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Prevalence of type 2 diabetes and impaired fasting glucose in patients affected by rheumatoid arthritis

Results from a cross-sectional study

Piero Ruscitti, MD[a,*], Francesco Ursini, MD, PhD[b], Paola Cipriani, MD, PhD[a], Francesco Ciccia, MD, PhD[c], Vasiliki Liakouli, MD, PhD[a], Francesco Carubbi, MD, PhD[a], Giuliana Guggino, MD, PhD[c], Onorina Berardicurti, MD[a], Rosadaniela Grembiale, MD[b], Giovanni Triolo, MD, PhD[c], Giovambattista De Sarro, MD, PhD[b], Roberto Giacomelli, MD, PhD[a]

Abstract

Although the better management of rheumatoid arthritis (RA) has significantly improved the long-term outcome of affected patients, a significant proportion of these may develop associated comorbidities including cardiometabolic complications. However, it must be pointed out that a comprehensive cardiometabolic evaluation is still poorly integrated into the management of RA patients, due to a limited awareness of the problem, a lack of appropriate clinical studies, and optimal strategies for cardiovascular (CV) risk reduction in RA. In addition, although several studies investigated the possible association between traditional CV risk factors and RA, conflicting results are still available.

On this basis, we planned this cross-sectional study, aimed at investigating the prevalence of type 2 diabetes (T2D) and impaired fasting glucose (IFG) in RA patients compared with age- and gender- matched control individuals. Furthermore, we analyzed the role of both traditional and RA-related CV risk factors in predicting T2D and IFG.

We observed an increased prevalence of T2D in RA patients when compared with age- and gender-matched controls. Regression analyses demonstrated that the presence of high blood pressure (HBP), a longer disease duration, and exposure to corticosteroids (CCS) were significantly associated with an increased likelihood of being classified as T2D. In addition, we observed an increased prevalence of IFG in RA patients when compared with age- and gender-matched controls. Regression analyses demonstrated that a higher body mass index (BMI), the presence of metabolic syndrome (MetS), higher levels of total cholesterol, the presence of radiographic damage, and higher serum levels of C-reactive protein (CRP) were significantly associated with an increased likelihood of presenting IFG.

In this cross-sectional study, we observed an increased prevalence of T2D and IFG in an Italian cohort of RA patients when compared with age- and gender-matched control individuals. Interestingly, both RA-specific features, such as disease duration, CCS exposure, and radiographic damage, and traditional CV risk factors, such as HBP and MetS, were significantly associated with glucose metabolism abnormalities.

Abbreviations: ACPA = anticyclic citrullinated peptide antibodies, ADA = American Diabetes Association, BMI = body mass index, CCS = corticosteroids, CRP = C-reactive protein, CV = cardiovascular, CVEs = cardiovascular events, DAS28 = Disease Activity Score including 28 joints, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, FPG = fasting plasma glucose, HAQ = Health Assessment Questionnaire, HBP = high blood pressure, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, IL = interleukin, MetS = metabolic syndrome, MTX = methotrexate, OGTT = oral glucose tolerance test, RA = rheumatoid arthritis, RF = rheumatoid factor, SJC = swollen joints count, T2D = type 2 diabetes, TJC = tender joints count, TNF = tumor necrosis factor, TNFi = TNF inhibitor, VIF = variance inflation factor.

Keywords: cardiovascular risk, impaired fasting glucose, inflammation, rheumatoid arthritis, type 2 diabetes

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[a] Division of Rheumatology, Department of Biotechnological and Applied Clinical Science, University of L'Aquila, L'Aquila, [b] Department of Health Sciences, University of Catanzaro "Magna Graecia", Catanzaro, [c] Division of Rheumatology, Department of Internal Medicine, University of Palermo, Palermo, Italy.

[*] Correspondence: Piero Ruscitti, Department of Biotechnological and Applied Clinical Science, Rheumatology Unit, School of Medicine, University of L'Aquila, Delta 6 Building, Via dell'Ospedale, 67100, L'Aquila, Italy (e-mails: pieroruscitti@live.com, piero.ruscitti@graduate.univaq.it).

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1. Introduction

In the last years, the advent of novel therapeutic options including biologics and small molecules significantly improved the outcome of rheumatoid arthritis (RA) patients and, in particular, their quality of life.[1–3] The deeper knowledge of pathophysiological mechanisms, the growing use of a treat-to-target management as well as the availability of powerful drugs strongly increased the percentage of patients achieving clinical remission and, consequently, reduced the percentage of those experiencing radiographic progression.[4–7] However, a significant proportion of patients may still develop associated complications and several studies demonstrated a close association between RA and cardiometabolic comorbidity.[8–10] To date, during RA, the leading cause of death are major cardiovascular events (CVEs); for this reason, growing research efforts are focusing on improving the management of these nonarticular outcomes.[11,12] In this context, it has been suggested that a large number of RA patients manifest traditional cardiovascular (CV) risk factors such as high blood pressure (HBP) and type 2 diabetes (T2D), thus worsening their overall CV risk profile.[12,13] In addition, the rheumatoid pro-inflammatory milieu may contribute to this clinical phenotype and the development of these comorbidities.[14,15] In fact, several well-known RA pathogenic inflammatory mediators including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNF), have been shown to play a pivotal role in atherosclerosis and metabolic dysregulation.[16] During T2D, pro-inflammatory cytokines contribute to beta-cell dysfunction and destruction, as observed in bone damage during RA[16–18]; similarly, they participate in the pathophysiology of insulin resistance.[19] Although these comorbidities frequently occur in RA patients, cardiometabolic diseases remain still underdiagnosed and undertreated in rheumatic patients.[20,21] In addition, despite specific European League Against Rheumatism (EULAR) recommendations,[22,23] a comprehensive evaluation of the cardiometabolic status in RA patients may be difficult to perform in the real-life clinical setting and the identification of clinical as well as laboratory biomarkers reflecting the CV risk profile is still awaited.[24–26] Overall, cardiometabolic evaluation is still poorly integrated into the management of RA patients for multiple reasons, including a limited awareness of the problem, a lack of well-designed clinical studies, and optimal strategies for CV risk estimation and reduction.[27] Although several groups investigated the possible association between T2D and RA, conflicting results are still available. Moreover, regional differences in T2D susceptibility may impair the possibility to generalize results from different geographic areas. In this regards, 2 studies investigated the prevalence of T2D in Italian RA patients; however, 1 study evaluated only hospitalized RA patients and the other investigated the prevalence of occult diabetes.[28,29]

On these bases, we performed this cross-sectional study, aimed at investigating the prevalence of T2D and impaired fasting glucose (IFG) in RA patients when compared with age- and gender-matched controls. Furthermore, we analyzed the role of both traditional and RA-related CV risk factors in predicting T2D and IFG.

2. Methods

2.1. Study design and patients

In this study, 500 consecutive RA patients attending our Department during a 5-year period (January 2011–December 2015) were evaluated. As a control group, we recruited 500 age- and gender-matched consecutive individuals referred to our Department for musculoskeletal complaints and in whose the diagnosis of inflammatory autoimmune disease, cancer, or other systemic diseases were excluded after appropriate clinical, imaging, and laboratory investigations. This population comprised a mixed pool of diagnoses including fibromyalgia or other forms of functional widespread pain (n = 84), local or generalized osteoarthritis (n = 227), and other noninflammatory painful musculoskeletal conditions (n = 189).

Inclusion criteria were predefined as follows: Adult age (≥18 years); RA classified according to 2010 American College of Rheumatology (ACR)/EULAR and/or 1987 ACR criteria.[30,31] Exclusion criteria were predefined as follows: a past diagnosis of T2D performed by a physician before the onset of RA; and treatment with antidiabetic medications (including oral antidiabetic drugs and insulin) started before the onset of RA.

The local Ethics Committee (Comitato Etico Azienda Sanitaria Locale 1 Avezzano/Sulmona/L'Aquila, L'Aquila, Italy) approved the study protocol. All investigations have been performed according to the Good Clinical Practice guidelines and written informed consent was obtained from all patients, according to the Declaration of Helsinki.[32]

2.2. Definition of T2D and IFG

Screening for T2D was performed in all patients according to American Diabetes Association (ADA) 2009 recommendations.[33] Briefly, patients underwent measurement of plasma glucose after overnight fasting (fasting plasma glucose, FPG). If FPG was 100 to 125 mg/dL, patients were classified as IFG. If FPG ≥126 mg/dL, patients were classified as having T2D. Abnormal results (≥100 mg/dL) were reassessed 1 week later. If there was inconsistency between the 2 values, a third evaluation was performed after an additional week. This FPG-based approach yielded 14 previously unrecognized diagnoses of T2D. In addition, patients were assigned to the T2D group independently of FPG values if presenting one or more of the following criteria: a past diagnosis of T2D performed by a physician following the diagnosis of RA; and past or current therapy with antidiabetic medications including oral antidiabetic drugs and insulin.

2.3. Clinical history and disease activity assessment

Relevant data were collected, including demographic characteristics, smoking habits, RA features and complications (extra-articular manifestations and/or a past history of RA-related joint surgery), relevant comorbidities including HBP, metabolic syndrome (MetS), and obesity, and medications used. The body mass index (BMI) was used to categorize patients as underweight (BMI $<18.5\,kg/m^2$), normal weight (BMI $18.5–25\,kg/m^2$), overweight (BMI $25–30\,kg/m^2$), or obese (BMI $>30\,kg/m^2$). Radiographic damage was defined as the presence of at least one marginal erosion on a previously performed hand radiography. Treatment details were collected in dichotomic variables, including methotrexate (MTX), TNF inhibitor (TNFi), or other biologics. In addition, cumulative exposure to corticosteroids (CCS) ≥450 mg prednisone-equivalent during the last 3 years was recorded as a dichotomic variable.

The Disease Activity Score including 28 joints (DAS28-ESR) was used to assess disease activity, evaluating the number of swollen joints (SJC), number of tender joints (TJC), and erythrocyte sedimentation rate (ESR, mm/h).[34] ESR was selected

for the assessment of DAS28 in order to maintain the independence of C-reactive protein (CRP), a well-established cardiometabolic risk factor in the general population,[35] for data analysis purposes. Functional status was evaluated using the Health Assessment Questionnaire (HAQ),[36] a patient-reported outcome widely used to assess the impact of RA on everyday functioning of patients.

2.4. Laboratory evaluation

Blood samples were obtained for laboratory evaluation after overnight fasting. Glucose, total cholesterol, and triglycerides were measured with an automated chemistry analyzer (Cobas 6000/Cobas e411; Roche Diagnostics, Monza, Italy). ESR was evaluated by capillary photometry (Test 1, Alifax). High-sensitivity CRP was measured by immunonephelometry (CardioPhase hsCRP; Siemens Healthcare, Milano, Italy). Rheumatoid factor (RF) was analyzed by nephelometry (BN II system; Siemens HealthCare). Anti-cyclic citrullinated peptide antibodies (ACPAs) were analyzed with a chemiluminescent immunoassay (Zenit RA CCP; Menarini Diagnostics, Firenze, Italy).

2.5. Sample size calculation

For the present study, we calculated a sample size of at least 432 patients for each group with a power of 80% and a confidence level of 95%. This sample size was calculated in order to detect a prevalence of T2D of at least 10%, which represents a conservative estimate based on a previous study reporting the prevalence of undiagnosed T2D in an Italian RA population.[29] The estimated prevalence in the control group was set at 5%, corresponding to the prevalence of T2D in the Italian general population as reported by the National Institute of Statistics (ISTAT, www.istat.it/).

2.6. Statistical analysis

Data are expressed as mean ± standard deviation or number (percentage) as appropriate. The Student *t* test was used to compare means for continuous variables. The Fisher exact test was used to compare proportions for dichotomic variables. Single- and multiple-logistic regression models were performed in order to evaluate the contribution of selected variables on the likelihood of having T2D or IFG. Multicollinearity between independent variables was evaluated by using the variance inflation factor (VIF) before entering each value in the regression models. A P value $<.05$ 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.

3. Results

3.1. Clinical characteristics

In this study, we evaluated 500 consecutive RA patients, classified according to the 2010 ACR/EULAR and/or 1987 ACR Criteria, and 500 age- and gender-matched controls. The clinical characteristics of these patients are summarized in Table 1. The majority of RA patients (70.2%) showed a seropositive disease with a mean duration of 10.1 ± 7.1 years. The presence of extra-articular manifestations was observed in 15% of patients and 7% underwent RA-related joint surgery. The most common synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) administered were MTX and TNFis, respectively. As expected, a large percentage of RA patients were exposed to CCS (80.4%). No significant differences were observed in smoking habits, serum levels of total cholesterol and triglycerides, the percentage of obese patients, and of patients affected by MetS when comparing RA patients and controls. Moreover, a significantly higher percentage of RA patients was affected by HBP (38.4% vs 27%, $P<.001$). Table 2 compares the most relevant variables between the 3 evaluated groups (RA, RA/IFG, RA/T2D).

Table 1

Clinical characteristics of the study population.

	RA (n = 500)	Controls (n = 500)	*P*
Female gender, n (%)	433 (86.6)	433 (86.6)	>.99
Age, years	59.3 ± 13.6	58.3 ± 7.4	.14
Smoking habit, n (%)	171 (34.2)	154 (30.8)	.28
Obese, n (%)	119 (23.8)	101 (20.2)	.17
MetS, n (%)	150 (30.0)	140 (28.0)	.53
HBP, n (%)	192 (38.4)	135 (27.0)	<.001
T2D, n (%)	68 (13.6)	42 (8.4)	.01
IFG, n (%)	102 (20.4)	62 (12.4)	.001
Fasting glucose, mg/dL	91.9 ± 16.5	93.6 ± 20.2	.16
Total cholesterol, mg/dL	195.9 ± 54.9	203.3 ± 40.1	.007
Triglycerides, mg/dL	112.7 ± 38.8	115.8 ± 75.1	.42
RA duration, y	10.1 ± 7.1	—	—
RF or ACPA positive, n (%)	351 (70.2)	—	—
Extra-articular features, n (%)	75 (15.0)	—	—
Joint surgery, n (%)	35 (7.0)	—	—
Radiographic damage, n (%)	115 (23.0)	—	—
DAS28-ESR	4.92 ± 1.00	—	—
HAQ	0.92 ± 0.61	—	—
ESR, mm/h	20.7 ± 15.0	—	—
CRP, mg/L	9.80 ± 15.49	—	—
MTX, n (%)	424 (84.8)	—	—
TNFi, n (%)	209 (41.8)	—	—
Other biologics, n (%)	62 (12.4)	—	—
Steroids, n (%)	402 (80.4)	—	—

ACPA = anticyclic citrullinated peptide antibodies, CRP = C-reactive protein, DAS28-ESR = disease activity score including 28 joints and erythrocyte sedimentation rate, HAQ = health assessment questionnaire, ESR = erythrocyte sedimentation rate, HBP = high blood pressure, IFG = impaired fasting glucose, MetS = metabolic syndrome, MTX = methotrexate, RA = rheumatoid arthritis, RF = rheumatoid factor, T2D = type 2 diabetes, TNFi = tumor necrosis factor inhibitors.

3.2. Prevalence and predictors of T2D

In our study, although FPG did not statistically differ between the evaluated groups, we observed an increased prevalence of T2D in RA patients when compared with age- and gender-matched controls (13.6% vs 8.4%, $P=.01$). Single- and multiple-logistic regression models were performed in order to evaluate the contribution of RA-specific and traditional CV risk factors on the likelihood of having T2D in RA patients (Table 3). The multivariate analysis demonstrated that the presence of HBP, a longer disease duration, and the treatment with CCS were significantly associated with an increased likelihood of being classified as T2D. In particular, the presence of HBP was associated with 1.77-fold higher risk of having T2D [odds ratio (OR) = 1.77, 95% confidence interval (95% CI) 1.05–3.05, $P=.033$]. A 1-year increase of disease duration was associated with 1.09-fold higher risk of having T2D (OR = 1.09, 95% CI: 1.02–1.13, $P<.001$). The Exposure to CCS was associated with 5.87-fold higher risk of having T2D (OR = 5.87, 95% CI 1.23–7.33, $P=.015$). The logistic regression model was statistically significant ($\chi^2=36.08$, $P<.001$).

Table 2

Clinical characteristics of RA patients with T2D or with IFG and RA patients without T2D and IFG.

	RA[†]	RA/T2D[‡]	RA vs RA/T2D *P*	RA/IFG[§]	RA vs RA/IFG *P*
Female gender, n (%)	281 (85%)	61 (89.7%)	.23	90 (88%)	.59
Age, y	59.2 ± 13.7	60.1 ± 13.5	.71	64.1 ± 12.6	.43
Smoking habit, n (%)	113 (34.2%)	27 (39.7%)	.27	29 (28.4%)	.19
Obese, n (%)	35 (10.6%)	16 (23.5%)	.036*	3 (2.9%)	.04*
MetS, n (%)	80 (24.2%)	16 (23.6%)	.21	54 (52.9%)	<.001*
HBP, n (%)	107 (32.4%)	30 (44.1%)	<.001*	55 (53.9%)	<.001*
Fasting glucose, mg/dL	89.6 ± 14.1	108.7 ± 22.1	<.001*	107.5 ± 6.3	<.001*
Total cholesterol, mg/dL	195.9 ± 56.1	188.1 ± 44.2	<.001*	223.9 ± 41.6	<.001*
Triglycerides, mg/dL	116.1 ± 51.1	101.1 ± 41.2	.98	132.9 ± 55.3	<.001*
RA duration, y	10.4 ± 7.01	9.7 – 8.7	.44	12.3 ± 6.3	.027*
RF and/or ACPA positive, n (%)	236 (71.5%)	40 (58.8%)	.017*	79 (77%)	.11
Extra-articular features, n (%)	47 (14.2%)	14 (20.6%)	.10	14 (13.7%)	.69
Joint surgery, n (%)	47 (7.3%)	7 (10.3%)	.25	4 (3.9%)	.17
Radiographic damage, n (%)	57 (17.3%)	12 (17.6%)	.26	46 (45.1%)	<.001*
DAS28-ESR	4.9 ± 0.9	4.7 ± 1.2	.121	5.2 ± 1.0	.29
HAQ	0.9 ± 0.6	0.9 ± 0.6	.90	1.0 ± 0.5	.018*
ESR, mm/h	20.9 ± 14.6	20.7 – 17.3	.038*	24.4 ± 17.2	.88
CRP, mg/L	9.4 ± 12.7	12.4 ± 27.6	.004*	13.8 ± 17.1	.87
MTX, n (%)	272 (82.4%)	61 (89.7)	.24	91 (89.2%)	.17
TNFi, n (%)	132 (40%)	32 (57.1%)	.34	45 (44.1%)	.59
Other biologics, n (%)	42 (12.7%)	4 (5.9%)	.79	16 (15.7%)	.25
Steroids, n (%)	256 (77.6%)	62 (91.2%)	.017*	84 (82.2%)	.59

ACPA = anti-cyclic citrullinated peptide antibodies, BMI = body mass index, CRP = C reactive protein, DAS28-ESR = disease activity score including 28 joints and erythrocyte sedimentation rate, ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire, HBP = high blood pressure, IFG = impaired fasting glucose, MetS = metabolic syndrome, MTX = methotrexate, RA = rheumatoid arthritis, RF = rheumatoid factor, T2D = type 2 diabetes, TNFi = tumor necrosis factor inhibitors.

* Indicates statistically significant result.

† Indicates RA patients without T2D and IFG.

‡ Indicates RA patients with T2D.

§ Indicates RA patients with IFG.

Table 3

Univariate regression analyses of predictors of T2D.

	Univariate analyses			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Gender	0.59	0.24–1.42	.24			
Age	1.01	0.99– 1.02	.56			
Smoke	0.71	0.40–1.25	.24			
BMI	1.13	0.83–1.54	.44			
MetS	0.68	0.38–1.24	.21			
HBP	1.86	1.11–3.11	.02*	1.77	1.05–3.05	.033*
Total cholesterol	0.99	0.99–1.00	.32			
Triglycerides	0.99	0.99–1.00	.74			
RA duration	1.09	1.05–1.13	<.001*	1.09	1.02–1.13	<.001*
FR or ACPA positive	0.75	0.43–1.28	.29			
Extra-articular features	1.11	0.55–2.23	.77			
Joint surgery	0.58	0.17–1.94	.37			
Radiographic damage	0.68	0.35–1.32	.26			
DAS28-ESR	0.80	0.62–1.04	.10			
HAQ	0.93	0.61–1.43	.76			
ESR	1.00	0.98–1.02	.97			
CRP	1.01	0.99–1.02	.17			
MTX	1.63	0.72–3.72	.24			
TNFi	1.28	0.77–2.14	.34			
Other biologics	0.40	0.14–1.15	.09			
Corticosteroids	2.77	1.16–6.60	.02*	5.87	1.23–7.33	.015*

ACPA = anti-cyclic citrullinated peptide antibodies, BMI = body mass index, CRP = C reactive protein, DAS28-ESR = disease activity score including 28 joints and erythrocyte sedimentation rate, ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire, HBP = high blood pressure, IFG = impaired fasting glucose, MetS = metabolic syndrome, MTX = methotrexate, RA = rheumatoid arthritis, RF = rheumatoid factor, T2D = type 2 diabetes, TNFi = tumor necrosis factor inhibitors.

* Indicates statistically significant result.

Table 4

Univariate regression analyses of predictors of IFG.

	Univariate analyses			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Gender	0.83	0.43–1.62	.59			
Age	1.04	1.02–1.05	<.001*	1.01	0.99–1.03	.39
Smoke	1.18	0.75– 1.85	.48			
BMI	2.26	1.71–2.97	<.001*	2.36	1.71–3.26	<.001*
MetS	3.54	2.25–5.56	<.001*	1.87	1.03–3.43	.041*
HBP	0.94	0.60–1.45	.79			
Total cholesterol	1.01	1.00–1.01	<.001*	1.01	1.004–1.016	.002*
Triglycerides	1.01	1.00–1.02	.001*	1.002	0.996–1.008	.43
RA duration	1.03	0.99–1.06	.07			
FR or ACPA positive	1.49	0.90–2.46	.12			
Extra-articular features	0.88	0.47–1.64	.69			
Joint surgery	0.35	0.10–1.15	.08			
Radiographic damage	3.90	2.44–6.24	<.001*	3.49	1.97–6.18	<.001*
DAS28-ESR	1.38	1.11–1.71	.004*	1.04	0.79–1.38	.78
HAQ	1.35	0.95–1.90	.09			
ESR	1.02	1.00–1.03	.005*	1.00	0.98–1.02	.98
CRP	1.02	1.00–1.03	.01*	1.02	1.001–1.034	.02*
MTX	1.59	0.80–3.14	.18			
TNFi	1.13	0.73–1.74	.60			
Other biologics	1.42	0.77–2.63	.26			
Corticosteroids	1.16	0.66–2.04	.61			

ACPA = anti-cyclic citrullinated peptide antibodies, BMI = body mass index, CRP = C reactive protein, DAS28-ESR = disease activity score including 28 joints and erythrocyte sedimentation rate, ESR = erythrocyte sedimentation rate, HAQ = health assessment questionnaire, HBP = high blood pressure, IFG = impaired fasting glucose, MetS = metabolic syndrome, MTX = methotrexate, RA = rheumatoid arthritis, RF = rheumatoid factor, T2D = type 2 diabetes, TNFi = Tumor necrosis factor inhibitors.

* Indicates statistically significant result.

3.3. Prevalence and predictors of IFG

Similar to T2D prevalence, we observed an increased presence of IFG in RA patients when compared with age- and gender-matched controls (20.4% vs 12.4%, $P = .001$). Single- and multiple-logistic regression models were performed in order to evaluate the contribution of RA-specific and traditional CV risk factors on the likelihood of having IFG in RA patients (Table 4). The multivariate analysis demonstrated that a higher BMI, the presence of MetS, higher levels of total cholesterol, the presence of radiographic damage, and higher serum levels of CRP were significantly associated with an increased likelihood of showing IFG, in RA patients. Increasing BMI was associated with 2.36-fold higher risk of IFG (OR = 2.36, 95% CI 1.71–3.26, $P < .001$), the presence of MetS with 1.87-fold higher risk (OR = 1.87, 95% CI 1.03–3.43, $P = .041$), and an increase of 1 mg/dL of serum levels of total cholesterol with 1.01-fold higher risk (OR = 1.01, 95% CI 1.004–1.016, $P = .002$). The presence of radiographic damage was associated with 3.49-fold higher risk of showing IFG (OR = 3.49, 95% CI 1.97–6.18, $P < .001$) and an increase of 1 mg/L of serum levels of CRP with 1.02-fold higher risk (OR = 1.02, 95% CI 1.001–1.034, $P = .02$). In this multivariate model, the serum levels of triglycerides, increasing ESR, and disease activity did not seem to be associated with the presence of IFG. The logistic regression model was statistically significant ($\chi^2 = 103.48$, $P < .001$).

4. Discussion

In this cross-sectional study, we observed an increased prevalence of T2D and IFG in an Italian cohort of RA patients when compared with age- and gender-matched control individuals. Interestingly, both RA-related features—disease duration, CCS exposure, and radiographic damage—and traditional CV risk factors, such as HBP and MetS, were significantly associated with glucose metabolism abnormalities.

In our cohort, we observed an increased percentage of RA patients affected by comorbid T2D when compared with controls and with the figures reported for Italian general population (ISTAT, www.istat.it/), confirming what was suggested in a recent meta-analysis.[37] Compared with previously published cohorts, our study has the major advantage of being specifically designed and adequately powered, whereas the results of the currently available literature derive from secondary outcomes and/or poor quality studies.[38,39] For this reason, to our knowledge, our study represents the most accurate estimate of the prevalence of T2D in an Italian RA cohort. The geographic variation of T2D prevalence, indeed, may avoid to generalize data from studies carried out in different countries and national estimates are needed in order to account for genetic, dietary, and lifestyle influences on T2D risk. In our study, the presence of HBP, a longer disease duration, and the exposure to CCS were significant predictors of having T2D. It is already well known that HBP represents an independent risk factor for T2D in the general population.[40] We also observed that a longer disease duration and the exposure to CCS were significantly associated with T2D. Although conflicting results are available in literature concerning the association between disease duration and cardiometabolic comorbidities,[14,15,41] according to our results, RA duration seems to be a strong predictor of T2D. To explain this association, patients with longer RA duration are more likely to have increased cumulative joint damage and functional disability due to longstanding inflammatory process, leading to an increased physical inactivity that, in turn, might exert a detrimental effect on glucose metabolism.[42,43] In addition, longer RA duration may be associated with a sustained exposure to drugs with a well-recognized diabetogenic effect[44] and this is

partially confirmed in our population with the evidence that a large percentage of patients was exposed to CCS, another significant predictor of T2D in our analysis. Conversely, some well-recognized T2D risk factors did not associate with T2D in our cohort. In particular, we did not observe any significant correlation between obesity and T2D in regression analysis; this result, however, must be interpreted in the light of the recent understanding of the impact of RA on body composition that questions the reliability of this measure in describing the cardiometabolic risk in RA setting.[45,46]

In addition, we observed a higher percentage of patients displaying IFG in RA patients when compared with controls, confirming the available literature.[29,47] IFG is a transitional abnormality during the natural history of T2D and may theoretically represent a powerful, inexpensive tool for cardiometabolic risk stratification. In fact, differently from impaired glucose tolerance (IGT), requiring the oral glucose tolerance test (OGTT) to be diagnosed, IFG may be easily identified with a simple FPG measurement.[48,49] However, to date, no study confirmed the predictive role of IFG in RA patients. Furthermore, we observed that a higher BMI, the presence of MetS, as well as a higher serum level of total cholesterol were significantly associated with IFG, confirming the well-known role of traditional CV risk factors in this context. Interestingly, the presence of radiographic damage and a higher serum level of CRP were also significantly associated with an increased likelihood of showing IFG, suggesting a possible concurrent role of the rheumatoid inflammatory process in the pathogenesis of earliest glucose metabolism abnormalities.[42] In fact, several lines of evidence pointed out the link between cardiometabolic comorbidities and RA, and the inflammatory process may modulate the pro-atherogenic metabolic effects observed in RA.[50,51]

Taking together the results of our study, it is possible to demonstrate a subset of RA patients characterized by glucose metabolism derangement that, at least theoretically, may be intercepted by some drugs currently used in RA with preliminary evidence of efficacy in T2D.[52–55] In this setting, targeting RA pathophysiology with molecules whose therapeutic effect may extend beyond the joints inflammation may be an interesting clinical progress in managing RA patients.[56–58]

Despite our study is specifically designed and powered to evaluate the prevalence of T2D, different limitations may be recognized as regularly observed in cross-sectional studies. In addition, it must be pointed out that, given the observational design of our study and the lack of treatment randomization, the possible association between treatments and different outcomes cannot be uniquely ascertained.[59,60] Moreover, we did not perform OGTT, the only procedure recognizing the presence of IGT, and thus we probably misclassified a small subset of IGT patients as normal, relying only on the absence of T2D and IFG. However, OGTT is a complex and time-consuming procedure and may expose the patients to some side events.[61] Another potential limitation of our study is the lack of testing for glutamic acid decarboxylase autoantibodies (GADA), in order to exclude the possible diagnosis of latent autoimmune diabetes in adults (LADA), an immune-mediated form of diabetes similar to T1D but characterized by an onset in adult age (<50 years).[62] Other features of LADA are genetic susceptibility, significant geographic differences in epidemiology, and a decline in its incidence with increasing age.[62] However, an Italian study demonstrated that only a small proportion (~5%) of previously diagnosed T2D patients had GADA positivity.[63] Moreover, this cohort had a mean age of ~55 years, that is significantly lower than ours (mean age of T2D patients in our study: 60 ± 13.5 years). Therefore, we can hypothesize of having misclassified only 3 patients, with a marginal impact on overall study results.

Finally, the control group comprised a large proportion of osteoarthritis and fibromyalgia patients; both of these diseases have been associated with an increased rate of comorbid obesity accounting for the not-statistically significant difference in BMI between patients and controls and the observed prevalence of T2D in control patients that is higher of what expected in the general population. This limitation, however, does not affect significantly the reliability of the estimate in the RA cohort, which remains clearly higher of that expected in unselected Italian adults.

In conclusion, results from our study may introduce a novel hypothesis on the interaction between traditional CV risk factors and inflammatory burden in determining T2D in RA; the former being involved in the earliest phases of glucose metabolism derangement and providing a permissive milieu for subsequent development of T2D following the exposure to the high-grade inflammatory process and to diabetogenic drugs in a "double-hit" fashion. Further studies are still awaited in order to fully clarify the association between RA and cardiometabolic comorbidities and to ascertain the optimal therapeutic strategy for these patients.

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