat mass (kg)	aVO2 peak (mL/min)	Patient-reported physical health	Patient-reported fatigue
Total HDL particles (µmol/L)	0.21	0.49*	0.04	-0.36	0.31
Very small TG-rich lipoproteins (nmol/L)	-0.21	-0.02	-0.50*	-0.30	-0.30
Apo A-I (mg/dL)	0.18	0.53*	0.08	-0.47*	0.33
Ketone bodies (µmol/L)	-0.45*	-0.23	0.11	-0.03	-0.31
Total BCAAs (µM)	-0.31	-0.20	0.27	0.06	-0.46*

For Tables 2-4, values are Spearman's rank correlation coefficients. *, **, and *** indicate P<0.05, P<0.01, and P<0.001, respectively, and are all bolded.