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Higher Prevalence and Degree of Insulin Resistance in Patients with Rheumatoid Arthritis than in Patients with Systemic Lupus Erythematosus

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Abstract

Objective. Since insulin resistance (IR) is highly prevalent in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), we aimed to determine whether differences in IR between the two conditions exist.

Methods. Cross-sectional study that encompassed 413 non-diabetic subjects, 186 SLE and 227 RA. Glucose, insulin and C-peptide serum levels, as well as IR by the homeostatic model assessment (HOMA2) were studied. A multivariable regression analysis was performed to evaluate the differences in IR indexes between patients with SLE and RA, and also to determine if IR risk factors or disease-related characteristics are differentially associated with IR in both populations.

Results. The insulin:C-peptide molar ratio was upregulated in RA compared to SLE patients (beta coef. 0.009 [95%CI 0.005-0.014], p=0.000) after multivariable analysis. HOMA2 indexes related to insulin sensitivity were found to be lower (HOMA2-S% beta coef. -27 [95%CI -46- -9], p=0.004) and beta cell function showed higher IR indexes (HOMA2-B% beta coef. 38 [95%CI 23-52], p=0.000) in RA than in SLE patients after multivariable analysis. RA patients more often fulfilled the definition of IR than those with SLE (odds ratio 2.15 [95%CI 1.25-3.69], p=0.005). The size effect of IR factors on IR indexes was found to be equal in both diseases.

Conclusions. IR sensitivity is lower and beta cell function is higher in RA than in SLE patients. The fact that traditional IR factors have an equal effect on IR in both SLE and RA supports the contention that these differences are related to the diseases themselves.

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Introduction

Insulin resistance can be broadly defined as a subnormal biological response to normal insulin concentrations. By this definition, it may pertain to many biological actions of insulin in many tissues of the body (1). Typically, in clinical practice, however, insulin resistance (IR) refers to a state in which a given concentration of insulin is associated with a subnormal glucose response. It more commonly occurs in association with obesity but may be the result of a number of different underlying causes that include induced stress (due to hormones like cortisol), medications (e. g. glucocorticoids,), pregnancy, insulin antibodies and/or genetic defects in insulin-signaling pathways. Long-term consequences of IR include the development of type 2 diabetes and cardiovascular (CV) disease (2).

In the last decade, it has become increasingly evident that the presence of inflammation constitutes a major component of IR. Studies on IR have revealed a clear association between the chronic activation of pro-inflammatory signaling pathways and decreased insulin sensitivity (3). For example, elevated levels of tumor necrosis factor (TNF)-α, interleukins 6 and 8, have all been reported in IR states (4–7). In this regard, the administration of anti-TNF-α and anti-IL-6 receptor therapy yielded a dramatic reduction of IR in non-diabetic individuals with rheumatoid arthritis (RA) (6,7).

With respect to this, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), both recognized inflammatory diseases, have been widely associated with IR (8,9). The mechanisms that lead to IR in patients with SLE and RA seem to be different from those implicated in the general population or type 2 diabetes mellitus (10). This may explain why the strong influence of traditional factors associated with IR in healthy individuals appears to have less impact on patients with RA (11). In addition, disease damage over time has also been found to contribute to IR in an independent manner in patients with SLE (9).

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Although SLE and RA share autoimmune mechanisms, they are completely different disorders that have their own unique pathogenic pathways. Most studies regarding IR in SLE and RA were performed using healthy controls as comparators. The aim of the present study was to determine if there were differences in the prevalence of IR between SLE and RA. We have also aimed to determine the effect of traditional IR risk factors on the development of IR in both conditions, and whether some disease-characteristic features relate to IR in a different manner depending on the condition.

Materials and Methods

Study participants

The main hypothesis of this work was to study if IR varies between patients with SLE and RA. If this were the case, since IR is a feature highly related to CV risk and subclinical atherosclerosis, we could identify if one disease is more predisposed to CV disease than the other. This was a cross-sectional study that included 413 individuals, 186 patients with SLE and 227 with RA. All were 18 years old or older and were included in the study if they fulfilled ≥4 American College of Rheumatology (ACR)-1997 classification criteria for SLE (12) and the 2010 ACR/EULAR Classification Criteria for RA (13). Although treatment with anti-TNF-α therapies has demonstrated improved insulin sensitivity (14,15), RA patients undergoing this therapy were not excluded from the present study. Likewise, patients taking prednisone or its equivalent at a dose ≤10 mg / day were not excluded. However, none of the patients included in this study were on glucose-lowering drugs or insulin therapy. Patients with diabetes mellitus were excluded. In this regard, all patients had a glycemia < 7 mmol/l. Patients were also excluded if they had a history of cancer or any other chronic disease, evidence of active infection or a glomerular filtration rate <60 ml/min/1.73 m2. A CONSORT flow diagram (16) including enrollment and drops outs is shown in

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Figure 1. The study protocol was approved by the Institutional Review Committee at Hospital Universitario de Canarias and Hospital Doctor Negrín, both in Spain, and all subjects provided informed written consent (Approval Number 2015/84).

Data collection

Patients were assessed for cardiovascular risk factors and medication. Hypertension was defined as a systolic or a diastolic blood pressure higher than 140 and 90 mmHg, respectively. SLE disease activity and damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) (17) and the SLICC/ACR Damage Index (SDI) (18), respectively. Disease severity was measured as well, using the Katz Index (19). In patients with RA, disease activity was measured using the Disease Activity Score in 28 joints (DAS28) (20), while disease disability was determined using the Multidimensional Health Assessment Questionnaire (HAQ) (21). Clinical Disease Activity Index (CDAI) (22) and Simple Disease Activity Index (SDAI) (23) scores for RA disease activity were calculated as previously described.

Assessments

Fasting serum samples were collected and frozen at −80 °C until analysis of circulating lipids, glucose, insulin and C-peptide. Cholesterol, triglycerides, and HDL cholesterol were measured using an enzymatic colorimetric assay (Roche Diagnostics, Indianapolis, IN, USA). Cholesterol levels ranged from 0.08 to 20.7 mmol/L (intra-assay coefficient of variation 0.3%); triglyceride levels ranged from 4 to 1.000 mg/dl (intra-assay coefficient of variation 1.8%); and HDL cholesterol levels ranged from 3 to 120 mg/dl (intra-assay variation coefficient 0.9%). LDL cholesterol was calculated using the Friedewald formula. Insulin (Architect Abbott, 2000I) and C peptide (Immulite 2000, Siemens) were determined by chemiluminescent immunometric assays. Reference values for glucose and insulin were, respectively, 60-110 mg/dl and <20 μU/ml. The

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homeostatic model assessment (HOMA) method was performed to determine IR. In this study we used HOMA2: the updated-computer HOMA model (24). In our study, all IR HOMA indexes were calculated using both insulin and C peptide. In this regard, C peptide better estimates β-cell function since it is a marker of secretion, while insulin data is preferable when calculating %S since HOMA-%S is derived from glucose disposal as a function of insulin concentration. The computer model gives a value for insulin sensitivity expressed as HOMA2-%S (where 100% is normal). HOMA2-IR (insulin resistance index) is simply the reciprocal of %S. The insulin to C-peptide ratio, which is thought to reflect hepatic insulin extraction, was also calculated. IR, as a binary variable, was defined according to HOMA2-IR $\geq$ 1.85 in men or greater than 2.36, 2.07 or 2.47 in women age 30, 50 or 70 years, respectively, as previously described (25).

Statistical analysis

Sample size calculations was performed assuming that, in previous reports of our group, IR was 0.15 points higher in RA patients compared to controls (10). We expected to find similar differences between SLE and RA patients. Therefore, to obtain a power of 80% to detect differences in the contrast of the null hypothesis (no differences between SLE and RA patients) by means of a bilateral T-Student Test for two independent samples, taking into account that the level of significance is 5%, and assuming that the mean of the reference group is 1.00 units, the mean of the experimental group being 1.15 units and the standard deviation of both groups 0.50 units, it will be necessary to include 220 units in the reference group (RA) and 147 units in the experimental group (SLE), totaling 367 experimental units in the study. Demographic and clinical characteristics in patients with SLE and RA were described as the mean ± standard deviation (SD) or percentages for categorical variables. For non-normally distributed continuous variables, data were expressed as a median and interquartile range (IQR). Univariable differences between patients with SLE and RA were assessed trough T Student, U Mann-Whitney, Chi squared or Fisher Exact tests according to

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normal distribution or number of subjects. To investigate the differences in IR indexes and glucose metabolism molecules between SLE and RA patients, we constructed three models: an unadjusted model for the univariable differences, an adjusted model 1 using those variables with a p value lower than 0.20 that had been previously identified via the differences between SLE and RA (sex, age, BMI, hypertension and dyslipidemia), and a model 2 adjusted for the same variables of model 1 plus variables related to the disease: disease duration and the use of prednisone, methotrexate and hydroxychloroquine. In this analysis, confounding factors were selected if they were related both to the independent variable and the IR indexes with a 'p' value inferior to 0.20. All the analyses used a 5% two-sided significance level and were performed using SPSS software, version 21 (IBM, Chicago, IL, USA) and STATA software, version 15/SE (Stata Corp., College Station, TX, USA). A *p* value < 0.05 was considered statistically significant.

Results

Demographic, laboratory and disease-related data

A total of 186 SLE patients (mean ± SD age of 50 ± 11 years) and 227 RA patients (mean 52 ± 10 years) were included in the present study. No significant difference was found in the comparison of age between both populations (p=0.053). Demographic and disease-related characteristics of the participants are shown in **Table 1**. Neither the BMI nor the frequency of obesity were different between the patients with SLE and RA. However, waist circumference (92 ± 13 cm vs. 96 ± 13 cm, p=0.000) was higher in RA patients. Traditional cardiovascular risk factors were common in both conditions. Nevertheless, only hypertension was found to be significantly different between groups, being higher in patients with SLE (38% vs. 25 %, p=0.004).

Regarding disease-related data, disease duration was found to be longer in SLE patients (17 ± 9 years vs. 10 ± 9 years in RA, p=0.000), with the current and cumulative dose of prednisone also proving higher in SLE patients. While the use of hydroxychloroquine was significantly higher in

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SLE patients, current use of methotrexate or leflunomide was more common in patients with RA. Further data including disease-related scores, the laboratory features of each condition and the use of biologic therapies are shown in **Table 1**.

Multivariable regression analysis of the differences in IR indexes between SLE and RA

In general, glucose homeostasis molecules were found significantly upregulated in RA patients when compared to patients with SLE in the univariable analysis (**Table 2**). In this sense, both insulin (7.2 [IQR 4.4-10.6] *vs.* 8.0 [5.5-16.40] μU/ml, p=0.032) and C-peptide serum levels (3.05 ± 2.65 *vs.* 3.57 ± 2.97 ng/ml, p=0.060) were higher in RA patients, although statistical significance was not reached for C-peptide. Similarly, most HOMA2 indexes were different in RA patients when compared to SLE patients. Remarkably, HOMA2-S% was lower and HOMA2B-%-C peptide was higher in RA patients than in those with SLE. Moreover, the frequency of IR status, defined as a binary variable, was higher in RA patients than in those with SLE (25% *vs.* 14%, p=0.005) (**Table 2**).

To assess if these differences were independent of other factors related to IR or independent of data related to the disease, we set up adjusted models (Models 1 and 2; see **Table 2**). First, we adjusted for the classic factors associated with IR that were different in patients with SLE and RA. Afterwards, we additionally included in Model 2 those variables related to both diseases that met the criteria to be considered confounding factors. Consequently, most of the differences regarding glucose homeostasis molecules and HOMA2 indexes mere maintained. In this regard, although insulin and C-peptide differences were lost after multivariable analysis, the insulin:C-peptide molar ratio upregulation persisted in RA patients (beta coef. 0.009 [95%CI 0.005-0.014], p=0.000). Similarly, HOMA2 indexes related to insulin sensitivity and beta cell function were found to be significantly lower and higher in RA, respectively. Additionally, the odds ratio (OR) for the

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presence of insulin resistance in RA patients showed a positive relation (OR 2.15 [95%CI 1.25-3.69], p=0.005) when compared to that of patients with SLE.

When patients were stratified according to prednisone intake, we observed that RA patients not taking prednisone exhibited a higher number of significant differences in glucose homeostasis molecules and IR indexes than those with SLE. In contrast, in the subgroup of patients taking prednisone, only beta cell function was found to be upregulated in RA patients when compared with SLE patients. See **Table 3**.

Differential effect of classic factors associated with IR between patients with SLE and RA

The influence of classic factors associated with IR and disease-related data on glucose homeostasis molecules and IR indexes is shown in **Table 4**. In general, these factors were strongly associated with IR and beta cell function in both diseases. Remarkably, comparisons of the size effect of these relationships between SLE and RA patients were not significant.

Similarly, CRP serum levels and the current use of prednisone was associated with higher HOMA2-IR, albeit only in SLE patients. However, the CRP-HOMA2-IR relationships did not differ among RA and SLE patients (interaction p=0.62).

Discussion

An increasing awareness of the role of inflammation-induced IR in rheumatic inflammatory diseases has emerged in recent years. However, previous reports mainly focused on comparisons between individuals with these inflammatory diseases and healthy controls. Most did not address the fact that the degree of IR can vary between different inflammatory diseases. In this regard, although the influence of traditional factors associated with IR in healthy populations is similar to

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that observed in SLE and RA, the results of our study indicate that IR is more prevalent in patients with RA than in those with SLE.

Differences in IR between immune-mediated diseases and controls have already been explored. For this reason, we did not include controls in our study. We were interested in assessing if differences in IR between SLE and RA exist. There are few studies comparing IR in patients with SLE versus those with RA. In a report that included 15 patients with SLE, 15 with RA and 15 with scleroderma, SLE patients exhibited higher HOMA2-B% than patients with RA and scleroderma (26). However, this study failed to show any differences in HOMA2-IR between groups. The study did not include a multivariable analysis, probably due to the small sample size. HOMA2-IR was found to be higher in RA compared to SLE patients in another report that included 103 patients with SLE and 124 patients with RA (27). However, this difference was not adjusted for covariables, and analysis of beta cell function via assessments of C-peptide serum levels were not performed. Besides, in a study of 100 women with SLE and 98 with RA, IR was significantly higher in women with RA as compared with those with SLE (28). This difference remained significant after adjustment for BMI and glucocorticoids. However, no adjustment was performed by factors related to the disease and no males were included in this study. Contrary, in another study on 95 RA and 57 SLE female patients that used a surrogate index of IR (triglycerides and glucose index), no differences were found between both diseases (29). Therefore, we believe that the high number of subjects included in our study and the inclusion of multivariable regression analysis are sufficiently powerful enough factors to render our results conclusive.

In our study, the differences in IR between patients with SLE and RA were mainly detected in those patients who had not undergone glucocorticoids treatment. We believe that the absence of differences in patients currently taking prednisone stems from the fact that they suffer from the deleterious effect of glucocorticoids and, therefore, experienced upregulated IR. The mechanisms by which glucocorticoids cause IR are multifactorial, and include the augmentation of hepatic

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gluconeogenesis, the inhibition of glucose uptake in adipose tissue, and the alteration of receptor and post-receptor functions (30). When we performed our analyses using the entire sample, the differences between SLE and RA in IR indexes were adjusted for prednisone intake. In this regard, we realize that the differences between SLE and RA were greater in patients without prednisone, which supports the concept that these differences cannot, in any case, be simply attributed to their use.

The insulin to C-peptide ratio is less than one in subjects without diabetes. This reflects the fact that a large fraction of endogenous insulin is cleared by the liver, whereas C-peptide, which is cleared primarily by the kidney and has a lower metabolic clearance rate than insulin, traverses the liver, thereby avoiding any extraction by hepatocytes. For this reason, the ratio of insulin to C-peptide has been assumed to reflect hepatic insulin extraction. A number of studies have suggested that reduced hepatic extraction of insulin is a major factor in the pathogenesis underlying the hyperinsulinemia observed in IR states (31). In our study, this ratio was higher in RA than in SLE patients after multivariable analysis. According to our results, insulin clearance may be amplified in patients with RA compared to those with SLE.

Classic factors associated with IR in the general population were also associated with HOMA2 indexes in our cohort of SLE and RA patients. In fact, an association of disease duration and current prednisone use with IR was found in our series of SLE patients. However, the size effect of these factors on IR was not higher in SLE than in RA. Although BMI has been reported to exert a greater influence on IR in SLE than in RA (27), we could find no such differences in our series.

The relation of disease activity and damage with IR in SLE and RA has been previously analyzed in reports of our group. In this sense, for example, SLICC damage index has been independently associated with IR in SLE (9). However, disease activity composite scores like DAS28 failed to demonstrated associations with IR. We believe that it may probably be due to the

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fact that these scores in RA only captured activity in a transversal manner. On the other hand, it is well known the potential antidiabetic properties of the hydroxychloroquine that is more commonly prescribed to SLE than RA patients in Spain (32). We feel that this effect that could have played some influence on our patients with SLE, was also controlled through multivariable analysis adjustment. However, hydroxychloroquine was not related to IR in a previous report in SLE patients (9).

Meta-analysis data indicated that IR increases the risk of incident CV disease in general population (33). Inflammation may worsen IR and impair pancreatic beta cell function (34). Consequently, an increased risk of premature CV death was observed in patients with SLE and RA. In this sense, a meta-analysis of 24 observational studies comprising 111,758 patients concluded that the risk of coronary artery disease mortality was 59% higher in patients with RA than in the general population (35). Similarly, a systematic review that included 28 studies showed that the risk of CV disease among SLE patients was at least double that of the general population (36). However, the incidence and prevalence of CV disease in patients with SLE and RA depended on specific manifestations of the disease, the population evaluated and/or the screening and diagnostic methods utilized. For this reason, it is difficult to establish whether CV disease is more prevalent in one disease or the other. The fact that IR was higher in RA than SLE in our population may be indicative of the higher CV risk borne by RA patients.

In our study, there were no differences in CRP between SLE and RA patients. Additionally, CRP was related to HOMA2-IR, albeit only in SLE patients. When the size effect of CRP on IR or beta cell function was compared between the two diseases, no significant differences were found. Therefore, we contend that CRP was not responsible for differences in IR observed between SLE and RA.

Statins intake was high in our patients with SLE and RA, being used in a quarter of patients. It is known that statins can have effects on glucose metabolism that may influence the development

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of diabetes mellitus in nondiabetics or affect glycemic control in patients with existing diabetes (37). Nevertheless, since statin use was the same in both diseases, we believe that its effect on IR was similar in SLE and RA. Therefore, the higher IR found in RA patients could not be attributed to them.

We acknowledge the limitation that patients were not sex-matched in this study. Nevertheless, the size effect of this difference was found to be small (95% vs. 81% of females in respectively analyzed SLE and RA cohorts). Moreover, identical results were reported regardless of matching, or not, when multivariable regression analysis was applied in epidemiological studies (38). We therefore believe that the multivariable analysis procedure performed in our study was able to handle confounding situations in the analysis regarding individuals not matched by sex. Adipokines may influence IR in patients with SLE and RA. However, the role of adipokines on IR was not assessed in our study. This could be a potential limitation of our study. However, the mechanisms by which cytokines or adipokines affect IR in the healthy population are still far from being fully understood.

In conclusion, IR is higher in RA than in SLE patients. This cannot be explained by factors classically associated with IR or disease-related data like CRP, disease duration or the use of prednisone. Specific mechanisms underlying each disease may be responsible for these differences. Identification of these mechanisms will lead to a greater understanding of each disease separately.

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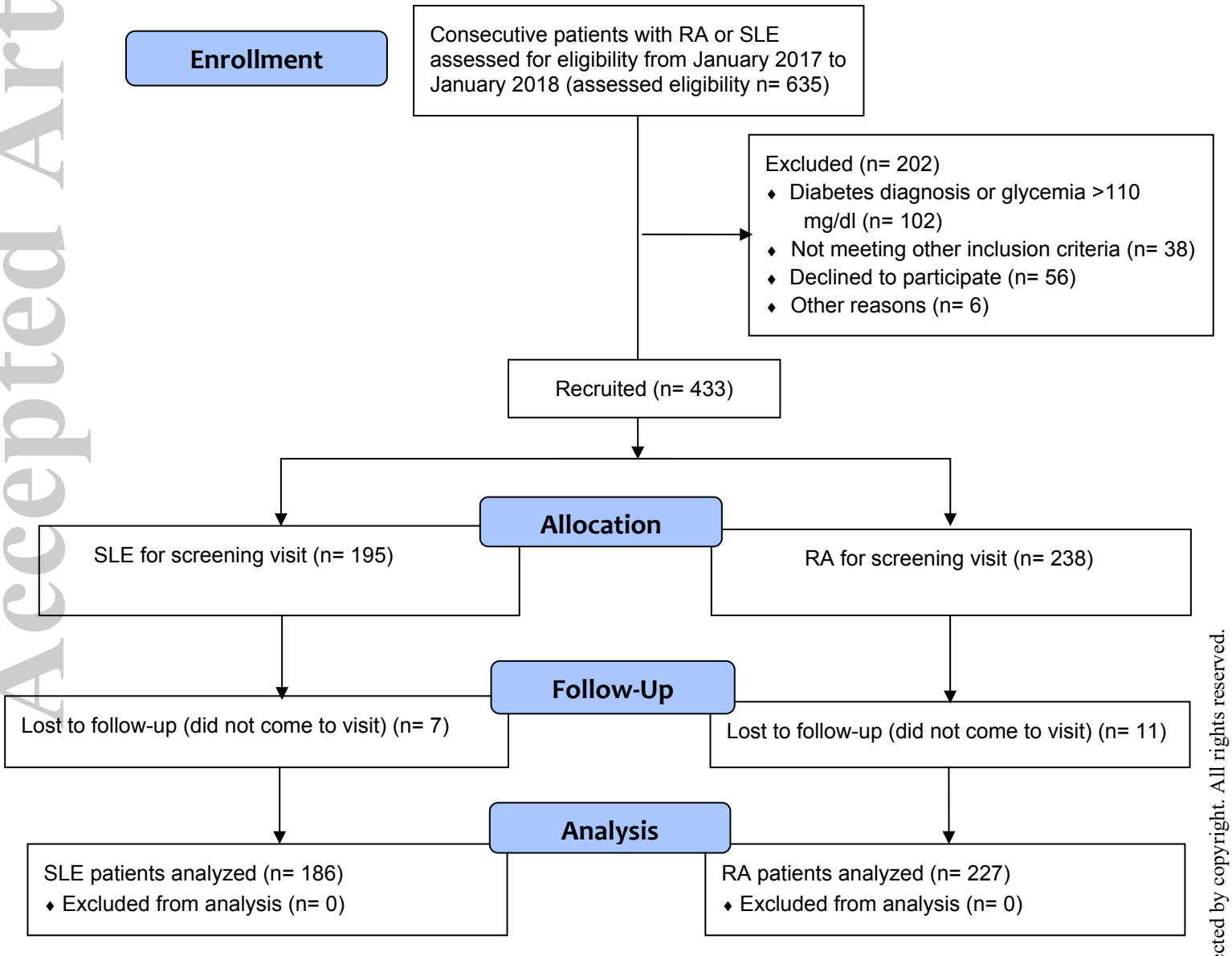

Figure 1. Recruitment flow chart diagram.

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Table 1. Characteristics of SLE and RA patients.

	SLE patients (n=186)	RA patients (n=227)	p
Age, years	50 ± 11	52 ± 10	0.053
Female, n (%)	177 (95)	184 (81)	**0.000**
Body mass index, kg/m2	27 ± 5	28 ± 5	0.065
Abdominal circumference, cm	92 ± 13	96 ± 13	**0.000**
Cardiovascular co-morbidity			
Smoking, n (%)	43 (23)	41 (18)	0.20
Diabetes, n (%)	0 (0)	0 (0)	-
Hypertension, n (%)	70 (38)	56 (25)	**0.004**
Obesity, n (%)	46 (25)	69 (30)	0.20
Dyslipidemia, n (%)	114 (61)	158 (70)	0.067
Statins, n (%)	45 (24)	65 (29)	0.31
Disease-related data			
CRP, mg/l	1.9 (0.9-4.9)	2.8 (1.3-5.5)	0.68
Disease duration, years	17 ± 9	10 ± 9	**0.000**
Rheumatoid factor, n (%)	20 (11)	158 (70)	**0.000**
ACPA, n (%)	-	141 (62)	-
Current prednisone treatment, n (%)	95 (51)	83 (37)	**0.002**
Prednisone, mg/day	6 ± 4	5 ± 3	**0.001**
Prednisone cumulative dose over 5 years, gr	6.8 ± 4.1	5.1 ± 3.5	**0.004**
DMARDs, n (%)	144 (77)	186 (82)	0.25
Hydroxychloroquine, n (%)	126 (68)	3 (1)	**0.000**
Methotrexate, n (%)	21 (11)	151 (67)	**0.000**
Leflunomide, n (%)	3 (2)	36 (16)	**0.000**
Salazopyrin, n (%)	-	1 (0)	-
Tofacitinib, n (%)	-	3 (1)	-
Baricitinib, n (%)	-	3 (1)	-
Mycophenolate mofetil, n (%)	15 (8)	-	-
Azathioprine, n (%)	25 (13)	-	-
Anti TNF-alpha therapy, n (%)	-	36 (16)	-
Rituximab, n (%)	6 (3)	-	-
Belimumab, n (%)	3 (2)	-	-
Cyclophosphamide, n (%)	1 (1)	-	-
SLICC	1 (0-2)	-	-
SLICC >= 1	136 (60)	-	-
Katz Index	2 (1-3)	-	-
Katz Index >= 3	70 (31)	-	-
SLEDAI	2 (0-5)	-	-
SLEDAI activity categories, n (%)		-	-
No activity	73 (32)	-	-

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Mild	61 (27)	-	-
Moderate	29 (13)	-	-
High or Very High	13 (6)	-	-
ANA profile			
Anti-DNA positive, n (%)	96 (42)	-	-
ENA positive, n (%)	63 (28)	-	-
C3, mg/dl	96 ± 27	-	-
C4, mg/dl	17 ± 7	-	-
DAS28	-	2.22 ± 1.09	-
DAS28-CRP	-	2.50 ± 1.00	-
CDAI	-	8 (4-15)	-
SDAI	-	13 (7-20)	-
Multidimensional HAQ	-	0.625 (0.250-1.125)	-

Data represent mean ±SD or median (interquartile range) when data were not normally distributed.

BMI: body mass index; C3 C4: complement; CRP: C reactive protein; LDL: low-density lipoprotein.

DMARD: disease-modifying antirheumatic drug; ACPA: anti-citrullinated protein antibodies.

HDL: high-density lipoprotein; ANA: antinuclear antibodies; ENA: extractible nuclear antibodies

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

SLEDAI categories were defined as: 0, no activity; 1-5 mild; 6-10 moderate; >10 activity.

SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index.

Dyslipidemia was defined if one of the following was present: total cholesterol > 200 mg/dl, triglyceride > 150 mg/dl, HDL cholesterol < 40 in men or < 50 mg/dl in women, or LDL cholesterol > 130 mg/dl.

DAS28: Disease Activation Score using 28 joints; HAQ: Health Assessment Questionnaire.

CDAI: Clinical Disease Activity Index, SDAI: Simple Disease Activity Index.

Significant 'p' values are depicted in bold.

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Table 2. Multivariable regression analysis of the differences in IR indexes between SLE and RA.

	SLE patients (n=186)	RA patients (n=227)	p	Model 1 beta coef. (95%CI), p	Model 2 beta coef. (95%CI), p
Glucose, mg/dl	100 ± 20	89 ± 18	**0.000**	**-12 (-16- -9), 0.000**	**-10 (-14- -6), 0.000**
Insulin, μU/ml	7.2 (4.4-10.6)	8.0 (5.5-16.40)	**0.032**	1.6 (-0.9-4.1), 0.20	
C-peptide, ng/ml	3.05 ± 2.65	3.57 ± 2.97	0.060	0.19 (-0.35-0.74), 0.48	
Insulin:C-peptide molar ratio	0.07 ± 0.02	0.08 ± 0.03	**0.001**	**0.009 (0.005-0.014), 0.000**	**0.009 (0.005-0.014), 0.000**
HOMA2-B%	90 ± 49	131 ± 66	**0.000**	**36 (25-48), 0.000**	**37 (26-48), 0.000**
HOMA2-S%	130 ± 91	109 ± 80	**0.011**	**-14 (-30-2), 0.093**	**-27 (-46- -9), 0.004**
HOMA2-IR	0.95 (0.59-1.44)	1.04 (0.70-2.02)	0.058	0.17 (-0.15-0.49), 0.30	
HOMA2-B%-C peptide	134 ± 67	178 ± 80	**0.000**	**37 (23-51), 0.000**	**38 (23-52), 0.000**
HOMA2-S%-C peptide	71 ± 49	65 ± 43	0.17	0 (-8-9), 0.94	
HOMA2-IR-C peptide	1.75 (1.07-2.70)	1.86 (1.12-3.13)	0.15	0.06 (0.37-0.49), 0.78	
Insulin resistance	26 (14)	57 (25)	**0.005**	**1.94 (1.10-3.39), 0.020***	**2.15 (1.25-3.69), 0.005***

HOMA2IR: Homeostatic Assessment Model for insulin resistance using insulin and glucose serum levels.
HOMA2%B-C peptide: Homeostatic Assessment Model for beta cell function using C peptide and glucose serum levels.
Model 1 was adjusted for age, sex, BMI, hypertension and dyslipidemia.
Model 2 was adjusted for Model 1 + disease duration and the use of prednisone, methotrexate and hydroxychloroquine.
Beta coefficients were calculated using SLE as the reference category. *Beta coef. were log-transformed to represent the odds ratios.
Insulin resistance is a binary variable and refers to HOMA2-IR > rather than a specific cut-off for age or sex.
Significant 'p' values are depicted in bold.

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Table 3. Differences in IR indexes between SLE and RA patients stratified according to prednisone intake.

	SLE patients n=89	RA patients n=144		SLE patients n=95	RA patients n=83	
	Not taking prednisone		p	On prednisone		p
Glucose, mg/dl	98 ± 16	87 ± 17	**0.000**	101 ± 23	93 ± 19	**0.006**
Insulin, µU/ml	6.6 (4.0-9.8)	7.7 (5.1-15.9)	**0.000**	7.6 (5.0-12.8)	9.8 (5.9-17.0)	0.66
C-peptide, ng/ml	2.45 ± 1.68	3.39 ± 2.85	**0.002**	3.61 ± 3.23	3.88 ± 3.15	0.58
Insulin:C-peptide molar ratio	0.07 ± 0.02	0.08 ± 0.03	**0.001**	0.07 ± 0.03	0.08 ± 0.02	0.12
HOMA2-B%	82 ± 37	134 ± 72	**0.000**	99 ± 57	125 ± 56	**0.002**
HOMA2-S%	141 ± 90	114 ± 82	**0.018**	121 ± 93	100 ± 77	0.11
HOMA2-IR	0.88 (0.52-1.30)	0.97 (0.65-2.00)	**0.000**	0.99 (0.67-1.69)	1.85 (1.61-1.24)	0.70
HOMA2-B%-C-peptide	119 ± 51	180 ± 85	**0.000**	148 ± 77	176 ± 70	**0.013**
HOMA2-S%-C-peptide	81 ± 52	70 ± 46	**0.093**	62 ± 45	56 ± 36	0.34
HOMA2-IR-C-peptide	1.61 (0.90-2.36)	1.67 (0.99-3.14)	**0.007**	2.07 (1.28-3.40)	1.97 (1-38-3.13)	0.70
Insulin resistance	7 (8)	35 (24)	**0.001**	19 (20)	22 (27)	0.30

HOMA2IR: Homeostatic Assessment Model for insulin resistance using insulin and glucose serum levels.
HOMA2%B-C peptide: Homeostatic Assessment Model for beta cell functionality using C peptide and glucose serum levels.
Insulin resistance refers to HOMA2-IR > cut-off for age and sex.
Significant 'p' values are depicted in bold.

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Table 4. Differential effects of classic factors associated with IR and disease-related features on IR in patients with SLE and RA.

	beta coef. (95CI), p					
	HOMA2-IR			HOMA2-B%-C peptide		
	SLE patients	RA patients	p*	SLE patients	RA patients	p*
Age, years	0.02 (-0.01-0.04), 0.14	**0.03 (0.01-0.05), 0.009**	0.66	0.71 (-0.17-1.58), 0.11	0.59 (-0.44-1.62), 0.26	-
Female, n (%)	0.17 (-0.94-1.28), 0.76	-0.39 (-0.94-0.17), 0.18	-	13 (-32-58), 0.57	**-33 (-60- -6), 0.015**	0.10
Body mass index, kg/m2	**0.08 (0.04-0.13), 0.000**	**0.09 (0.05-0.13), 0.000**	0.76	**4 (2-6), 0.000**	**5 (3-7), 0.000**	0.68
Abdominal circumference, cm	**0.04 (0.02-0.06), 0.000**	**0.04 (0.02-0.06), 0.000**	0.83	**2 (1-3), 0.000**	**2 (1-3), 0.000**	0.84
Cardiovascular co-morbidity						
Smoking, n (%)	-0.26 (-0.82-0.30), 0.36	0.05 (-0.52-0.62), 0.86	-	-17 (-40-6), 0.15	1 (-26-29), 0.92	-
Diabetes, n (%)	-	-		-	-	
Hypertension, n (%)	**0.73 (0.25-1.22), 0.003**	0.25 (-0.25-0.76), 0.33	0.18	**40 (21-59), 0.000**	**28 (4-52), 0.023**	0.45
Obesity, n (%)	**0.60 (0.05-1.14), 0.032**	**0.73 (0.26-1.20), 0.002**	0.71	**26 (3-48), 0.024**	**35 (12-58), 0.003**	0.57
Dyslipidemia, n (%)	0.38 (-0.12-0.87), 0.14	0.22 (-0.26-0.69), 0.38	-	11 (-9-31), 0.27	**23 (0-46), 0.049**	0.45
Statins, n (%)	0.35 (-0.21-0.91), 0.21	0.36 (-0.12-0.85), 0.14	-	**29 (7-52), 0.012**	**33 (10-56), 0.005**	0.36
Diseases related data						
CRP, mg/l	**0.03 (0.01-0.04), 0.005**	0.00 (-0.01-0.02), 0.70	0.62	**0.98 (0.26-1.69), 0.008**	0.47 (-0.18-1.13), 0.16	0.32
Disease duration, years	0.02 (-0.01-0.04), 0.20	-0.01 (-0.03-0.02), 0.59	0.20	0.27 (-0.76-1.31), 0.61	-0.14 (-1.36-1.08), 0.82	0.60
Current prednisone use, n (%)	**0.67 (0.19-1.93), 0.006**	0.20 (-0.26-0.65), 0.40	0.16	**28 (9-48), 0.004**	-4 (-26-18), 0.71	0.27
Prednisone, mg/day	-0.00 (-0.13-0.12), 0.91	0.09 (-0.03-0.21), 0.13	0.27	3 (-1-7), 0.18	2 (-3-7), 0.42	0.80
Cumulative 5 years prednisone, gr	-0.0 (-0.12-0.12), 0.96	0.07 (-0.03-0.17), 0.18	0.37	3 (-2-7), 0.22	2 (-2-6), 0.38	0.83

HOMA2IR: Homeostatic Assessment Model for insulin resistance using insulin and glucose serum levels.

HOMA2%B-C peptide: Homeostatic Assessment Model for beta cell functionality using C peptide and glucose serum levels.

* 'p' value for the interaction factor in the comparison of beta coefficients between SLE and RA patients

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