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Prevalence of Undiagnosed Diabetes in Rheumatoid Arthritis: an OGTT Study

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by an excess of cardiovascular disease (CVD) risk, estimated to be at least 50% greater when compared to the general population. Although the widespread diffusion of type 2 diabetes mellitus (T2DM) awareness, there is still a significant proportion of patients with T2DM that remain undiagnosed. Aim of this cross-sectional study was to evaluate the prevalence of undiagnosed diabetes and prediabetes in RA patients.

For the present study, 100 consecutive nondiabetic RA patients were recruited. Age- and sex-matched subjects with noninflammatory diseases (osteoarthritis or fibromyalgia) were used as controls. After overnight fasting, blood samples were obtained for laboratory evaluation including serum glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, uric acid, erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (*hs*-CRP), rheumatoid factor (RF), and anti-Cyclic Citrullinated Peptide Antibodies (ACPA). A standard Oral Glucose Tolerance Test (OGTT) with 75 g of glucose was performed and blood samples were collected at time 0, 30, 60, 90, and 120 minutes, for measurement of plasma glucose concentrations.

The prevalence of impaired fasting glucose (IFG) (9/100 vs 12/100, $P = 0.49$), impaired glucose tolerance (IGT) (19/100 vs 12/100, $P = 0.17$), and concomitant IFG/IGT (5/100 vs 9/100, $P = 0.27$) was similar between groups, whereas the prevalence of diabetes was significantly higher in RA patients (10/100 vs 2/100, $P = 0.02$). In a logistic regression analysis, increasing age (OR = 1.13, 95% CI 1.028–1.245, $P = 0.01$) and disease duration (OR = 1.90, 95% CI 1.210–2.995, $P = 0.005$) were both associated with an increased likelihood of being classified as prediabetes (i.e. IFG and/or IGT) or T2DM. A ROC curve was built to evaluate the predictivity of disease duration on the likelihood of being diagnosed with T2DM. The area under the ROC curve was 0.67 (95% CI: 0.56–0.78, $P = 0.004$). We identified the best cut-off of 33 months that yielded a sensitivity of 61% and a specificity of 70% for classification of T2DM patients.

According to our data, RA seems to be characterized by an elevated prevalence of undiagnosed diabetes, especially in patients with longer disease duration.

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Abbreviations: ACPA = anti-Cyclic Citrullinated Peptide Antibodies, ACR = American college of rheumatology, ADA = American diabetes association, BMI = body mass index, CRP = C-reactive protein, CVD = cardiovascular disease, DAS28 = disease activity score including 28-joints, ESR = erythrocyte sedimentation rate, EULAR = European league against rheumatism, GH-VAS = global health visual analogue scale, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, IL-6 = interleukin 6, NGT = normal glucose tolerance, OGTT = oral glucose tolerance test, RA = rheumatoid arthritis, RF = rheumatoid factor, ROC = receiver-operating characteristic, SJC = swollen joint count, T2DM = type 2 diabetes mellitus, TJC = tender joint count, TNF = tumor necrosis factor.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by an excess of cardiovascular disease (CVD) risk, estimated to be at least 50% greater when compared to the general population.[1] Cardiovascular disease has been recognized as the main cause of mortality in established RA patients,[2] but recent data confirm this trend also in earlier stages of the disease.[3] Several factors have been evoked as determinants of this additional risk, but the most consolidated theory attributes this phenomenon to the interplay between chronic high-grade inflammation and elevated prevalence of ''*classical*'' cardiovascular risk factors, including diabetes.[4,5] Although well-identified, cardiometabolic comorbidities are still under-recognized and under-treated in clinical practice, as underlined by recent researches such as the COMOrbidities in Rheumatoid Arthritis (COMORA) study.[6] Recent evidences suggest that the risk of CVD (coronary, cerebral and peripheral arterial events) could be as high as that conferred by type 2 diabetes mellitus (T2DM).[7] In a large nationwide Danish study, the risk of myocardial infarction in RA was similar in magnitude to that conferred by T2DM and corresponded to the risk reported for 10 years older non-RA subjects.[8] Similar results were obtained in the CARdiovascular research and RhEumatoid arthritis (CARRE) cohort, a longitudinal 3-years study that confirmed

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an incidence of CVD in RA at least equal to that observed for T2DM.[9] For all these reasons, in 2009 the European League Against Rheumatism (EULAR) published recommendations for the management of CVD risk in RA and other inflammatory arthritides.[10] This set of recommendations emphasize the need for cardiovascular monitoring in RA and the inadequacy of classic tables for CVD risk stratification when applied to RA patients, especially those with longer disease duration (> 10 years).[11]

In recent years, several categories of individuals at increased risk for diabetes have been identified.[2,12] Specifically, a stratification according to oral glucose tolerance test (OGTT) results has been proposed by American Diabetes Association (ADA) to identify subjects with ''*prediabetes*.''[13] According to ADA criteria, patients are classified as normotolerant (NGT) if fasting plasma glucose (FPG) is < 100 mg/dL and 2-h postload glucose is < 140; as impaired fasting glucose (IFG) if FPG 100 to 125 mg/dL and 2-h postload glucose < 140 mg/dL; impaired glucose tolerance (IGT) if FPG < 100 and 2-h postload glucose 140 to 199 mg/dL and diabetic if 2-h postload glucose ≥ 200 mg/dL. Patients classified as IFG or IGT, or with a combination of both defects (IFG/IGT), are considered ''prediabetic.'' Prediabetes is burdened by an accelerated progression to T2DM, with an incidence rate of respectively 47.4 per 1000 person-years for IFG 45.5 per 1000 person-years for IGT and 70.4 per 1000 person-years for combined IFG/IGT.[14] In addition, prediabetes is independently associated with cardiovascular mortality.[15]

Notwithstanding the widespread diffusion of T2DM awareness, there is still a significant proportion of patients withT2DM that remains undiagnosed in the general population [16–18] and in selected categories of individuals at high CVD risk, for example those hospitalized for acute myocardial infarction [19] or for non-ST-segment elevation acute coronary syndrome.[20] In these populations, the presence of undiagnosed diabetes seems to be characterized by a worst outcome [20,21] and a higher percentage of complications [22].

Despite the evidence that the coexistence of RA and T2DM could synergistically increase CVD risk,[23] neither EULAR nor ADA guidelines [10,13] recommend systematic screening for diabetes in RA patients. Therefore, the aim of the present study was to evaluate the prevalence of undiagnosed diabetes and prediabetes in RA patients.

METHODS

Patients

The study protocol was approved by the local Ethics Committee (Ethics Committee, University Hospital ''*Mater Domini*,'' Catanzaro, Italy). Informed consent was obtained from all subjects involved. For the present cross-sectional study, 100 consecutive nondiabetic RA patients were prospectively recruited at Rheumatology Outpatient Clinic, Department of Medical and Surgical Sciences, University of Catanzaro, Catanzaro, Italy. All patients satisfied the 2010 ACR/EULAR classification criteria for RA.[24] According to these criteria, the classification as ''definite RA'' is based on the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0–5), serologic abnormality (score range 0–3), elevated acute-phase response (score range 0–1), and symptom duration (2 levels; range 0–1).[24]

For comparison 100 age- and sex-matched patients with noninflammatory diseases (osteoarthritis or fibromyalgia) were used. Only adult individuals, aged > 18 years were included in the study. RA patients and control subjects were excluded if one of the following criteria was present: past or current diagnosis of diabetes or prediabetes; past or current treatment with glucose lowering drugs; fasting plasma glucose repeatedly ≥ 126 mg/dL in the absence of a definite diagnosis of T2DM made by a physician. According to these criteria, 12 RA patients and 16 controls were excluded, respectively.

Anthropometric Measurements and Disease Activity Evaluation

Height and weight were measured with patients wearing light clothing and no shoes, to the nearest 0.1 cm and 0.1 kg respectively. Body mass index (BMI) was calculated with the standard formula:

$$BMI = Weight/Height^2$$

Waist circumference (WC) was assessed with a flexible tape at midpoint between the lowest rib margin and the iliac crest. Systolic (sBP) and diastolic (dBP) blood pressure were measured on the left arm with a mercury sphygmomanometer, with the patient supine and after 5 minutes of rest. For RA assessment, the Disease Activity Score including 28 joints (DAS28-CRP) was used. DAS28-CRP is a combined index assessing the number of swollen joints (SJC), number of tender joints (TJC), patients' global assessment of health measured on a visual analogic scale (GH-VAS, range 0–100 mm), and *high sensitivity C-reactive protein plasma concentration (*hs-*CRP, mg/L)*.

Laboratory Evaluation

After overnight fasting, blood samples were obtained for laboratory evaluation. Plasma glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and uric acid were measured with automated chemistry analyzer (Cobas 6000/Cobas e411, Roche Diagnostics). The erythrocyte sedimentation rate (ESR) was analyzed by capillary photometry (Test 1, Alifax). *Hs*-CRP was measured by immunonephelometry (CardioPhase® hsCRP, Siemens HealthCare). Rheumatoid Factor (RF) was analyzed by nephelometry (BN II system, Siemens HealthCare). Anti-Cyclic Citrullinated Peptide Antibodies (ACPA) were analyzed with chemiluminescent immunoassay (Zenit RA CCP, Menarini Diagnostics).

OGTT Case Definition and Insulin Sensitivity

A standard OGTT was performed in all patients according to the recommendations of World Health Organization.[25] Briefly, after overnight fasting, the patient was invited to drink a solution with 75 g of anhydrous glucose dissolved in 200 mL of water over a time of 5 minutes; blood samples were collected at time 0, 30, 60, 90, and 120 minutes, and plasma glucose concentrations were measured.

According to OGTT results patients were classified in subgroups of glucose tolerance; according to ADA patients were classified as normotolerant if FPG< 100 mg/dL and 2-h postload glucose < 140; IFG if FPG 100–125 mg/dL and 2-h postload glucose < 140 mg/dL; IGT if FPG < 100 and 2-h postload glucose 140–199 mg/dL and diabetic if 2-h postload glucose ≥ 200 mg/dL.

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Statistical Analysis

A sample size of at least 73 patients was calculated with a confidence level of 95% and a precision of ± 5%. For this calculation, the population size was set at 6600 individuals, corresponding to the theoretical number of RA patients in our Region (Calabria, Italy, 2 million inhabitants), according to previously published prevalence of RA in Italy of 0.33%; the estimated prevalence of undiagnosed diabetes was set at 5%, slightly higher of that reported for undiagnosed diabetes in the general Italian population.[16]

Data are expressed as mean ± standard deviation (SD), median (25th–75th percentile), or number (percentage) as appropriate. Continuous variables that were not normally distributed were *ln*-transformed before analysis. Student's *t* test was used to compare means. Fisher's exact test was used to compare prevalences. The Pearson product-moment correlation coefficient was used to evaluate correlation between variables. A logistic regression analysis was used to evaluate the contribution of selected variables on the likelihood of being classified as prediabetic or diabetic. Receiver operating characteristic (ROC) curves were built to evaluate the predictivity of selected variables on the likelihood of being classified as diabetes.

A *P*-value <0.05 was considered statistically significant. All tests were 2-tailed. The Statistics Package for Social Sciences (SPSS for Windows, version 17.0, SPSS Inc., Chicago, IL) was used for all analyses.

RESULTS

Characteristics of the Study Population

General characteristics of the study population are summarized in Table 1. In comparison to age- and sex-matched controls, RA patients had a significantly higher waist circumference (103.0 ± 14.5 cm vs 97.4 ± 10.4 cm, $P = 0.002$), systolic (131 ± 17 mm Hg vs 124 ± 12 mm Hg, $P = 0.001$) and diastolic (82 ± 11 mm Hg vs 76 ± 9 mm Hg, $P = 0.001$) blood pressure, ESR (21.1 ± 13.9 mm/h vs 11.3 ± 8,7 mm/h, $P < 0.001$), and *hs*-CRP (5.79[2.40–10.19] mg/L vs 1.82 [0.88–3.16] mg/L, $P < 0.001$) whereas no significant differences were observed for BMI, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and uric acid.

Prevalence of Prediabetes and Diabetes

The prevalences of prediabetes and diabetes in RA patients and controls are reported in Table 2. The prevalence of IFG (9/100 vs 12/100, $P = 0.49$), IGT (19/100 vs 12/100, $P = 0.17$), and combined IFG/IGT (5/100 vs 9/100, $P = 0.27$) was similar

TABLE 1. Clinical Characteristics of the Study Population

	RA (n = 100)	Controls (n = 100)	*P* Value
Males (n)	39	39	1
Age (years)	56.6 ± 11.3	56.2 ± 10.2	0.80
Weight (kg)	77.0 ± 16.8	74.1 ± 13.5	0.18
BMI (kg/m^2)	28.8 ± 6.1	27.5 ± 3.8	0.09
Waist (cm)	103.0 ± 14.5	97.4 ± 10.4	0.002
sBP (mm Hg)	131 ± 17	124 ± 12	0.001
dBP (mm Hg)	82 ± 11	76 ± 9	<0.001
Disease duration (months)	32.9 ± 24.7	NA	NA
Tender joint count (n)	6.7 ± 4.9	NA	NA
Swollen joint count (n)	2.0 ± 2.5	NA	NA
Global health VAS (mm)	60.0 ± 23.1	NA	NA
DAS28-CRP	4.14 ± 1.33	NA	NA
Only-sDMARDs treated	71	NA	NA
Methotrexate (n)	67	NA	NA
Hydroxychloroquine (n)	2	NA	NA
Cyclosporin A (n)	1	NA	NA
Sulfasalazine (n)	1	NA	NA
sDMARDs*plus*bDMARDs	19	NA	NA
All anti-TNFα (n)	11	NA	NA
Abatacept (n)	7	NA	NA
Tocilizumab (n)	1	NA	NA
Glucocorticoids (n)	17	NA	NA
ESR (mm/h)	21.1 ± 13.9	11.3 ± 8.7	< 0.001
hs-CRP(mg/L)	5.79 (2.40–10.19)	1.82 (0.88–3.16)	< 0.001
Total cholesterol (mg/dL)	203.2 ± 45.7	208.4 ± 35.4	0.36
HDL-cholesterol (mg/dL)	57.1 ± 21.1	54.3 ± 12.6	0.26
LDL-cholesterol (mg/dL)	130.4 ± 34.0	131.3 ± 33.7	0.86
Triglycerides (mg/dL)	106.6 ± 51.8	119.0 ± 68.5	0.15
Uric acid (mg/dL)	4.9 ± 1.4	5.0 ± 1.4	0.70

bDMARDs = biologic disease-modifying antirheumatic drugs, BMI = body mass index, DAS28-CRP = disease activity score including 28-joints, dBP = diastolic blood pressure, ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, sBP = systolic blood pressure, sDMARDs = synthetic disease-modifying antirheumatic drugs.

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TABLE 2. Prevalence of Undiagnosed Prediabetes and Diabetes in Rheumatoid Arthritis Patients and Controls

	RA (n = 100)	Controls (n = 100)	*P* Value
NGT	57	65	0.25
IFG	9	12	0.49
IGT	19	12	0.17
IFG/IGT	5	9	0.27
T2DM	10	2	0.02

IFG = impaired fasting glucose, IGT = impaired glucose tolerance, NGT = normal glucose tolerance, T2DM = type 2 diabetes mellitus.

between groups, whereas the prevalence of diabetes was significantly higher in RA patients (10/100 vs 2/100, $P = 0.02$).

Accordingly, analysis of single time-point of plasma glucose during OGTT revealed a statistically significant difference between RA patients and controls in 60 minutes (170.2 ± 47.9 mg/dL vs 156.2 ± 46.3 mg/dL, $P = 0.03$) and 120 minutes (134.3 ± 45.5 mg/dL vs 121.6 ± 31.2 mg/dL, $P = 0.02$) afterload glucose (Table 3). However, 60 minutes plasma glucose is not considered for classification purposes in ADA criteria for diabetes and prediabetes.

Predictors of Prediabetes and Diabetes

Partial correlational analysis of disease-related variables revealed a significant correlation of age ($R = 0.40$, $P < 0.001$), disease duration ($R = 0.26$, $P = 0.01$), DAS28-CRP ($R = 0.24$, $P = 0.02$), ESR ($R = 0.23$, $P = 0.03$), and hs-CRP ($R = 0.32$, $P = 0.002$) with 120 minutes plasma glucose. When glucose tolerance was set as the dependent variable, similar results were obtained except for ESR (Table 4). When fasting glucose was set as the dependent variable, only disease duration maintained its correlation ($R = 0.27$, $P = 0.008$).

Univariate ANOVA was used to evaluate differences between glucose tolerance groups of RA patients (Table 5). The groups differed significantly for disease duration ($P = 0.02$), TJC ($P = 0.02$), *hs*-CRP ($P = 0.04$), DAS28-CRP ($P = 0.03$), and triglycerides ($P = 0.004$). No significant differences were detected in medication used between groups (Table 5).

Based on the results reported above, a logistic regression model was constructed to ascertain the effects of selected variables (age, disease duration, waist circumference, *hs*-CRP, DAS28-CRP, and triglycerides) on the likelihood that patients have diabetes or any subtype of prediabetes. The logistic regression model was statistically significant ($\chi 2 = 71.24$, $P < 0.001$). The model explained 55.7% (Nagelkerke R^2) of the variance in glucose metabolism classification. Increasing age and disease duration were both associated with an increased likelihood of being classified as prediabetes or T2DM. In particular, increase in 1 year of disease duration was associated with 1.90 fold higher risk of having T2DM (OR = 1.90, 95% CI 1.210–2.995, $P = 0.005$), whereas increase in 1 year of age was associated with a risk of 1.13 (OR = 1.13, 95% CI 1.028–1.245, $P = 0.01$).

Finally, we constructed an ROC curve to evaluate the predictivity of disease duration on the likelihood of being diagnosed with T2DM. The area under the ROC curve was 0.67 (95% CI: 0.56–0.78), $P = 0.004$). We identified the best cut-off of 33 months that yielded a sensitivity of 61% and a specificity of 70% for classification of T2DM patients.

TABLE 3. Glucose Values During Oral Glucose Tolerance Test in Rheumatoid Arthritis Patients and Controls

	RA (n = 100)	Controls (n = 100)	*P* Value
Fasting glucose (mg/dL)	91.7 ± 12.6	93.3 ± 11.6	0.33
30 min glucose (mg/dL)	159.1 ± 36.4	154.6 ± 35.5	0.41
60 min glucose (mg/dL)	170.2 ± 47.9	156.2 ± 46.3	0.03
90 min glucose (mg/dL)	147.2 ± 49.4	139.5 ± 40.9	0.25
120 min glucose (mg/dL)	134.3 ± 45.5	121.6 ± 31.2	0.02

TABLE 4. Partial Correlation Analysis* of Disease-Related Variables Using Fasting Glucose, 120 Minutes Plasma Glucose and Glucose Tolerance as Dependent Variable

	Fasting Glucose		120 min Glucose		Glucose Tolerance (0–4)†	
	R	*P*	R	*P*	R	*P*
Age	0.14	0.18	0.40	< 0.001	0.32	0.002
Disease Duration	0.27	0.008	0.26	0.01	0.29	0.005
DAS28-CRP	0.04	0.71	0.24	0.02	0.21	0.04
ESR	0.04	0.72	0.23	0.03	0.13	0.21
hs-CRP	0.08	0.42	0.32	0.002	0.24	0.02

DAS28-CRP = disease activity score 28-joint, ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein.

* The partial correlation analysis was built in single models to avoid overfitting. In each correlation, one of the disease-related features was introduced in a model with fixed covariates selected on the basis of univariate correlations: waist circumference, systolic blood pressure, use of corticosteroids (binomial), use of sDMARDs (binomial), and use of biologics (binomial).

† Glucose tolerance was classified as an ordinal variable with the following values: 0, normal glucose tolerance; 1, impaired fasting glucose; 2, impaired glucose tolerance; 3, impaired fasting glucose *plus* impaired glucose tolerance; 4, diabetes.

DISCUSSION

In the present study, we reported for the first time an elevated prevalence of undiagnosed diabetes in RA patients compared to age- and sex-matched control individuals. In addition, we found significantly higher glucose values 60 and 120 minutes after the oral load. We failed however to find a significant difference in the prevalence of prediabetes in the study population. We reasoned that this apparently surprising finding could be caused by an accelerated progression of the metabolic disease in RA patients that may increase the probability to find subjects with metabolic parameters within the diabetic range rather than in the prediabetic range. On the other hand, sample size was calculated considering the outcome diabetes only; therefore the study could be underpowered to catch differences in the prevalence of prediabetes. Compared to previous studies, in which the diagnosis of T2DM was based on medical records or anamnestic data, our work has the advantage

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TABLE 5. Clinical and Laboratory Differences Between Different Groups of Glucose Tolerance

	NGT (n = 57)	IFG (n = 9)	IGT (n = 19)	IFG-IGT (n = 5)	T2DM (n = 10)	*P* Value
Age	53.3 ± 11.7	53.9 ± 7.7	61.2 ± 9.5	65.8 ± 7.2	64.3 ± 8.4	0.34
BMI	27.6 ± 6.4	29.4 ± 5.2	30.5 ± 6.0	30.1 ± 6.0	30.6 ± 4.2	0.31
WC	99.9 ± 14.7	103.8 ± 11.1	108.9 ± 14.4	106.6 ± 17.8	106.3 ± 11.9	0.16
sBP	127.2 ± 17.3	135.1 ± 25.0	136.2 ± 12.6	142.0 ± 4.5	133.4 ± 13.9	0.11
dBP	80.5 ± 11.6	81.8 ± 8.6	86.4 ± 10.2	84.0 ± 5.5	79.3 ± 10.7	0.31
Total cholesterol	202.7 ± 49.6	194.9 ± 34.0	214.3 ± 42.8	193.8 ± 33.6	196.8 ± 45.5	0.77
HDL cholesterol	59.1 ± 24.7	54.6 ± 16.1	55.4 ± 13.1	49.8 ± 16.2	54.7 ± 18.5	0.84
LDL cholesterol	129.9 ± 34.9	125.3 ± 24.9	138.3 ± 32.5	126.8 ± 34.3	125.1 ± 41.3	0.82
Triglycerides	93.5 ± 33.2	91.2 ± 21.7	142.4 ± 84.0	124.4 ± 59.7	118.4 ± 46.6	0.004
Disease duration	26.5 ± 19.6	44.7 ± 27.0	37.7 ± 32.9	28.8 ± 10.7	51.6 ± 25.3	0.02
TJC	6.1 ± 4.5	4.3 ± 2.8	8.9 ± 5.0	4.2 ± 2.3	9.6 ± 7.3	0.02
SJC	2.0 ± 2.7	1.2 ± 1.5	2.0 ± 2.5	0.4 ± 0.9	2.8 ± 1.9	0.41
ESR	18.8 ± 13.5	17.3 ± 16.9	23.7 ± 11.0	27.8 ± 14.1	28.4 ± 16.3	0.15
*ln*CRP	4.5 (2.1–9.3)	5.0 (1.9–8.2)	8.0 (2.5–27.4)	17.3 (4.9–44.8)	6.9 (3.9–23.3)	0.04
DAS28-CRP	3.9 ± 1.3	3.7 ± 0.8	4.6 ± 1.1	3.8 ± 0.7	4.9 ± 1.0	0.03
*s*DMARDs	41	7	13	3	7	0.88
*s*DMARD*splusb*DMARDs	12	3	3	0	1	0.54
Corticosteroids	11	1	2	2	1	0.53

bDMARDs = biologic disease-modifying antirheumatic drugs, BMI = body mass index, DAS28-CRP = disease activity score 28-joints, dBP = diastolic blood pressure, ESR = erythrocyte sedimentation rate, hs-CRP = high-sensitivity C-reactive protein, sBP = systolic blood pressure, sDMARDs = synthetic disease-modifying antirheumatic drugs, SJC = swollen joints count, TJC = tender joint count, WC = waist circumference.

of being based on a systematic screening with OGTT, the gold-standard technique for diabetes diagnosis. In our opinion, the necessity to recognize early diabetes in RA patients is driven by the ''classic'' evidence that CVD risk factor tends to act in a synergistic way, thus increasing the risk conferred by a single risk factor. In support of this hypothesis, Baghdadi et al demonstrated that the risk of myocardial infarction was significantly higher in RA patients with comorbid T2DM compared to those with RA only [23]. The main finding of our work is consistent with the more recent literature, showing a high prevalence of comorbid T2DM in RA patients. In particular, a recent meta-analysis of 11 case-control studies and 8 cohort studies confirmed an increased risk of T2DM in patients with RA.[26] Conversely, T2DM patients, especially if females, have an elevated risk of developing RA.[27] Despite this well-recognized epidemiologic relationship, the coexistence of RA and diabetes seems still to be characterized by a worse diabetes management and less frequent hemoglobin A1c testing,[28] as well as by higher rates of underlying cardiovascular disease and diabetes-related complications (renal and vascular).[28]

The correlation between diabetes and RA, however, is a long-lasting story, hypothesized many years ago,[2] and was attributed mainly to the diabetogenic effect of corticosteroid treatment, although recent evidences suggest a ''neutral'' effect.[29] Nowadays 2 main theories have been proposed: on one hand, a privileged clustering of cardiovascular risk factors (such as obesity, alcohol consumption, or smoke) seems to characterize RA patients;[30] on the other hand, the chronic high-grade inflammation has a well-established diabetogenic effect.[31] Recent evidences suggest that, independently of corticosteroids and classic cardiovascular risk factor, inflammatory disease activity, *per se*, is a key mechanism of this increased risk. This is attributed to the interference of inflammatory cytokines, in particular TNF-α [32] and IL-6,[32] on insulin signaling and consequent development of insulin resistance.[33] Several studies demonstrated an elevated prevalence of insulin resistance in RA and a strict connection between visceral adiposity and inflammation.[34,35]

In our study, this theory is reflected once again by the evidence that both metabolic measures (such as BMI and waist circumference) and disease severity features (such as disease duration, DAS28 and *hs*-CRP) are significantly higher in RA patients with comorbid prediabetes or diabetes compared to NGT RA individuals and correlate with glucose tolerance classification and 2-hours postload glucose. Furthermore, postload glucose values at 60 and 120 minutes were significantly higher in RA patients compared to controls. Whereas glucose values in the first part of the curve reflect hepatic insulin sensitivity, the second part of the curve reflects more accurately peripheral insulin sensitivity, suggesting increased muscle insulin resistance in RA patients.[36]

In addition, controlling inflammation and disease activity with appropriate therapy seems to be beneficial in reducing insulin resistance and the risk of developing diabetes.[31,37] In particular, hydroxycloroquine [37,38] and anti-TNF-alpha medications [37,39] have been demonstrated to improve insulin resistance and the risk of diabetes in inflammatory arthritis patients. In our study, probably because of a low statistical power, no significant differences were observed in treatment used between different groups of glucose tolerance.

In our study, the main disease-related feature, which correlated with the likelihood of being classified as diabetic, was disease duration. This finding seems to mirror the recent data regarding CVD risk in RA subjects that is estimated to be comparable to this of normal individuals 10 years older.[8] Therefore, we can hypothesize that RA confers an ''*accelerated aging phenotype*'' to both the cardiovascular and metabolic profile of patients, as suggested by recent studies.[40]

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Our study has a major limit, as the sample size is too small to allow us to firmly establish the true prevalence of prediabetes in RA patients. In addition, we found a significantly higher waist circumference in the RA group, but similar BMI in comparison with control individuals. This phenotype is consistent with published literature, in which lower muscle mass and increased visceral [41] and total body fat [42] were reported. A similar shift of body composition in the direction of increased visceral adiposity is independently associated with insulin resistance.[43] In addition, we found higher levels of blood pressure in our patients. This is consistent with past literature on RA and it is associated with a lower percentage of individuals receiving a diagnosis of hypertension and thus appropriate treatment.[44] Hypertension is associated with insulin resistance,[45] and regardless of the cause that generated it (idiopathic, iatrogenic, or disease-related) could contribute to increase the risk of diabetes in RA patients.

In conclusion, our data, although limited by the relatively low number of patients and consequently the lack of subanalysis for confounding factors (such as sex, visceral adiposity, and hypertension), suggest an elevated prevalence of undiagnosed diabetes in RA patients and higher 1- and 2-hour postload glucose levels. Beside their role in the diagnosis of diabetes, these latest measures of glycemic burden are independently correlated with cardiovascular risk.[46–48]

If these data are confirmed on larger populations from different countries, subsequent studies will be necessary to evaluate the potential benefits on CVD outcomes of a systematic screening for T2DM in RA patients.

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