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Adipose Depots, not Disease Related Factors, Account for Skeletal Muscle Insulin Sensitivity in Established and Treated Rheumatoid Arthritis

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Abstract

Objectives—In prior reports, individuals with rheumatoid arthritis (RA) exhibited increased insulin resistance. However, these studies were limited by either suboptimal assessment methods for insulin sensitivity or a failure to account for important determinants, adiposity and physical activity. Our objectives were to carefully assess, compare and determine predictors of skeletal muscle insulin sensitivity (S_I) in RA, accounting for adiposity and physical activity.

Methods—Thirty-nine individuals with established (seropositive or erosions) and treated RA and 39 age, gender, race, BMI, and physical activity-matched controls underwent a frequently-sampled intravenous glucose tolerance test to determine S_I. Inflammation, body composition, and physical activity were assessed with systemic cytokine measurements, CT scans, and accelerometry, respectively. Exclusions were diabetes, cardiovascular disease, medication changes within three months, and prednisone use over 5 mg/d. This investigation was powered to detect a clinically significant, moderate effect size for S_I difference.

Results—Despite elevated systemic inflammation (interleukin (IL)-6, IL-18, tumor necrosis factor-alpha; $P<0.05$ for all), persons with RA were not less insulin sensitive (S_I geometric mean

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(SD): RA 4.0 (2.4) versus Control 4.9 (2.1)*10^{-5} min^{-1}/[pmol/l]; P=0.39). Except for visceral adiposity being slightly greater in controls (P=0.03), there were no differences in body composition or physical activity. Lower S_I was independently associated with increased abdominal and thigh adiposity, but not with cytokines, disease activity, duration, disability, or disease modifying medication use.

Conclusions—In established and treated RA, traditional risk factors, specifically excess adiposity, play more of a role in predicting skeletal muscle insulin sensitivity than systemic inflammation or other disease-related factors.

Keywords

Skeletal muscle; insulin resistance; physical activity; body composition

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In persons with rheumatoid arthritis (RA), two-fold increased rates of cardiovascular disease have been attributed, in part, to insulin resistance. (1, 2) Potential explanations for insulin resistance in RA have included higher systemic inflammation associated with active disease, use of glucocorticoids, and increased traditional risks such as abdominal obesity and inactivity. (2, 3)

Most prior investigations of insulin resistance in RA have relied largely on fasting measures which better reflect hepatic rather than skeletal muscle insulin sensitivity. Assessing skeletal muscle insulin sensitivity is critical, since this organ is responsible for as much as 90% of glucose uptake after a meal. Further, skeletal muscle insulin resistance initiates and perpetuates the development of type two diabetes and serves as the central feature of the metabolic syndrome.(4, 5) Of the few investigations in persons with RA that have used glucose challenge-based measures of insulin sensitivity, none has accounted for potential differences in adiposity and physical activity. (6-10) To improve understanding of how insulin resistance might contribute to increased cardiovascular risk in persons with RA, our objectives were to determine 1) if persons with RA, as compared to age, gender, race, body mass index (BMI), and physical activity-matched controls, exhibit more skeletal muscle insulin resistance assessed by intravenous glucose tolerance tests (IVGTT), and 2) in persons with RA, if disease-specific and/or traditional predictors are related to skeletal muscle insulin resistance.

Methods

Patient Population

In this cross-sectional investigation, persons were included if they had 1) RA which met American College of Rheumatology 1987 criteria,(11) 2) seropositive disease (positive rheumatoid factor or anti-cyclic citrullinated peptide) or evidence of erosions, and 3) no medication changes within the three months prior to study enrollment. Persons using prednisone 5 mg or less daily were included. Any prednisone taper must have been completed at least 3 weeks prior to enrollment. Healthy individuals without a diagnosis of rheumatoid arthritis or joint pain or swelling lasting more than a week were matched to an RA participant by gender, race, age (within 3 years) and BMI (within 3 kg/m^2). For one African American participant where a race match was not identified, a White/Caucasian that

was otherwise well-matched was included. Exclusion criteria included a history of diabetes or cardiovascular disease, current pregnancy, and use of medications known to affect carbohydrate or lipid metabolism (including insulin, oral anti-diabetic agents, statins, fibrates, nicotinic acid, ACE inhibitors, angiotensin receptor blockers, or beta blockers). Participants with RA were recruited from Duke University and Durham Veterans Affairs Medical Center Rheumatology Clinics and from the local community with newspaper and web-site advertisements. Controls were recruited from the local community with newspaper and web-site advertisements. This study was in compliance with the Helsinki Declaration and was approved by the Duke University Institutional Review Board. All participants underwent written informed consent.

Questionnaires and Physical Exam

Participants completed questionnaires for medications, disability (Health Assessment Questionnaire Disability Index [HAQ-DI]),(12) comorbidities,(13) a visual analog scale for health rating, and the Stanford Brief Activity Survey (SBAS) for physical activity.(14) Each completed a visual analog scale (VAS) for health, and underwent anthropometric measures, a 28- joint exam and fasting blood collection for glucose, insulin, and sedimentation rate (ESR). The VAS, exam, and ESR were used to compute a disease activity score (DAS-28).(15)

Accelerometry

Participants wore an RT3 tri-axial accelerometer (Stayhealthy, Inc., Monrovia, CA) for seven days. Data were obtained from accelerometers as activity calories per minute (Stayhealthy RT3 Assist Version 1.0.6, Monrovia, CA). Ninety consecutive minutes of no measured activity was used to indicate and eliminate periods of time when individuals were not wearing the device. Also, if there were less than 10 hours of measured activity in a single day, all data from that day were excluded from analysis. Similarly, we excluded data from participants (n=7) who had less than four days of valid data (each of 10 hours or more of wear time). Two participants did not return the device.

Systemic Inflammatory Measures

A panel of pro-inflammatory cytokines including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α were measured in plasma samples using a multi-array quantitative immunoassay (MSD, Gaithersburg, MD). IL-18 and high sensitivity C reactive protein (hsCRP) were measured using sandwich ELISAs (R&D, Minneapolis, MN and MP Biomedicals, Solon, OH, respectively). Mean intra-assay (within plate) coefficients of variation (CV) were as follows: IL-1β 9.3%, IL-6 3.4%, IL-8 3.9%, TNF-α 2.9%, IL-18 2.4%, and hsCRP 3.5%. A human plasma control was run on each plate, and mean inter-assay (between plates) CV were as follows: IL-1β 5.5%, IL-6 3.0%, IL-8 7.8%, TNF-α 7.7%, IL-18 6.0%, and hsCRP 3.9%.

Insulin Sensitivity and Fatty Acids

Insulin sensitivity was determined using a frequently sampled IVGTT. Glucose (50%) was injected through a catheter at 0.3 g/kg body mass. Insulin was injected at minute 20 at 0.025

units/kg body mass. Twenty-nine blood samples were obtained over three hours, centrifuged, and stored at −80°C. Glucose was measured on a Beckman-CoulterDxC600 analyzer and insulin by electrochemilumescent assay from Meso Scale Discovery (Gaithersburg, MD). Insulin Sensitivity index (S_I) was calculated using Bergman's minimal model.(16) Nonesterified free fatty acids (NEFA) were measured by colorimetric enzymatic assay using a Beckman-Coulter DxC600 analyzer, with reagents from Wako (Richmond, VA).

Abdomen and Thigh Computerized Tomography (CT) scans

Single 10-mm-thick axial sections at the liver and mid-thigh were performed using a General Electric CT/I scanner (GE Medical Systems, Milwaukee, WI). Cross-sectional areas for adipose tissue depots and liver and muscle density were measured using OsiriX (Pixmeo, Geneva, Switzerland). CT scan determinations of adipose tissue depots are very accurate, precise, and reliable.(17, 18)

Statistical Analyses

Cytokines, NEFAs, and S_I were logarithmically transformed prior to group comparisons. Comparisons between persons with RA and controls were performed with mixed models, which accounted for the repeated measure of matched participants. Bivariate associations were assessed with Spearman correlations. Multivariable modeling for S_I (log) was performed using linear models with backward stepwise variable selection. Initial variable inclusion was based on conceptual hypotheses regarding traditional risk factors and disease-associated factors impacting S_I and included age, gender, waist circumference, physical activity, disease activity (DAS-28), disease modifying agent use, biologic agent use, and prednisone use. Waist circumference was selected rather than BMI based on the high levels of correlation between the two (r=0.87) and that waist circumference was more strongly correlated with S_I. For the laboratory model, based on results from bivariate analyses, visceral adiposity and thigh inter-muscular adiposity were included rather than waist circumference, and IL-6 was included rather than disease activity; all other variables from the clinical model were included.

Statistical power

This investigation was designed to detect a difference in insulin sensitivity which corresponded to a moderate effect size (0.4-0.5) (19). Based on 39 matched pairs and an alpha of 0.05, we had 80% power to detect a standardized difference in S_I of 0.46.

Results

As shown in Table 1, persons with RA were well-matched to controls in age, gender, and BMI. While persons with RA had slightly less abdominal visceral adiposity (P=0.03), otherwise there were similar amounts of fasting NEFAs, abdominal and thigh adipose tissue depots, and thigh muscle area and density (P>0.05 for all). There were no differences in physical activity, measured as total energy expended (P>0.05). In the context of a wide range of disease activity (DAS-28 0.78-6.4) and duration (5-506 months), individuals with RA exhibited a pro-inflammatory profile, as demonstrated by elevated TNF-α, IL-6, and

IL-18 (P<0.05 for all). Despite elevated systemic inflammation, persons with RA were not significantly less insulin sensitive than controls (S_I geometric mean (SD) = 4.0 (2.4) versus 4.9 (2.0)*10^{-5} min^{-1} /[pmol/l]; mean standardized difference for log S_I=0.23; P=0.39).

Table 2 shows correlations of key traditional and disease-specific risks with insulin sensitivity. In persons with RA, lower S_I was associated with a larger body mass index (r=-0.45, P<0.002), a greater waist circumference (r=-0.47, P<0.001), and increased amounts of total abdominal adipose tissue, visceral adiposity, total thigh area, thigh inter-muscular adiposity, and thigh muscle area (r=-0.3-0.5, P<0.05 for all).

Multivariable modeling was performed using variables available in a clinic setting: age, gender, waist circumference, physical activity, disease activity, biologic use, DMARD use, and prednisone use. After backwards variable selection, the model retained only waist circumference and accounted for 26% of the variance in S_I (Table 3, P<0.0005). To better understand the contribution of inflammation and adiposity, a “laboratory” model was constructed. For this model, initial variables included visceral adiposity and thigh inter-muscular adiposity rather than waist circumference, IL-6 rather than disease activity, and all of the other variables in the initial clinical model. In the laboratory model, visceral adiposity, thigh inter-muscular adiposity, and IL-6 and accounted for 46% of the variance in S_I (Table 3, P<0.0005). Visceral adiposity (P<0.005) and thigh inter-muscular adiposity (P<0.02) were each independently related to S_I.

Discussion

In 39 persons with established RA, well-controlled and reflective of many clinic cohorts, skeletal muscle insulin sensitivity, as measured with an intravenous glucose tolerance test, was not significantly lower than matched controls. Also, for persons with RA, insulin sensitivity was related to traditional risk factors of large adipose tissue depots. Other than concentrations of IL-6, disease-specific factors, including disease activity, biologic agent use, and disease modifying agent use had little apparent influence on this outcome.

To our knowledge, this is the first well-controlled comparison of skeletal muscle insulin sensitivity for persons with established and treated RA. Previously, most studies addressing insulin sensitivity in RA used fasting glucose- and insulin-derived indices such as homeostasis model assessment or HOMA and the quantitative insulin sensitivity check index, QUICKI(2); however, these fasting-derived indices reflect insulin sensitivity mainly in the liver. In contrast, glucose tolerance tests better reflect insulin sensitivity in skeletal muscle. Since skeletal muscle is responsible for the majority (up to 90%) of systemic glucose uptake after a glucose load such as during a meal, assessing skeletal muscle insulin sensitivity with glucose challenge tests is critical for understanding insulin action.

Despite the importance outlined above, glucose challenge tests, including oral and IV glucose loads as well as euglycemic clamps, have been used to compare insulin sensitivity between RA and controls in a relatively small number of investigations.(6-10, 20) Findings from these have been conflicting, likely because of a failure to adequately assess and account for the significant contributors to insulin resistance, adiposity and physical

inactivity. Specifically, several investigations demonstrated that persons with untreated RA had greater insulin resistance, but none included BMI-matched controls or assessed physical activity. (8, 9, 20) Also, in two investigations, persons with RA had similar insulin sensitivity to controls, but in one, the comparison was confounded by the control group having more males and higher BMIs. (6) The second investigation was limited to normal weight, premenopausal females, limiting generalizability. Our study shows definitively that despite elevated amounts of systemic inflammation when compared to controls matched for adiposity and physical inactivity, persons with RA have similar insulin sensitivity.

Thus, in typical clinical cohorts of established and well-controlled RA, the average reduction in skeletal muscle insulin sensitivity imposed by RA-associated factors appears both statistically and clinically insignificant. Statistical power for this investigation aimed to detect a difference in insulin sensitivity corresponding to a moderate effect size, and, as such the observed small difference was not statistically significant. Clearly, a larger sample might have been able to detect the small difference as statistically significant, but the critical issue is the clinical relevance of such a small difference in insulin sensitivity.

Clinical relevance for specific insulin sensitivity values is difficult to determine, but some investigations linking insulin sensitivities to outcomes can provide insight into this issue. When persons were followed longitudinally for 25 years for diabetes development, the difference was much larger than ours between those that developed type two diabetes and those who did not [3.2 ± 2.4 vs. 8.1± 6.7 10^{-5} min^{-1} / [pmol/l]] (21). Also, when comparing tertiles of insulin sensitivity, the upper tertile (≥2.39*10^{-5} min^{-1} /[pmol/l]) was associated with an incidence of progression of less than 10%.(22) This low incidence suggests that the impact of the small difference observed between persons with well-controlled RA and matched controls is clinically negligible.

As a means of confirming that risk of insulin sensitivity in well-controlled RA is similar to that of matched controls, we observed that predictors of insulin sensitivity in RA are largely traditional cardio-metabolic risk factors rather than RA-specific ones. Prior predictors of RA-associated insulin resistance include both altered body composition and inflammation (2, 3, 6, 9). Covering a wide range of insulin sensitivities and disease activities, our sample provided a rich source to identify potential unique mediators of insulin resistance development in persons with RA. Nonetheless, except for IL-6 concentrations, all correlates of insulin sensitivity were to body composition. These findings imply that in persons with established and treated RA, traditional risk factors, specifically excess adiposity, play more of a role in predicting skeletal muscle insulin sensitivity than do inflammation or medication use.

A wide range of hypotheses and evidence link adipose tissue and skeletal muscle insulin resistance. Adipose tissue contributes to skeletal muscle insulin resistance by providing a source of free fatty acids, which inhibit insulin-stimulated glucose uptake in skeletal muscle both directly and indirectly (by promoting production of acyl-CoAs and reactive oxygen species) (reviewed in (23)). Additionally, adipose tissue triggers skeletal muscle insulin resistance via the production of a number of insulin resistance promoting inflammatory cytokines and adipokines (reviewed in (24))

While adipose tissue clearly contributed, skeletal muscle insulin resistance in RA appeared to have little relation to disease-specific factors. Of these, only IL-6 was related. Specifically, higher IL-6 was related to poorer insulin sensitivity with a *P* value of 0.05 in bivariate analyses and a trend towards statistical significance in a multi-variable model. In persons without systemic inflammatory disease, IL-6 has shown a complex relationship with insulin sensitivity (25). Acutely, increases in IL-6 associated with exercise have been shown to improve insulin sensitivity, but chronic elevations appear to worsen insulin sensitivity (25). Here, in persons with elevated systemic concentrations of IL-6, this cytokine was related to poorer insulin sensitivity in contrast to other disease-related variables.

We are aware that this investigation has limitations. One of the main limitations is a small sample size, in turn reducing study power and increasing the likelihood of a Type II statistical error. That, and the heterogeneity of our population, may have contributed to our lack of statistical significance in the difference in insulin sensitivity between RA and matched controls. However, we believe heterogeneity provided a valuable opportunity to determine predictors of insulin sensitivity in persons with RA. Nonetheless, we recognize that the predictive capability of the models presented is relatively modest. However, developing models as tools for predicting insulin sensitivity was not the study goal, but rather the objective was to determine the relative contribution of disease-related and traditional risk factors for insulin resistance in RA. Also, we believe this sample of persons with established and treated RA reflects what is seen in many rheumatology clinic cohorts, thus allowing generalizability of our findings regarding risks for insulin sensitivity in RA. One of the main strengths is using IVGTT to assess skeletal muscle insulin sensitivity in RA, thus emphasizing that stimulated tolerance tests allow a more complete assessment of insulin action.

Thus, in a population of persons with RA reflective of typical clinical cohorts, as compared to well-matched controls, skeletal muscle insulin sensitivity was not significantly lower in those with RA. Increased abdominal and thigh adiposity contributed to poorer insulin sensitivity but not disease activity or medication use. These findings imply that in established and treated RA, adipose depots, not disease-related factors, account for skeletal muscle insulin sensitivity.

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Table 1

Participant Characteristics*

Variable	All Participants (n=78)	Rheumatoid Arthritis (n=39)	Matched Controls (n=39)
Age (years)	55.5 (11.8)	56.1 (12.4)	54.9 (11.4)
BMI (kg/m^2)	30.2 (6.3)	30.5 (7.3)	30.0 (5.3)
Waist circumference (cm)	94.9 (15.5)	95.1 (17.7)	94.6 (13.7)
Race			
Caucasian	59 (76%)	29 (74%)	30 (76%)
African American	19 (24%)	10 (26%)	9 (24%)
Gender			
Female	54 (69%)	27 (69%)	27 (69%)
Male	24 (32%)	12 (31%)	12(31%)
Physical activity (kCal/day)	572.8 (290.8)	546.6 (291.4)	605.1 (292.7)
Physical activity (MET hr/day)	29.5 (2.5)	29.2 (2.5)	29.9 (2.4)
Disease duration (months)	NA	159 (135)	NA
HAQ-Disability Index	0.5 (0.7)	0.7 (0.7)†	0.00 (0.00)
Comorbidity Index	1.2 (1.2)	1.5 (1.2)†	0.6 (0.9)
DAS-28 mean (SD)	NA	3.1 (1.5)	NA
Remission (DAS-28 <2.6)		16 (42%)	
Low activity (DAS-28 2.6-3.2)		6 (16%)	
Moderate activity (DAS-28 3.2-5.1)		11 (29%)	
High activity (DAS-28 >5.1)		5 (13%)	
Rheumatoid factor positive	NA	30/35 (86%)	NA
Anti-cyclic citrullinated antibody positive	NA	14/15 (93%)	NA
Erosions on radiographs present	NA	18/30 (60%)	NA
Medication Use	NA		
Etanercept		8 (21%)	NA
Infliximab		2 (5%)	NA
Adalimumab		4 (10%)	NA
Abatacept		5 (13%)	NA
Methotrexate		29 (74%)	NA
Leflunomide		1 (3%)	NA
Sulfasalazine		0	NA
Hydroxychloroquine		6 (13%)	NA
Nonsteroidal anti-inflammatory agents*		16 (41%)	1 (5.5%)
Prednisone (<0.5 mg/day)		11 (28%)	NA
Systemic inflammation			
hsCRP (mg/L)	3.14 (4.1)	4.1 (5.5)	2.4 (2.9)
IL-1beta (pg/mL)	0.22 (5.4)	0.32 (4.2)	0.15 (6.3)
IL-6 (pg/mL)	5.3 (2.8)	9.9 (2.9)†	2.9 (1.6)
IL-8 (pg/mL)	8.5 (2.1)	9.4 (1.9)	7.7 (2.4)

Variable	All Participants (n=78)	Rheumatoid Arthritis (n=39)	Matched Controls (n=39)
TNF-alpha (pg/mL)	14.1 (2.3)	21.6 (2.4)†	9.4 (1.6)
IL-18 (pg/mL)	413.0 (1.3)	446.7 (1.2)†	316.2 (1.4)
Insulin Sensitivity Index 10^{-5} min^{-1} / [pmol/L]			
All	4.5 (2.2)	4.0 (2.4)	4.9 (2.1)
Women	5.0 (2.3)	4.7 (2.4)	5.2 (2.2)
Men	3.6 (2.1)	3.1 (2.3)	4.0 (1.9)
Biologic Use = Yes	NA	4.8 (2.4)	NA
Biologic Use = No	NA	3.7(2.4)	NA
DMARD Use = Yes	NA	4.0 (2.5)	NA
DMARD Use = No	NA	5.4 (1.7)	NA
Prednisone Use = No	NA	3.2 (2.1)	NA
Prednisone Use = No	NA	4.8 (2.4)	NA
Non-esterified free fatty acids (mmol/L)	0.55 (1.47)	0.57 (1.57)	0.53 (1.36)
Adiposity and Muscle Tissue			
Abdominal Total Adipose Area (cm^2)	430 (179)	407 (199)	453 (157)
Abdominal Subcutaneous Adiposity (cm^2)	306(144)	302 (149)	309 (141)
Abdominal Visceral Adiposity (cm^2)	125 (98)	105 (81)†	144 (109)
Abdominal Liver Density (Hu)	60 (10)	60 (9)	60 (10)
Thigh Total Area (cm^2)	254 (65)	253 (69)	255 (61)
Thigh Total Adipose Area (cm^2)	127 (66)	137 (61)	116 (70)
Thigh Subcutaneous Adiposity (cm^2)	121 (57)	125 (58)	117 (57)
Thigh Inter-Muscular Adiposity (cm^2)	11 (8)	12 (7)	11 (8)
Thigh Muscle Area (cm^2)	120 (36)	116 (39)	125 (33)
Thigh Muscle Density (Hu)	51 (5)	50 (6)	52 (4)

BMI= Body mass index; NA= Not applicable; HAQ= Health Assessment Questionnaire; DAS- 28 = Disease activity score with 28 joint count; hsCRP = High sensitivity C-reactive protein; IL = Interleukin.

*Data are presented as means (SD) for continuous variables and number (percentages) of participants for dichotomous variables. Data that were not normally distributed (systemic inflammatory markers, cytokines, and insulin sensitivity) are presented as geometric means (SD).

†$p \leq 0.05$ for comparison with matched controls.

Table 2

Spearman correlations for insulin sensitivity (n=44)

Variable	Spearman Rho (R)	P value
Age (years)	−0.16	0.29
BMI (kg/m^2)	− **0.45**	**0.002**
Waist Circumference (cm)	− **0.47**	**0.001**
Gender (Male=0, Female=1)	0.20	0.20
Physical activity (kCal/day)	−0.08	0.66
Physical activity (MET hrs/day)	0.19	0.27
Disease duration	0.16	0.32
HAQ-Disability Index	−0.21	0.17
DAS-28	−0.12	0.44
Biologic Use (Yes=1, No=0)	0.14	0.37
DMARD Use (Yes=1, No=0)	−0.16	0.29
Prednisone Use (Yes=1, No=0)	−0.28	0.07
hsCRP (mg/L)	−0.18	0.25
IL-1beta (pg/ml)	0.04	0.82
IL-6 (pg/ml)	− **0.30**	**0.05**
IL-8 (pg/ml)	−0.09	0.56
TNF-alpha (pg/ml)	−0.08	0.62
IL-18 (pg/ml)	−0.20	0.20
NEFAs	−0.28	0.06
Abdominal Total Adipose Area (cm)	− **0.43**	**0.005**
Abdominal Subcutaneous Adiposity (cm^2)	−0.30	0.06
Abdominal Visceral Adiposity (cm)	− **0.48**	**0.002**
Abdominal Liver Density (Hu)	0.27	0.10
Thigh Total Area (cm^2)	− **0.38**	**0.01**
Thigh Total Adipose Area (cm)	−0.20	0.20
Thigh Subcutaneous Adiposity (cm)	−0.15	0.32
Thigh Inter-Muscular Adiposity (cm)	− **0.52**	**0.0004**
Thigh Muscle Area (cm^2)	− **0.36**	**0.02**
Thigh Muscle Density (Hu)	0.12	0.45

BMI= Body mass index; HAQ = Health Assessment Questionnaire;DAS-28 = Disease activity score with 28 joint count; DMARD = non-biologic Disease Modifying Anti-Rheumatic Drug; hsCRP = High sensitivity C-reactive protein, HOMA=Homeostatic Model Assessment.

Table 3

Multivariable model for insulin sensitivity index (log) in persons with rheumatoid arthritis.

	Parameter Estimate	Partial R^2	P value
Clinical Model: R^2=0.26			
Waist circumference (cm)	−0.01	0.26	0.0005
Laboratory Model: R^2=0.46			
Visceral adiposity area (cm^2)	−0.002	0.28	0.005
Thigh inter-muscular adiposity area (cm^2)	−0.02	0.12	0.02
IL-6 (log pg/ml)	−0.22	0.07	0.07

Multivariable modeling was performed using linear models with backward stepwise variable selection. For the clinical model, variable inclusion was based on conceptual hypotheses regarding traditional risk factors and disease associated factors impacting S_I and included age, gender, waist circumference, physical activity, disease activity (DAS-28), disease modifying agent use, biologic use, and prednisone use. Based on results from bivariate analyses, for the laboratory model, waist circumference was replaced with visceral adiposity and thigh inter-muscular adiposity, and disease activity was replaced with interleukin (IL)-6; all other variables from the clinical model were included.