Editorial

Is Visceral Fat the Missing Link in the Relationship Between Inflammation and Insulin Resistance in RA?

Several groups of investigators evaluating insulin resistance in rheumatoid arthritis (RA; Table 1)[1,2,3,4,5,6,7,8,9] have reported that patients with RA have more insulin resistance than non-RA control subjects, even with similar body mass index (BMI)[1,2,3,4,5]. In many RA studies, insulin resistance was associated with markers of inflammation or disease activity[5,6,7,8]. Moreover, some studies that examined insulin resistance before and after treatment of RA with anti-tumor necrosis factor-α (TNF-α) or antiinterleukin 6 (IL-6) agents found that treatment with these drugs, and presumably the consequent decrease in inflammation, resulted in a significant improvement in insulin sensitivity[10,11]. These and other studies provide support for the notion that inflammation in RA promotes insulin resistance.

The concept that there is a relationship between the inflammation in RA and insulin resistance is also supported by studies performed in animals showing that inflammation promotes insulin resistance. For example, administration of TNF-α and IL-6 caused insulin resistance in rats and mice[12,13]. This finding is not surprising because cytokines such as IL-6 and TNF-α contribute to insulin resistance through downstream repression of insulin signaling (reviewed[14]).

In this issue of *The Journal*, AbouAssi and colleagues present a meticulous and thorough evaluation of insulin sensitivity in 39 patients with RA and 39 control subjects matched for not only age and sex, but also for BMI and physical activity[15]. Insulin sensitivity was quantified by frequently sampled intravenous glucose tolerance test (FSIVGTT). Factors assessed were disease activity, levels of proinflammatory cytokines, and potential confounders including physical activity measured by accelerometry over 7 days and adiposity determined by computerized tomography of the abdomen and thigh.

Three of their findings were unexpected and therefore thought-provoking: (1) insulin resistance was not increased in RA, (2) inflammation was not independently associated with insulin resistance, and (3) visceral adiposity was not increased in RA. We discuss some interpretations of the findings below.

Potential explanations for the finding that insulin sensitivity was not significantly altered in patients with RA compared to controls (in contrast to the studies described earlier) seem most likely to be found in the patient population studied and the method for measuring insulin sensitivity.

The RA patient population studied is similar to that in several other studies with respect to age, race, sex, disease duration, and seropositivity. One difference was that patients were excluded for use of any medication known to affect carbohydrate or lipid metabolism (such as statins, angiotensin-converting enzyme inhibitors, β-blockers, and angiotensin receptor blockers). This strategy has the important benefit of reducing the confounding effect of drugs on insulin sensitivity, but it has the potential disadvantage of decreasing generalizability by excluding many patients receiving treatment for hypertension and hyperlipidemia, 2 components of the metabolic syndrome. A second difference, reflecting therapeutic advances and changes in practice, was that a larger proportion (about 50%) of patients was receiving therapy with biologic agents; some biologic agents may improve insulin sensitivity in patients with RA[10,11].

To measure insulin resistance/sensitivity, the investigators used the FSIVGTT. This contrasts with many of the previous studies, which used the simpler and less rigorous fasting homeostatic model assessment of insulin resistance (HOMA-IR) to evaluate insulin resistance in RA (Table 1). As the authors indicate, the fasting HOMA-IR reflects mostly hepatic insulin resistance and hepatic glucose production, rather than peripheral insulin sensitivity. The FSIVGTT method used by the investigators includes both hepatic and peripheral insulin sensitivity (reviewed[16]), but peripheral insulin sensitivity would likely be a much greater

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Table 1. Select publications evaluating insulin resistance in RA versus non-RA control subjects.

Reference	No. Subjects	BMI	Visceral Fat	Insulin Resistance/sensitivity	Notes
Ferraz-Amaro 2011[1]	16 RA starting anti-TNF, 34 RA control, and 70 healthy control	Non-significant trend for lower in RA	ND in controls, in RA unchanged after anti-TNF-α	Greater IR (HOMA2-IR) in RA	
Ferraz-Amaro 2013[2]	101 RA, 99 control	Similar	ND, but trend for larger waist in RA	Greater IR (HOMA-IR) and impaired insulin processing (split proinsulin levels) in RA	
Chung 2008[3]	154 RA, 85 control	Similar	ND, but larger waist in RA	Greater IR (HOMA-IR) in RA	Average BMI overweight
Rosenvinge 2007[4]	9 RA, 9 control	Similar	ND	Greater IR (hyperinsulinemic euglycemic clamp) in RA.	Average BMI overweight
Paolisso 1991[5]	8 RA (+8 with other CTD), 10 healthy control	Similar	ND	Greater IR (IVGTT and hyperinsulinemic euglycemic clamp) in the RA/CTD group	Average BMI overweight. IR did not improve after anti-TNF
Penesova 2013[6]	22 RA, 15 controls	Similar	ND	Similar IR (OGTT, HOMA-IR). AUC for insulin inverse association with IL-6	Controlled diet 2 weeks prior to study. IR correlated with inflammation
Hoes 2011[7]	140 RA, 50 controls (selected for normal glucose tolerance)	Lower in RA	ND, but lower waist circumference in RA	Decreased IS and beta cell function (FSOGTT) in RA	Premenopausal females. BMI limit 18–25 kg/m^2
Dessein 2002[8]	38 RA (+49 with other CTD), 30 control	Higher in RA/CTD	ND	Greater IR (HOMA-IR and QUICKI) in RA/CTD, but no difference after adjustment for ESR and BMI	More females in RA group. RA waist circumference associated with all measures of IS
Toussirot 2013[9]	30 RA, 51 control	Similar	Greater visceral fat in RA by DEXA	Similar IR (HOMA-IR)	

RA: rheumatoid arthritis; BMI: body mass index; DEXA: dual-energy X-ray absorptiometry; IR: insulin resistance; HOMA-IR: homeostatic model assessment of insulin resistance; ND: not done; IS: insulin sensitivity; FSOGTT: frequently sampled oral glucose tolerance test; OGTT: oral glucose tolerance test, IVGTT: intravenous glucose tolerance test; CTD: connective tissue disease; QUICKI: quantitative insulin sensitivity check index; TNF: tumor necrosis factor; AUC: area under the curve; IL: interleukin; ESR: erythrocyte sedimentation rate.

contributor. Thus, one possibility is that RA affects insulin sensitivity of the liver to a greater extent than the peripheral tissues.

The authors found that IL-6, but not C-reactive protein (CRP) or 28-joint Disease Activity Score (DAS28), was weakly associated with insulin resistance in RA. One consideration is that this unimpressive relationship between inflammation and insulin resistance may have been affected not only by the RA population studied, but also by their relatively low disease activity. The average DAS28 score of 3.1 is not unusual, but over 40% of patients were in remission, and CRP was not higher in the patients with RA (although IL-6 and TNF-α were). IL-6, one of the pro-inflammatory cytokines increased in the patients with RA, was correlated with insulin sensitivity only in univariate analysis ($\rho = -0.3$, $p = 0.05$); however, visceral adiposity was more strongly associated with insulin sensitivity, independent of IL-6 concentrations ($p = 0.005$). One can speculate that if the degree of inflammation in the subjects with RA had been higher, IL-6 might have been the stronger predictor of insulin sensitivity.

Total adiposity was found to be similar in RA and control subjects, but contrary to much of the literature[9,16,17,18] (Table 1), visceral adiposity was about 25% lower among patients with RA. Given the matching for physical activity between RA and control subjects, this observation could suggest that the previously observed increase in visceral adiposity (and decrease in muscle mass) in RA is mainly due to inactivity. A different study, however, showed that RA patients with similar levels of physical activity to control subjects had greater central obesity and higher fat mass[7]. Thus, the lower visceral adiposity observed in the RA patients in the current study may have been related to patient selection (i.e., exclusions for many antihypertensive and lipid-lowering drugs leading to a lower proportion of patients with metabolic syndrome, as discussed), but it also suggests new possibilities regarding the relationship between visceral fat, inflammation, and insulin resistance in RA.

The authors found that visceral adiposity and waist circumference, which could be considered a surrogate for visceral adiposity, were most strongly independently

associated (inversely) with insulin sensitivity in statistical models that focused on clinical variables and in models focused on laboratory variables. Although IL-6 concentrations were significantly inversely correlated with insulin sensitivity, this relationship was not independent of visceral adiposity. We wonder if the visceral adiposity is particularly important to insulin resistance in RA, and if the 2 synergistically contribute to insulin resistance in RA. Thus, the lower visceral adiposity in this group of patients may have contributed to the authors finding no significant alterations in insulin sensitivity.

Visceral fat may be altered in a state of high inflammation. For example, comparing RA and control subjects with the highest quartile of visceral adipose tissue, patients with RA had a 29% greater probability of elevated fasting blood glucose compared to control subjects[19], raising the possibility that an interaction between visceral adipose tissue and inflammation contributes to insulin resistance.

Adipose tissue is an organ containing members of the innate and acquired immune systems. Macrophages accumulate to a greater extent in visceral than subcutaneous adipose tissue, and their proinflammatory cytokine release is considered a major contributor to the increased insulin resistance associated with obesity (reviewed[20]).

The role of cytokines in adipose tissue is complex. Systemically, proinflammatory cytokines promote insulin resistance through direct effects on insulin signaling and indirect effects by stimulating lipolysis; however, locally within the adipose tissue, IL-6 has a protective, homeostatic role. For example, obese mice with inactivated IL-6 receptor paradoxically showed increased tissue inflammation with greater proportion of proinflammatory M1 macrophages and insulin resistance[21].

There is little information about how exactly RA affects adipose tissue, particularly in the visceral compartment. Perhaps in the setting of excess systemic inflammation as seen in RA, the homeostatic function of IL-6 within adipose tissue is deranged. Interestingly, a study that compared paired samples of articular and subcutaneous adipose tissue from patients with RA found a similar degree of infiltration of M2 macrophages, which would typically promote healing and secrete antiinflammatory cytokines. The M2 macrophages from the articular adipose tissue, however, were primed to produce an exaggerated inflammatory response to stimuli compared to those from the subcutaneous fat[22]. Although that study did not examine visceral fat, it showed altered function of macrophages within adipose tissue, which had likely been chronically exposed to high levels of proinflammatory cytokines.

The interesting clinical study reported by AbouAssi and colleagues provides new insights into insulin resistance in RA and has raised many questions about the relationship between visceral fat, inflammation, and insulin resistance, not only in RA but also in other diseases.

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