Occurrence and predictive factors of high blood pressure, type 2 diabetes, and metabolic syndrome in rheumatoid arthritis: findings from a 3-year, multicentre, prospective, observational study

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Abstract

Objective

In rheumatoid arthritis (RA), "traditional" cardiovascular (CV) risk factors continue to be underdiagnosed and undertreated, thus increasing the risk of developing atherosclerosis. In this work, we evaluated the occurrence and predictive factors of "traditional" cardiovascular risk factors, with a focus on high blood pressure (HBP), type 2 diabetes (T2D), and metabolic syndrome (MetS), in participants with RA, in a 3-year, multicentre, prospective, observational study.

Methods

To assess the occurrence and predictive factors of HBP, T2D, and MetS, consecutive participants with RA, admitted to Italian Rheumatology Units, were evaluated in the GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) cohort, a 3-year, multicentre, prospective, observational study.

Results

In the present evaluation, 841 participants, who were fully followed up with 3-year of prospective follow-up were assessed. At the end of follow-up, a significant increased incidence of HBP, T2D, and MetS was recorded. Assessing predictive factors, the mean values of C-reactive protein during the follow-up were independent predictors of occurrence of those comorbidities, whereas participants maintaining remission showed a significant lower risk. Furthermore, therapy with hydroxychloroquine (HCQ) reduced the risk of occurrence of T2D and MetS.

Conclusion

An increased incidence of HBP, T2D, and MetS was observed in assessed participants, prospectively followed-up. Furthermore, the analysis of predictive factors suggested that the rheumatoid pro-inflammatory process could increase the occurrence of these comorbidities. Conversely, metabolic and cardiovascular benefits of maintaining remission as well as of therapy with HCQ were reported.

Key words

rheumatoid arthritis, type 2 diabetes mellitus, hypertension, metabolic syndrome, cardiovascular diseases

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Introduction

Rheumatoid arthritis (RA) is an inflammatory disease which is associated with an increased risk of morbidity and mortality, mainly due to cardiovascular disease (CVD) (1, 2). This typical clinical phenotype is considered the consequence of the interaction between rheumatoid inflammation and increased rate of "traditional" cardiovascular (CV) risk factors (3, 4). In fact, it has been shown that some well-known pathogenic pro-inflammatory RA mediators, including interleukin-1β (IL-1β). IL-6, and tumour necrosis factor (TNF), may play a role in the development of atherosclerosis (5, 6). On the other hand, a large number of RA patients are affected by "traditional" CV risk factors, such as high blood pressure (HBP) and type 2 diabetes (T2D) (7, 8). In addition, although the European League Against Rheumatism (EULAR) provided specific recommendations for the management of CV risk in inflammatory arthritis (9), "traditional" CV risk factors continue to be underdiagnosed and undertreated in RA, thus contributing to the development of CVD (10). The prevalence of HBP and T2D remains high, indicating significant under-diagnosis (7, 8, 11, 12). In fact, the evaluation of "traditional" CV risk factors is still poorly integrated into the management of RA patients, due to a limited awareness of the problem and a lack of specific designed studies. Furthermore, many RA patients with hypertension and T2D do not achieve the treatment goals as defined by therapeutic guidelines (10-12). Moreover, regional differences in "traditional" CV risk factor susceptibility may impair the possibility to generalise results from different geographic areas. Finally, a comprehensive evaluation of these factors in RA could be complex as well as time-consuming and, thus, the identification of biomarkers, accurately reflecting this issue is still awaited (9-13).

In this work, we aimed to evaluate both the occurrence and the predictive factors of "traditional" cardiovascular risk factors, with a focus on HBP, T2D, and metabolic syndrome (MetS), in participants with RA, in a 3-year, multicentre, prospective, observational study.

Methods

Study design

The *Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale* (GIRRCS) cohort of RA, is a 3-year, multicentre, prospective, observational study, in which consecutive participants were assessed, from January 1, 2015 to December 31, 2015. In previous analyses, prevalence and incidence of subclinical and clinical atherosclerosis were assessed (14, 15), whereas in the present evaluation the occurrence and the predictive factors of HBP, T2D, and MetS were further evaluated. In reporting the results, we followed the STROBE guidelines.

The local Ethics Committee (*Comitato Etico Azienda Sanitaria Locale 1 Avezzano/Sulmona/L'Aquila, L'Aquila*, Italy; protocol no. 000331/17) approved the study, which was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki. Informed consent was obtained from each participant for the use of clinical and laboratory data for the purposes of the study.

Participants and settings

All participants, who were included in the GIRRCS cohort, fulfilled the ACR/EULAR criteria for RA, either 1987 and/or 2010 classification criteria (16, 17); whereas those not fulfilling these criteria were not considered in this study. Consecutive participants, meeting these criteria, who attended Rheumatologic Units of GIRRCS from January 1, 2015 to December 31, 2015, throughout Italy, were assessed. The data of the participants were recorded during the scheduled visits, at baseline and after 36 months of prospective follow-up.

Variables to be assessed

The main endpoint of the present evaluation was the occurrence and the predictive factors of traditional cardiovascular risk factors, with a focus on HBP, T2D, and MetS, in participants with RA, at the end of a 3-year prospective follow-up. HPB was defined when participant blood pressure was consistently measured >130 mmHg for systolic and >80 mmHg for diastolic,

or the need for anti-hypertensive drugs (18). Participants were defined as having T2D if fasting plasma glucose ≥126 mg/dL in two different evaluations, or in the presence of classic symptoms of hyperglycaemia or hyperglycaemic crisis with a random plasma glucose 200 mg/dL (11.1 mmol/L), or if anti-diabetic therapies were administered (19). MetS was codified in the presence of any 3 of following 5 risk factors: elevated waist circumference, elevated triglycerides (or drug treatment for elevated triglycerides), reduced HDL cholesterol (or drug treatment for reduced HDL), elevated blood pressure (or anti-hypertensive treatment in a patient with a history of hypertension), elevated fasting glucose (or drug treatment for elevated glucose) (20). Other assessed "traditional" CV risk factors included: gender, age, smoking habit, body mass index (BMI) to evaluate obesity, hypercholesterolaemia defined considering the value of cholesterol and the limit less than 240 mg/dl, and/or therapy with drugs lowering the blood cholesterol levels. Presence of rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA), disease duration, extra-articular features, values of erythrocyte sedimentation rate (ESR, mm/h) and C-reactive protein (CRP), radiographic damage, joint surgery, disease activity and remission were assessed as already performed (14, 15, 21). ESR was included in the assessment of DAS28 in order to maintain the independence of CRP, a well-established CV risk factor in the general population, for the purpose of data analysis. In addition, CRP was estimated as mean value over time during the follow-up (assessing values at baseline, after 12 and 36 months), to avoid the limitation of a single evaluation without considering its possible fluctuations. Participants in remission were defined as those reaching and maintaining after 36 months a value of DAS28-ESR <2.6. The administered therapeutic strategies, including synthetic or biologic DMARDs, glucocorticoids (GCs), were recorded during the follow-up and codified as already performed (14, 15, 22). For those participants, who underwent sequential therapy with synthetic or biologic DMARDs, a category was identified according to a longer exposition.

Data sources, bias and study size

Relevant data were collected at study beginning and reassessed after 36 months, during the scheduled visits for each involved participant by an extensive clinical history. Considering the observational design, it is possible that our study was subjected to a number of biases. We tried to minimise the main methodological problems by a careful definition of each variable to be assessed. Furthermore, participants with significant missing data, which were considered to be meaningful for the analyses, were removed. No specific sample size estimation was provided, since an evaluation was made of consecutive participants with RA, admitted to Italian Rheumatology Units from January 1, 2015 to December 31, 2015, who were assessed and prospectively followed-up.

Statistical methods

Statistics firstly provided descriptive analysis of the collected data, expressed as mean ± standard deviation (SD) or median and range interquartile, according to the distribution. McNemar test was used to compare the rate of HBP, T2D, and MetS between the beginning in 2015 and the end of follow-up in 2018. Incident cases were assessed as incidence proportion and incidence rate per 1000 person-years at risk. Cox regression analyses assessed predictive factors, exploiting the HRs by multivariate models to estimate predictive factors for the occurrence of HBP, T2D, and MetS. In addition to age and gender, in the multivariate models, the variables that resulted statistically in the univariate analyses were added. In the multivariate models assessing predictive factors of MetS, some positive results in univariate analyses were excluded, since these features are included in the definition of such outcome. Two-sided p-values <0.05 were considered statistically significant. The Statistics Package for Social Sciences (SPSS for Windows v. 17.0, SPSS Inc., Chicago, IL, USA) was used for all the analyses.

Results

Participants and descriptive data

In the evaluation of clinical and subclinical atherosclerosis, 841 participants were assessed and followed in a 3-year prospective follow-up (15). The descriptive characteristics of the participants are described elsewhere in more detail (14, 15). Concisely, in the GIRRCS cohort, the participants were mostly female (82.2%), with a median age of 60 years (range 21–90). Concerning RA characteristics, they had a median disease duration of 8.20 years (range 0.1–35), 73.1% displayed a seropositive disease, being positive for RF and/or for ACPA, CRP during the follow-up was 4.31±3.62 mg/L. Remission was reached and maintained by 41.8% of participants during the follow-up. Analysing the therapies, 60.0% were treated with a low dosage of GCs, 85.1% with methotrexate (MTX), 28.5% with hydroxychloroquine (HCQ), and 61.5% with biologic DMARDs, either TNFis 36.6% or non-TNFis 24.9%. Regarding other "traditional" CV risk factors, BMI was 27.01±4.02, 31.6% of the participants reported smoking habit and 32.1% were affected by hypercholesterolaemia. In Table I, other descriptive characteristics are reported according to the achievement and maintenance of remission and to the therapy with HCQ.

Occurrence of HBP and predictive factors

Out of 841 participants with 3 years of follow-up evaluated for clinical and subclinical atherosclerosis, 811 were assessed for HBP; the others were excluded because of the lack of data on that comorbidity. At the end of the 3-year follow-up, 400 out of 811 participants (49.3%) were codified as affected by HBP, an increased rate with respect to the beginning of the study (63 participants *vs*. 337 participants, p<0.0001). Analysing the incident cases of HBP, we estimated an incidence proportion of 45.0% (41.1–48.9) and, considering over 2433 person-years, an incidence rate of 112.6 • 1000 (100.2–125.0) person-years. Excluding participants with baseline evidence of HBP, a logistic multivariate regression model was built to assess the possible predic-

Table I. Descriptive statistics of assessed participants according to the achievement and maintenance of remission and the therapy with HCQ.

Clinical variables						
Participants, n (%)	Remission* 349 (41.8%)	No remission* 487 (58.2%)	*p*-values Remission *vs.* no remission	HCQ** 240 (29.5%)	No HCQ** 573 (70.5%)	*p*-values HCQ *vs.* no HCQ
Demographic characteristics						
Age, mean ± SD	56.1 ± 12.2	60.6 ± 11.5	**0.0001**	58.8 ± 11.0	59.2 ± 12.4	0.709
Female gender, n (%)	303 (86.8%)	388 (79.7%)	0.202	197 (82.1%)	475 (82.9%)	0.780
RA-related features						
RF and/or ACPA, n (%)	265 (75.9%)	350 (71.9%)	0.854	172 (71.7%)	422 (73.6%)	0.360
Disease duration, years, median (IQR)	7.9 (7.8)	8.7 (7.7)	0.123	7.8 (7.3)	8.4 (7.1)	0.291
Extra-articular features, n (%)	62 (17.8%)	76 (15.6%)	0.707	31 (12.9%)	107 (18.7%)	0.065
Radiographic damage, n (%)	125 (35.8%)	258 (52.9%)	**<0.0001**	118 (49.2%)	258 (45.0%)	0.092
Joint surgery, n (%)	40 (11.5%)	61 (12.5%)	0.203	33 (13.7%)	71 (12.4%)	0.328
Maintenance of remission, n (%)	/	/	/	138 (57.5%)	307 (54.6%)	0.061
CRP mg/L, mean ± SD	5.49 ± 4.23	7.68 ± 4.68	0.448	4.5 ± 2.7	4.1 ± 2.4	0.443
"Traditional" CV risk factors						
BMI, mean ± SD	27.50 ± 3.73	27.01 ± 4.02	0.195	26.7 ± 3.9	27.3 ± 4.1	0.074
High cholesterol, n (%)	101 (28.9%)	155 (31.8%)	0.349	79 (32.9%)	210 (36.6%)	0.429
Smoking habit, n (%)	117 (33.5%)	147 (30.2%)	0.414	88 (36.7%)	174 (30.4%)	0.186
HBP first observation, n (%)	31 (8.9%)	32 (6.5%)	0.334	30 (12.5%)	33 (5.7%)	0.061
HBP 36 months, n (%)	160 (45.8%)	240 (49.2%)	0.432	101 (42.1%)	299 (52.2%)	**0.006**
T2D first observation, n (%)	11 (3.1%)	9 (1.8%)	0.980	10 (4.2%)	11 (1.9%)	0.321
T2D 36 months, n (%)	34 (9.7%)	64 (13.1%)	0.601	18 (7.5%)	80 (13.9%)	**0.005**
MetS first observation, n (%)	25 (7.2%)	26 (5.3%)	0.089	21 (8.7%)	30 (5.2%)	0.243
MetS 36 months, n (%)	74 (21.2%)	106 (21.7%)	0.078	26 (10.8%)	154 (26.9%)	**<0.0001**
RA therapies						
GCs low dosage, n (%)	240 (68.7%)	264 (54.2%)	**<0.0001**	165 (68.7%)	378 (65.9%)	0.256
MTX, n (%)	316 (90.5%)	399 (81.9%)	0.107	190 (79.2%)	507 (88.5%)	**0.001**
HCQ, n (%)	95 (27.2%)	136 (27.9%)	0.981	/	/	/
Biologic DMARDs, n (%)	195 (55.9%)	322 (66.1%)	**<0.0001**	129 (53.7%)	357 (62.3%)	**0.014**
TNFi, n (%)	120 (34.4%)	188 (38.6%)	0.059	67 (27.9%)	230 (40.1%)	**0.001**
Non TNFi, n (%)	72 (20.6%)	137 (28.1%)	**0.001**	68 (28.3%)	131 (22.9%)	0.062

RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: Anti-citrullinated protein antibodies; CRP: mean values of C-reactive protein during the follow-up; SD: standard deviation; CV: cardiovascular; BMI: mean body mass index during the follow-up; MetS: metabolic syndrome; HBP: high blood pressure; T2D: type 2 diabetes; GCs: glucocorticoids; MTX: methotrexate; HCQ: hydroxychloroquine; TNFi: tumour necrosis factor inhibitor.
*calculated on 836 participants according to data availability. **calculated on 813 participants according to data availability.

tive role of selected variables (age, male gender, CRP, obesity, hypercholesterolaemia, T2D, HCQ) on the likelihood of HBP occurrence, after 36 months, as shown in Table II. Participants with higher mean values of CRP during the follow-up (H=1.09, 95%CI=1.04–1.14, $p<0.0001$) were significantly associated with a higher risk of that comorbidity. Participants with T2D (HR=1.43, 95%CI=1.08–1.89, $p=0.011$) and with hypercholesterolaemia (HR=1.67, 95%CI=1.33–2.08, $p<0.0001$) also showed a significant higher risk of HBP occurrence.

Occurrence of T2D and predictive factors

Out of 841 with 3 years of follow-up evaluated for clinical and subclinical atherosclerosis, 811 participants were assessed for T2D; the others were excluded because of the lack of data on that comorbidity. At the end of 3-year follow-up, 98 out of 811 participants (12.1%) were classified as affected by T2D, an increased rate than the beginning of the study (20 participants *vs.* 78 participants, $p<0.0001$). Analysing the incident cases of T2D, we estimated an incidence proportion of 9.9% (7.0–10.9) and, considering over 2433 person-years, an incidence rate of 23.8 • 1000 (17.8–29.8) person-years. Excluding participants with baseline evidence of T2D, a logistic regression model was built to assess possible predictive role of selected variables (age, male gender, CRP, hypercholesterolaemia, HBP, HCQ) on the likelihood of T2D occurrence, after 36 months as shown in Table III. Participants with HBP (HR=2.94, 95%CI=1.67–5.20, $p<0.0001$) showed a significantly higher risk of T2D occurrence. Conversely, the achievement and maintenance of remission during the follow-up reduced the risk of T2D occurrence (HR=0.61, 95%CI=0.37–0.92, $p=0.046$). Finally, participants who were treated with HCQ (HR=0.54, 95%CI=0.29–0.92, $p=0.048$) showed a significantly lower risk of T2D.

Occurrence of MetS and predictive factors

Out of 841 with 3 years of follow-up evaluated for clinical and subclinical atherosclerosis, 807 participants were assessed for MetS; the others were

Table II. Cox regression analyses assessing predictive factors of HBP.

Clinical variables	HR	95%CI	*p*-value
Univariate analyses			
Age	1.01	0.97 – 1.05	0.250
Male Gender	0.97	0.74 – 1.26	0.820
RF	1.31	0.82 – 1.29	0.789
ACPA	0.84	0.68 – 1.06	0.086
Disease duration	1.01	0.99 – 1.03	0.141
Extra-articular features	1.07	0.82 – 1.38	0.638
Radiographic damage	1.08	0.89 – 1.33	0.411
Joint surgery	1.16	0.87 – 1.55	0.309
Maintenance of remission	1.02	0.82 – 1.27	0.858
CRP	1.02	1.01 – 1.03	**<0.0001**
Obesity	1.04	1.01 – 1.06	**0.003**
Hypercholesterolaemia	1.85	1.51 – 2.27	**<0.0001**
Smoking habit	1.05	0.86 – 1.29	0.596
T2D	1.72	1.33 – 2.21	**<0.0001**
GCs low dosage	1.05	0.84 – 1.30	0.684
MTX	1.09	0.82 – 1.45	0.556
HCQ	0.79	0.62 – 0.92	**0.048**
TNFi	1.02	0.83 – 1.25	0.846
Non-TNFi	0.42	0.66 – 1.07	0.158
Multivariate analysis			
Age	1.03	0.99 – 1.09	0.989
Male gender	0.90	0.66 – 1.22	0.500
CRP	1.03	1.01 – 1.07	**0.004**
Obesity	1.02	0.99 – 1.04	0.089
Hypercholesterolaemia	1.67	1.33 – 2.08	**<0.0001**
T2D	1.43	1.08 – 1.89	**0.011**
HCQ	0.82	0.64 – 1.07	0.828

RF: rheumatoid factor; ACPA: Anti-citrullinated protein antibodies; CRP: mean values of C-reactive protein during the follow-up; BMI: mean body mass index during the follow-up; HBP: high blood pressure; T2D: type 2 diabetes; GCs: corticosteroids; MTX: methotrexate; HCQ: hydroxychloroquine; TNFi: tumour necrosis factor inhibitor. Bolded values are statistically significant ($p<0.05$).

excluded because of the lack of data on that comorbidity. At the end of the 3-year follow-up, 180 out of 807 participants (22.3%) were categorised as affected by MetS, an increased rate when compared with the beginning of the study (51 participants vs 129 participants, $p<0.0001$). Analysing the incident cases of MetS, we estimated an incidence proportion of 17.1% (15.1–19.1) and, considering over 2421 person-years, an incidence rate of 32.2 • 1000 (25.2–39.2) person-years. Excluding participants with baseline evidence of MetS, a logistic regression model was built to assess the possible predictive role of selected variables (age, male gender, remission, CRP, HCQ) on the likelihood of MetS occurrence, after 36 months, as shown in Table IV. The achievement and maintenance of remission during the follow-up reduced the risk of T2D occurrence (HR=0.75, 95%CI=0.51–0.95, $p=0.046$). Finally, participants who were treated with HCQ (HR=0.43, 95%CI=0.27–0.67, $p<0.0001$) showed a significantly lower risk of MetS.

Discussion

In this 3-year, multicentre, prospective study, an increased incidence of HBP, T2D, and MetS has been reported in participants with RA. Furthermore, the analysis of predictive factors suggested that the rheumatoid pro-inflammatory process could increase the occurrence of these comorbidities, whereas the maintenance of remission as well as therapy with HCQ could reduce this risk. All these findings suggest the importance of assessing "traditional" CV risk factors, since their increased incidence may contribute to an increased risk of developing atherosclerosis in RA (23, 24).

During the follow-up, a large percentage of participants (about 45%) developed HBP, highlighting the relevance of this feature in the disease, which is a well-known predictor of CVD in RA (25). Interestingly, participants with higher mean values of CRP over time showed a higher risk of HBP. In fact, a growing body of evidence suggests that chronic inflammation and immune-mediated mechanisms may affect blood-pressure control during rheumatic diseases (26), modulating the expression and activity of sodium transporters along the nephrons, the bioavailability of nitric oxide, and the activity of the renin-angiotensin system (27, 28). In addition, it has been shown that the inhibition of inflammatory cytokines could also improve the vascular function in RA (29, 30). Analysing further predictive factors of HBP in this cohort, we found that participants with T2D and hypercholesterolaemia showed an increased risk of HBP. Several mechanisms have been proposed, such as renin-angiotensin-aldosterone system, oxidative stress, endothelial dysfunction, and aberrant production of endothelin-1, to unmask the relationship between these comorbidities, considered as being mutually interdependent and related to an accelerated atherosclerosis (31-34).

In the present cohort, an increased occurrence of T2D, about 12% of participants, was observed at the end of follow-up. Analysing predictive factors of T2D, higher levels of CRP over time increased the risk of T2D whereas the achievement of remission reduced this risk, suggesting a relationship between the inflammatory process and glucose derangement (35, 36). Multiple lines of evidence have recently suggested that IL-1β, IL-6, and TNF, which are involved in the pathogenesis of RA, may also play a pivotal role in the development of insulin resistance and T2D (37). In fact, inflammatory cytokines have shown to be cytotoxic to pancreatic β-cells, inducing both apoptotic and necrotic β-cell death (37). In addition, targeting inflammatory cytokines has shown to improve glucose abnormalities in RA, suggesting the pathogenic relevance of these mediators (38-40). In this cohort, participants with HBP showed a higher risk of T2D. The presence of HBP is a well-established risk factor for T2D in the gen-

Table III. Cox regression analyses assessing predictive factors of T2D.

Clinical variables	HR	95%CI	*p*-value
Univariate analyses			
Age	1.01	0.98 – 1.02	0.565
Male Gender	0.90	0.53 – 1.54	0.904
RF	0.99	0.64 – 1.54	0.981
ACPA	0.87	0.58 – 1.31	0.508
Disease duration	1.01	0.98 – 1.04	0.255
Extra-articular features	1.22	0.74 – 2.02	0.428
Radiographic damage	1.19	0.85 – 1.93	0.225
Joint surgery	1.07	0.60 – 1.92	0.811
Maintenance of remission	0.69	0.44 – 0.93	**0.046**
CRP	1.02	1.01 – 1.07	**0.003**
Obesity	1.04	0.99 – 1.09	0.083
Hypercholesterolaemia	1.93	1.28 – 2.89	**0.001**
Smoking habit	0.99	0.66 – 1.49	0.980
HBP	3.37	2.13 – 5.34	**<0.0001**
GCs low dosage	1.08	0.69 – 1.68	0.725
MTX	0.98	0.56 – 1.70	0.946
HCQ	0.50	0.29 – 0.85	**0.011**
TNFi	0.95	0.62 – 1.44	0.813
Non-TNFi	0.87	0.54 – 1.40	0.569
Multivariate analysis			
Age	0.99	0.97 – 1.01	0.950
Male gender	0.98	0.53 – 1.82	0.889
CRP	1.01	0.99 – 1.03	0.141
Hypercholesterolaemia	2.13	0.80 – 2.08	0.292
HBP	2.94	1.67 – 5.20	**<0.0001**
Maintenance of remission	0.61	0.37 – 0.92	**0.046**
HCQ	0.54	0.29 – 0.92	**0.048**

RF: rheumatoid factor; ACPA: Anti-citrullinated protein antibodies; CRP: mean values of C reactive protein during the follow-up; BMI: mean body mass index during the follow-up; HBP: high blood pressure; T2D: type 2 diabetes; GCs: corticosteroids; MTX: methotrexate; HCQ: hydroxychloroquine; TNFi: tumour necrosis factor inhibitor. Bolded values are statistically significant ($p<0.05$).

eral population independently of the drugs used to decrease the blood pressure (31-34). Moreover, participants treated with HCQ showed a lower risk of developing T2D. Through an improvement of insulin secretion and peripheral insulin sensitivity, HCQ may benefit the metabolic profile of patients with RA, thus reducing the occurrence of this comorbidity (41-43). Recently, five subgroups of diabetic patients with different long-term outcome and risk of complications were proposed by data-driven cluster analysis, considering glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and homoeostatic model assessment 2 estimates of β-cell function and insulin resistance (44). Based on that intriguing hypothesis, further studies are warranted to elucidate if the occurrence of diabetes in RA could specifically meet one of these subsets to better manage these patients.

An increased rate of participants at the end of follow-up were codified as having MetS. In fact, it is well-know that RA is associated with most components of the MetS, including body weight changes, quantitative and qualitative dyslipidaemia, and insulin resistance (45). Interestingly, participants, who achieved and maintained remission, showed a lower risk of MetS, highlighting that remission ought to be considered the pivotal goal for CV risk management in patients with RA (46-48). As observed for T2D, participants treated with HCQ also showed a lower risk of MetS, pointing out the metabolic and cardiovascular benefits of this drug in managing RA (49-51).

In our study, therapy with GCs did not seem to predict the occurrence of either HBP, T2D, or MetS. Unlike the general population, the finding of incident "traditional" CV factors and CVD in patients with RA, who are exposed to GCs, may be strongly confounded by indication due to high disease activity (52, 53). In fact, adverse CV effects of GCs might be balanced by positive effects on controlling the inflammatory burden (54, 55). Indeed, it has been suggested that the initiation of anti-rheumatic drugs, counteracting the rheumatoid process, may reduce the CV burden in RA (56, 57). The benefits of HCQ, which we observed, could also be related to the combination of this drug with other synthetic DMARDs, including MTX and biologic DMARDs.

Despite providing a prospective evaluation of "traditional" CV risk factors in RA, this study is affected by different limitations due to the observational design, limiting the generalisation of the results and the external validity. Considering the more pronounced presence of female and of elderly participants in our cohort, our results should be cautiously generalised to the whole population with RA, suggesting the need for specific studies to evaluate the CV burden in male gender as well as in younger ages. The lack of a control group prevented us from quantifying the relative risk of occurrence of HBP, T2D, and MetS when compared with matched healthy controls, thus suggesting a prudent interpretation of our findings. Furthermore, the original study design did not allow us to fully ascertain the role of therapeutic strategies on the development of those comorbidities, since the therapies were not systematically administered and the choice of medications was left to the physicians. On these bases, our results should be moderated by the possibility of confounding bias. Because of its moderate efficacy in RA, HCQ might be more likely prescribed to patients with RA with mild disease than to patients with RA with more severe disease characterised by a high risk for CVD. Consequently, the lower CV risk recording for the participants treated with HCQ could also be related to the characteristics of these patients. Furthermore, HCQ was often combined with other synthetic DMARDs, thus drawing firm conclusions on HCQ could be difficult. Taking together all these observations, specific designed studies are certainly needed to fully clarify these issues in RA.

In conclusion, an increased incidence of HBP, T2D, and MetS was observed

Table IV. Cox regression analyses assessing predictive factors of MetS.

Clinical variables	HR	95%CI	*p*-value
Univariate analyses			
Age	0.99	0.98 – 1.01	0.704
Male gender	1.36	0.97 – 1.97	0.075
RF	1.24	0.88 – 1.73	0.210
ACPA	1.05	0.77 – 1.41	0.766
Disease duration	1.01	0.98 – 1.02	0.619
Extra-articular features	1.25	0.87 – 1.79	0.227
Radiographic damage	0.77	0.58 – 1.04	0.091
Joint surgery	1.23	0.82 – 1.84	0.314
Maintenance of remission	0.65	0.46 – 0.91	**0.013**
CRP	1.02	1.01 – 1.03	**0.005**
Obesity	1.13	1.03 – 1.20	**<0.0001**
Hypercholesterolaemia	2.84	2.09 – 3.86	**<0.0001**
Smoking habit	1.10	0.83 – 1.46	0.497
HBP	5.95	4.01 – 8.84	**<0.0001**
T2D	2.80	2.03 – 3.86	**<0.0001**
GCs low dosage	1.87	0.97 – 3.56	0.059
MTX	1.10	0.73 – 1.67	0.638
HCQ	0.45	0.30 – 0.67	**<0.0001**
TNFi	1.04	0.77 – 1.39	0.795
Non-TNFi	0.86	0.40 – 1.04	0.062
Multivariate analysis			
Age	0.99	0.98 – 1.01	0.821
Male gender	1.34	0.93 – 1.94	0.114
Maintenance of remission	0.75	0.51 – 0.95	**0.046**
CRP	1.01	0.99 – 1.03	0.073
HCQ	0.43	0.27 – 0.67	**<0.0001**

RF: rheumatoid factor; ACPA: Anti-citrullinated protein antibodies; CRP: mean values of C-reactive protein during the follow-up; BMI: mean body mass index during the follow-up; HBP: high blood pressure; T2D: type 2 diabetes; GCs: corticosteroids; MTX: methotrexate; HCQ: hydroxychloroquine; TNFi: tumour necrosis factor inhibitor. Bolded values are statistically significant ($p<0.05$).

in the assessed participants, prospectively followed-up. Furthermore, the analysis of predictive factors suggested that the rheumatoid pro-inflammatory process could increase the occurrence of these comorbidities. Conversely, our prospective follow-up pointed out metabolic and cardiovascular benefits of maintaining remission as well as therapy with HCQ. Taken together, these findings suggest the importance of assessing "traditional" CV risk factors, since the increased incidence of those comorbidities may increase risk of atherosclerotic disease in RA.

Finally, a multi-expertise management of RA could be desirable, since it would counteract the synergy between the systemic inflammatory process and the "traditional" CV risk factors in reducing the CV burden and, thus, improve the long-term outcome of patients with RA.

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