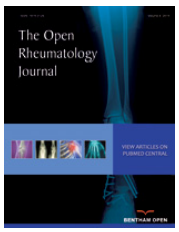

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SYSTEMATIC REVIEW

# Association between Diabetes and Rheumatoid Arthritis: A Systematic Literature Review

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**Abstract:**

***Objective:***

To examine the risk of diabetes mellitus (DM) in patients with rheumatoid arthritis (RA) and whether the risk is related to conventional risk factors, RA disease activity, and treatment.

***Methods:***

A systematic literature review (SLR) query was conducted using specified MeSH terms, searching PubMed and EMBASE databases from inception to March 2020. Both cohort or case-control design studies assessing the incidence or prevalence of DM in RA patients were included.

***Results:***

Of the 1948 articles, 43 peer-reviewed observational studies were selected. A high degree of heterogeneity in study design and reporting was observed, precluding final conclusions.

Based on the studies included, it was observed that DM prevalence ranged between 1% and 20% in RA patients, which was similar to controls (1–29%). The cumulative incidence of DM in RA patients ranged between 1.3% and 11.7% over different time frames. DM incidence rates in patients with RA per 1000 person-years ranged from 5.2 to 16.7.

RA patients may be at higher risk of DM, particularly among those receiving glucocorticoids (GC), while patients on hydroxychloroquine and biological disease-modifying anti-rheumatic treatments (DMARDs) may be at lower risk.

***Conclusion:***

DM incidence may be increased in patients with RA as a result of more concomitant traditional risk factors and GC exposure. It is unclear whether biologics may have a true protective effect or provide a GC-sparing effect. High-quality studies in large cohorts of RA patients with appropriate adjustment for covariates are warranted to fully investigate the interplay between DM and RA.

**Keywords:** Rheumatoid arthritis, Risk factors, Diabetes mellitus, Comorbidity, Hyperglycemia, Treatment, Systematic review.

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|---|---|---|---|

## 1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disease affecting 0.5–1% of the general adult population, causing joint damage, pain and disability [1, 2]. While the complete aetiology of RA remains unelucidated, it includes a complex interplay between genetic, epigenetic, and environmental risk factors [3, 4]. In addition to persistent joint inflammation, RA patients may also have extra-articular morbidities [4], namely cardiovascular (CV) with related risk factors such as diabetes mellitus (DM), dyslipidaemia, obesity and hypertension [5, 6] all of which can impact long term mortality.

Biological disease-modifying antirheumatic drugs

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(DMARDs) are a cornerstone in the improved management of RA in the past decade, particularly with the introduction of the 'treat-to-target' approach around 2010 [7]. The CV mortality in RA patients remains higher than that of the general population [8, 9].

It is thought that in addition to traditional CV risk factors, RA-specific risk factors and RA treatment might impact CV morbidities in patients with RA [10]. Research in this field aims to reduce health burdens, improve quality of life, and extend life expectancy [8, 9, 11]. In this study, we undertook a systematic literature review (SLR) to examine the evidence on DM prevalence and incidence among RA patients, related risk factors, and the potential impact of RA treatment.

Objectives: This study sets out to examine whether:

- DM is more common in patients with RA compared with the general population
- Conventional risk factors of DM are more common in RA patients than in the general population
- RA treatment impacts the risk of DM

## 2. METHODS

### 2.1. Search Strategy

EMBASE and Medline (PubMed) electronic bibliographic databases were searched using the terms shown in appendices 1 and 2, restricting results to articles published before 12 March 2020 that were written in English. A manual search of the reference lists of articles selected in database searches was also performed to identify other relevant studies.

Peer-reviewed articles were assessed for their relevance to the study objectives using the 'PICO' criteria: Population or problems; Interventions or exposures; Comparisons; Outcomes. Articles were considered eligible:

- The exposure of interest was RA, which was defined by the American College of Rheumatology (ACR) 1987/2010 ACR/EULAR criteria or using diagnosis codes, such as ICD-9/10 definitions
- The primary outcome for selected studies reported DM prevalence/incidence and DM risk factors. DM was defined using the World Health Organization 1998 diagnostic criteria, with 2 determinations of fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2-h plasma glucose ≥200 mg/dL (11.1mmol/L), diagnosis code, self-report, and/or hypoglycaemic medication use.
- The study design was observational, with a case-control or cohort design

Conventional risk factors for DM including age, body mass index (BMI), gender, ethnicity, smoking, alcohol consumption, hypertension, family history, and dyslipidaemia were extracted whenever reported. RA-specific factors were also assessed, including RA duration and treatment with glucocorticoid (GC) and DMARD therapies.

Studies that were randomised controlled trials, congress abstracts, letters, reviews, or case reports were considered ineligible, as were studies not meeting the PICO criteria. Those that exclusively investigated type 1 DM were also excluded. Furthermore, to avoid redundancy, if data were presented in >1 presentation, the most recent or full peer-reviewed publication was selected.

### 2.2. Study Screening and Extraction

Full study selection was performed independently by 2 investigators and discrepancies were resolved by consensus. The following data were extracted from each eligible study:

1. Publication details: Authors, study type, participants, and country in which the study was conducted.

2. Participant details: number of exposed patients and control subjects, eligibility criteria, average disease duration and RA therapy.

3. Prevalence/incidence of DM and DM risk factors (dyslipidaemia, BMI, hypertension, ethnicity/ ethnic origin, smoking, alcohol consumption, familial history of DM/metabolic syndrome)

The included studies were observational in design, hence, the quality of the included studies was assessed based on the Newcastle-Ottawa Scale (NOS), as described in the method: "A Newcastle Ottawa Score quality assessment was performed for each study to grade the level of evidence in the reported outcomes". The NOS uses a rating system to judge the quality (0 -9 stars). Studies scoring 5 stars or greater were considered of sufficient quality.

The statistical analysis was descriptive in light of significant heterogeneity in the study characteristics. A Newcastle Ottawa Score quality assessment was performed for each study to grade the level of evidence in reported outcomes. Studies were also analyzed as pre-and post 2010 to search for the potential effects of the 'treat-to-target' treatment paradigm that was recommended in 2010 [7] on DM prevalence and incidence.

The study protocol was prospectively registered on PROSPERO (Jad Okaris, Eduardo Mysler, Fouad Fayad, Rafic Baddoura, Krystel Aouad, Ouidade Aitisha. Association between diabetes and rheumatoid arthritis: a systematic review. PROSPERO 2021 CRD42021164424 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021164424) and was assigned the identification number 164424.

## 3. RESULTS

### 3.1. PRISMA Study Flow

From the 1948 citations identified in the searches, 37 studies that evaluated DM incidence or prevalence in RA patients were included in the SLR and 6 were manually identified from the reference lists (Fig. **1**) [12 - 54].

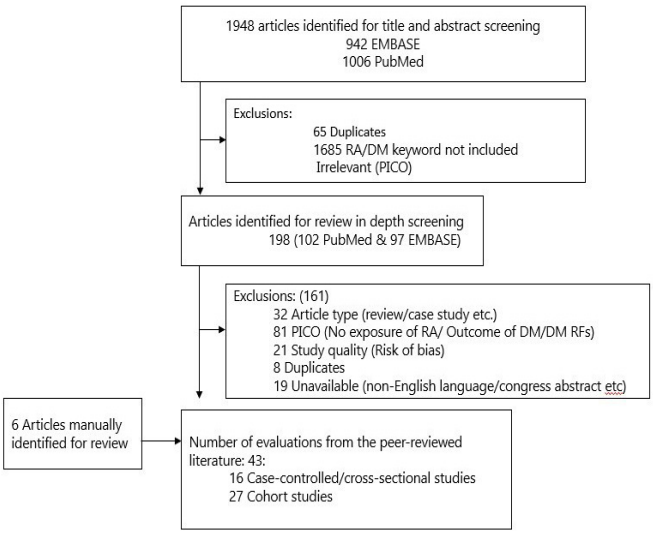


**Fig. (1).** PRISMA diagram illustrating the selection and disposition of studies. A total of 1948 relevant studies were identified during the initial search and 43 studies remained after selective screening (27 cohort and 16 case-control studies). DM, diabetes mellitus; PICO, Population or problem, Intervention or exposure, Comparison, Outcome; RA, rheumatoid arthritis; RF, rheumatoid factor.

The studies identified were conducted in Europe (Austria, UK, Italy and Netherlands), North and South America (USA and Brazil), Asia (Taiwan, India and Japan), Australia and South Africa; and publication dates ranged from 2002 to 2018. Studies adopted both cohort (n=27) and case-control/cross-sectional (n=16) designs.

### 3.2. Prevalence of DM in RA Patients

Fifteen case-control or cross-sectional studies and a single cohort study [12, 19, 21, 22, 26, 28, 29, 32, 33, 36, 40, 43, 45, 47, 48, 51] reported prevalence rates in RA versus non-RA patients (Table **1**). Studies were then arranged by year of the publication into pre and post 2010.

**Table 1. Diabetes mellitus prevalence and incidence.**

| **Diabetes Mellitus Prevalence in RA *versus* Non-RA Control Subjects** | | | | | | |
|---|---|---|---|---|---|---|
| **Study and Country** | **Population RA /Non-RA) (n/n)** | **Mean Disease Duration** | **Mean/ Median RA Age** | **%DM among RA/Controls** | **RR/OR And other Key Findings** | **Nos Score** |
| **Studies Post 2010** | | | | | | |
| Agarwal (2013) [12] India | 56/31 normal controls | NR | Median, 50.4 | 17.9/19.4 | • Prevalence of T2D and HTN and hyperlipidaemia were not significantly different between RA and non-RA<br>• BMI and LDL were significantly elevated in RA (P<0.05) | 5 |
| Chung (2012) [21] USA | 197/274 frequency matched controls | NR | 59.4±8.7 | 7.0/9.0 | • Odds ratio (OR) of T2D (unadjusted OR 1.0 [0.95–1.05] and adjusted OR 0.99 [0.93–1.05])<br>• RA disease duration was not associated with increased odds of T2DM<br>• There were no statistically significant differences in the frequency of T2D in patients with RA *vs* non-RA<br>• Rates of newly identified T2D was similar between RA *vs* non-RA<br>• HTN was more prevalent in the RA group (57%) than in non-RA (42%, P=0.001) | 6 |
| Dregan (2017) [26] UK | 5764[†]/ 483,559 | NR | 46, SD 14 | 6.0/4.0 | • There was an increased risk of cardiometabolic events within inflammatory disorders *vs* those without | 5 |
| Emamifar (2017) [28] Denmark | 439[‡]/NR Data from general population from Statens Serum Institut | (2.6±1.7 years) Danish Danbio registry (2.6+/-1.7 years) | 64.6±15.0 | 11.8/0.0 | • RR of T2D= 2.21 [1.40–3.42], P<0.001<br>• Prevalence T2D 52/439 (11.8%)<br>• Most of the patients with RA and T2D were diagnosed with T2D before their diagnosis of RA<br>• Prevalence of T2D in newly diagnosed RA patients was greater than the general population)<br>• Prevalence in Danish populations 5.7% *vs* DM in RA patients 12.9% (8.8% T2D) | 6 |

*(Table 1) contd.....*

| **Diabetes Mellitus Prevalence in RA *versus* Non-RA Control Subjects** | | | | | | |
|---|---|---|---|---|---|---|
| **Study and Country** | **Population RA /Non-RA) (n/n)** | **Mean Disease Duration** | **Mean/ Median RA Age** | **%DM among RA/Controls** | **RR/OR And other Key Findings** | **Nos Score** |
| Gomes (2018) [29] Brazil | 338‡/84 age and gender matched controls | (12.2±8.7 years) | 53.5±12.0 *vs* 50.3±12.3 | 18.8/6.2 | • Prevalence of T2D was higher in RA patients (18.0% *vs* 6.2%; P=0.008), as was HTN (46.7% *vs* 23.5%; P<0.001), BMI (27.4±4.8 kg/m$^2$*vs* 25.9±3.7 kg/m$^2$; P=0.011) and WC (93.7±12.4 cm *vs* 87.1±10.1 cm; P<0.001)<br>• Smoking was more frequent in the control group (5.6% *vs* 13.4%; P=0.014)<br>• The prevalence of MetS was 51.3% in RA patients and 21.8% in non-RA (P<0.001)<br>• In the independent association analysis only age, dyslipidemia, sedentary lifestyle, BMI and DAS28 were significantly associated with MetS in RA pts<br>• RA patients with MetS were significantly older, and had significantly higher frequencies of HTN, T2D, BMI, WC and fasting glucose (P<0.001) | 5 |
| Hoes (2011) [33] Netherlands | 140/50 controls with normal glucose tolerance and without first-degree relatives with T2D | (13±8 years) RA with disease duration of >2 years | 59±12 *vs* 56±8 | | • T2D was comparable between the 2 RA groups (RA-GC 9% *vs* RA+GC 14%, P=0.3).<br>• If those patients with RA who were excluded because of known T2D would have been included, then prevalence would have been 19% (RA-GC 18% *vs* RA+GC 21%, P=0.9)<br>• Prednisolone dose was associated with T2D in univariate analysis, this was sustained after adjusting for disease activity and patient characteristics | 5 |
| Pieringer (2012) [43] Austria | 203/208 sex matched controls | (12.8±9.3 years) | 56.3±12.2 | 3.4/29.0 | • DM% RA *vs* non-RA: 3.4 *vs* 29.0 (P<0.001)<br>• The augmentation index is increased in RA patients regardless of the coexistence of traditional CV risk factors (P<0.001) | 6 |
| Ruscitti (2017) [45] Italy | 500‡†/500, age, gender matched. This population comprised a mixed pool of fibromyalgia or other forms of functional widespread pain (n=84), osteoarthritis (n=227), and other noninflammatory musculoskeletal conditions (n=189) | (10.1±7.1 years) | 59.3±13.6 | 13.6/8.4 | • **T2D% RA *vs* non-RA (P=0.01)**<br>• Presence of HBP, longer disease duration, and treatment with CCS were significantly associated with an increased likelihood of being diagnosed with T2D in RA patients<br>• HBP was associated with 1.77-fold higher risk of having T2D OR=1.77, 95% CI 1.05–3.05, P=0.033<br>• 1-year increase of disease duration associated with 1.09-fold higher risk of having T2D OR=1.09, 95% CI:1.02–1.13, P<0.001<br>• Exposure to CCS was associated with 5.87-fold higher risk of having T2D OR=5.87, 95% CI 1.23–7.33, P=0.015<br>• The logistic regression model was statistically significant ($\chi^2$=36.08, P<0.001) | 7 |
| Sakai (2016) [47] Japan | 2,762§/27,620 age and sex matched controls | NR | Median, 51.0 | See key findings | • **OR for DM=2.54 (2.13–3.02)**<br>• DM prevalence per 100 patient-years (95% CI): 6.05 (5.22–7.00) for RA *vs* 2.47 (2.30–2.66)<br>• ORs for cerebral infarction (in RA *vs* non-RA) were significantly elevated after adjusting for T2D (P=0.024 for IHD and P<0.001<br>• Prevalence of comorbidities, including DM, was much higher in RA cohort *vs* the control cohort | 7 |
| Ursini (2016) [51] Italy | 100‡/100 age and sex matched controls, with osteoarthritis or fibromyalgia | (32.9±24.7 months) | 56.6±11.3 | 10.0/2.0 | • The prevalence of T2D was significantly higher in RA patients (P=0.02)<br>• 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 booth associated with a diagnosis of T2D or pre-diabetes<br>• Data suggest an elevated prevalence of undiagnosed T2D in RA patients and higher 1- and 2-hour post-load glucose levels | 8 |
| **Studies pre 2010** | | | | | | |

*(Table 1) contd.....*

| **Diabetes Mellitus Prevalence in RA *versus* Non-RA Control Subjects** | | | | | | |
|---|---|---|---|---|---|---|
| **Study and Country** | **Population RA /Non-RA) (n/n)** | **Mean Disease Duration** | **Mean/ Median RA Age** | **%DM among RA/Controls** | **RR/OR And other Key Findings** | **Nos Score** |
| Brady (2009) [19] Australia | 50[†]/150 age and sex matched controls, referred for CV risk assessment | NR | 64.9 | 8.0/7.14 | • Difference between T2D and SBP was nonsignificant between RA and non-RA<br>• RA subjects were more likely to smoke (P<0.001), be physically inactive (P=0.006), and have higher mean measurements of BMI (P=0.040) and WC (P=0.049)<br>• RA patients exhibited a significantly greater absolute risk of CVD (P=0.005) | 7 |
| del Rincon 2005 [22] USA | 234[†]/102 | NR | 59 (range, 40–84) | 17.0/1.0 | • T2D% RA *vs* non-RA (P≤0.001)<br>• BMI RA *vs* non-RA 28.2 *vs* 25.8 (P≤0.001) | 5 |
| Han (2006) [32] USA | 28,208[§]/112,832 age, sex, and location matched controls | NR | 51.9 | 10.4/7.6 | • RR of T2DM=1.4, 95% CI 1.3–1.4, P<0.01<br>• RA patients had increased risk for CVD than non-RA (IHD RR=1.5, 95% CI 1.4–1.6, P<0.01; atherosclerosis RR=1.9, 95% CI 1.7–2.1, P<0.01; CHF RR=2.0, 95% CI 1.9–2.2, P<0.01; PVD RR=2.4, 95% CI 2.3–2.6, P<0.01; CVD RR=1.6, 95% CI 1.5–1.8, P<0.01) | 4 |
| Jonsson (2001) [36] Sweden | 39 (RA patients registered at Rheumatology Department of 1974–1979)/ 39 control subjects selected at random from the population register | 19–23 year disease duration | 51.6 | 1.9/0 | • T2D% RA *vs* non-RA: absolute prevalence, definition not described<br>• T2D prevalence was higher in RA patients 1 (2.6%) and was not present in non-RA | 5 |
| McEntegart (2001) [40] UK | 76[†]/641 | (12.5 years) | 57 | 1.0/3.0 | • T2D% was NS after adjusting for age, sex and smoking status | 6 |
| Simard (2007) [48] USA | 144[‡]/5152 | NR | 72.9±8.4 | 16.0/17.0 | • OR of DM=1.3, 95% CI 0.68–2.30, P=0.46<br>• There was no statistically significant association between prevalent RA and T2D<br>• Neither age and sex adjusted models (OR 1.3, 95% CI 0.68–2.4, P=0.47), nor multivariable analysis showed a significant non-null cross-sectional association (OR 1.3, 95% CI 0.67–2.3, P=0.44) | 6 |

**Note**: [†]RA defined using ACR 1987 criteria; [‡]RA defined using 2010 ACR/EULAR classification; [§]RA defined using ICD-9 or ICD-10 codes.

**Abbreviations**: ACR, American College of Rheumatology; ADA, American Diabetes Association; BMI, body mass index; BP, blood pressure; CCS, corticosteroids; CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; CVD, CV disease; EULAR, European League Against Rheumatism; FPG, fasting plasma glucose; HBP, high BP; ICD, International Classification of Diseases; IHD, ischaemic heart disease; HTN, hypertension; LDL, low-density lipoprotein; MetS, metabolic syndrome; NR, not reported; NS, non-significant; OR, odds ratio; PVD, peripheral vascular disease; RA, rheumatoid arthritis; RR, relative risk; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes; WC, waist circumference.

## Table 1B. Incidence and risk of diabetes mellitus in RA

| **Study and Country** | **Population RA /non-RA) (n/n)** | **Mean Disease Duration** | **Mean/ Median RA Age** | **Follow-up, Years** | **% Baseline DM among RA/ non-RA** | **HR, Incidence Rate and Cumulative Incidence of DM and other Key Findings** | **NOS Score** |
|---|---|---|---|---|---|---|---|
| **Studies Post 2010** | | | | | | | |
| Alemao (2016) [14] UK | 24,859[¶]/ 87,304 | NR | 60.0±15.1 | 5.7±4.4 | 7.0/8.0 | • There were fewer diabetic RA patients than non-RA at baseline, RA-T2D n=1742 (7.0%) *vs* control-T2D n=7012 (8.0%) P<0.0001 d=-0.038<br>• The proportion of patients receiving antidiabetic treatments increased over the 5 years similarly in the RA and control groups (+1.3 [0.8–1.8] in the RA group and +1.0 [0.7–1.2] in the control group) | 7 |

*(Table 1b) contd.....*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| An (2016) [16] USA | 9,440[§]/ 31,009 KPSC database: (1) general KPSC population in a ratio of 4:1 (general controls), (2) matched RA patients to individuals with OA in a ratio of 1:1 (OA controls) | NR | 56.8±14.1 | 1 year | 13.5/13 | • RA patients were more likely to receive anti–DM medications (OR 1.26 [95% CI 1.01–1.56]) *vs* general non-RA<br>• There were similar proportions of RA and non-RA with DM at baseline (P=0.1949) | 7 |
| Antohe (2012) [17] USA | 1,587[§] | NR | 57 (46–68) | 44.9 months for anti-TNF users and 37.1 months for anti-TNF non-users | Patients baseline T2D at RA diagnosis were excluded based on the ICD-9 code of 250, non-fasting blood glucose level of 200 mg/dL, an HbA1c of ≥6.5%, or hypoglycaemic medication | • Cumulative T2D incidence was 5.7% over follow-up (44.9 and 37.1 months for anti-TNF and non-anti-TNF users, respectively)<br>• Of the 91 patients developing T2D, 16 were ever and 75 were never anti-TNF users, yielding IRs of 8.6 and 17.2 per 1000 person-years (P=0.048), respectively<br>• Risk of developing T2DM for ever-TNF users versus non-anti-TNF users (HR 95% CI) 0.40 (0.024, 0.99) P=0.049 when adjusted for NSAID, GC, HCQ and MTX | 6 |
| Bili (2011) [18] USA | 1127[§] | NR | 60.7 | 26.0 and 23.0 months for HCQ users and HCQ non-users, respectively | T2D excluded at baseline | • Of the 48 cases developing T2D during observation, 3 were exposed to HCQ at time of development and 45 were nonexposed, yielding IRs of 6.2 and 22.0 per 1000 per year (P=0.03), respectively<br>• The adjusted HR for incident T2D among HCQ users was 0.29 (95% CI, 0.09–0.95; P=0.04) *vs* non-users<br>• The adjusted HR for incident T2D among HCQ users was 0.29 (95% CI, 0.09–0.95; P=0.04) *vs* non-users | 6 |
| Chen (2017) [20] Taiwan | 33,112[§] | NR | 38.2–50.3 | N/A | DM excluded at baseline | • HR for developing DM in RA (95% CI):<br>o Crude HR:1.99 (1.81–2.20) P<0.001<br>o Adjusted HR: 1.90 (1.61–2.25) P<0.001<br>• HR for DM in RA by disease duration<br>o ≤5 yrs adjusted HR:1.82 (1.52–2.18) P<0.001<br>o 5-10 yr adjusted HR: 2.79 (1.51–5.17) P<0.001<br>o >10 yrs adjusted HR: 0.83 (0.23–2.97) P=0.7<br>Confounding variables included age, sex, disease duration, CCI, and GC | 7 |
| Dubreuil (2014) [27] UK | 11,158[¶] | | 58.4 (14.2) RA *vs* 58.2 (14.1) controls | 5.5 | Baseline DM not reported but relative to the comparison cohorts, the exposed cohorts had a higher baseline prevalence of overweight or obese status | • DM incidence rate was 6.3 per 1000 person years and 5.7 for non-RA<br>• HR for incident DM (95% CI)<br>o HR adjusted for baseline GC use 0.94 (0.84–1.06)<br>o HR adjusted for age, sex, entry-time 1.12 (1.01–1.25)<br>o HR adjusted for BMI, smoking, alcohol 1.00 (0.89–1.12)<br>o Risk of DM is due to obesity and smoking<br>• New diagnoses of DM occurred among 383 persons during 61,087 person-years in the RA cohort | 9 |

*(Table 1b) contd.....*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Guin (2019) [31] India | 50[†]/23 Normal controls | 0.46±0.36 years <1 year RA, 9.6±3.3 years >5 years RA | • RA<1 yr = 38.8 ± 11.4 • RA≥5 yr = 41.2 ± 6.8 • non-RA = 36.58 ± 4.6 | Short duration <1 yr; long duration ≤5 yr | T2D excluded at baseline | • Long duration RA patients had higher incidence of increased HOMA-IR values when *vs* controls (OR=10.86; P=0.001) and to short duration RA (OR=0.23; P=0.05) | 7 |
| Jafri (2017) [34] UK | 53,215[¶]/ 389,263 matched controls | | RA: 60.73 non-RA: 51.33 | 10 years | 8.6/6.2 | • Incidence of HTN, hyperlipidaemia, and DM was elevated in PsA and RA • DM incidence rate per 10,000 person-years was 110.5 for RA and 77.5 for non-RA • HR for DM in RA were 1.16 (1.12–1.21) age/sex adjusted and 1.21 (1.15–1.26) fully adjusted • RA patients have increased incidence of a new diagnosis of CV risk factors • Confounding variables included age, sex, other CV risk factors, heart disease, Charlson comorbidity index and health care utilization | 7 |
| Janssens (2017) [35] Netherlands | 513[¥]/ 1, 850 matched controls | NR | 59.2±14.8 RA *vs* 58.4 ± 14.6 non-RA | 32.6 months | 11.7/8.5 | • RA patients did not have a statistically significant increased incidence of DM (11.7%) compared with non-RA (9.6%), P=0.17 • When stratified, to only subjects who had no CVD at baseline, RA patients did not have a statistically significant increased incidence of DM (9.2%) compared with non-RA (8.5%), P=0.64 | 9 |
| Movahedi (2016) [41] UK | 21,962[¶] | 2±3 years CPRD, 14±11 years | Median, 59 | Median, 5.4 | T2D excluded at baseline | • In 1 database, 10% were diagnosed with new-onset T2D during median follow-up of 5.4 years. In the other, 6.8% after 3.4 years • T2D incidence rate was 14.2–16.7 per 1000 person-years | 9 |
| Ozen (2017) [42] USA | 13,669[$] | 14.4±12.4 years | 58.6±13.4 | 4.6 (2.5–8.8) | DM excluded at baseline; 8.3% after follow-up | • DM incidence rate per 100 person years was 1.59 (95% CI 1.50–1.68) | 9 |
| Ruscitti (2017) [46] Italy | 439[‡] | 5.1±3.8 years | 58.38±13.50 | | T2D excluded at baseline; 7.1% at follow-up | • After 12 months of follow-up, high blood pressure, impaired fasting glucose at the first observation and the poor EULAR-DAS28 response were significantly associated with an increased likelihood of being classified as T2D ($\chi 2 = 128.73$, P<0.0001) • 7.1% developed T2D in 12 months | 6 |
| Su (2013) [50] Taiwan | 4193[§]/ 596,497 | NR | NR | ≤12 | T2D excluded at baseline | • T2D RR was 1.68 (95% CI 1.53–1.84) in men and 1.46 (95% CI 1.39–1.54) in women • RA appears to be associated with an increased risk for T2D in Taiwan • Adjusted HR with GCs 1.34 (1.22–1.47) P<0.0001 | 8 |
| **Studies Pre 2010** | | | | | | | |
| Dessein (2004) [23] South Africa | 92[†] | 11 years, (95% CI 9–13 years) | 56 (54–58 years) | 6 (5–6) | 13 | • GCs were not associated with obesity, HTN, or dyslipidaemia • Having taken prednisone and high yearly frequencies of pulsed GC administrations were associated with decreased insulin sensitivity (P<0.05) • After controlling for body mass index, ever having taken prednisone and high doses of pulsed GCs were independently associated with decreased insulin sensitivity (P<0.05) • Confounding variables included effects of RA, HTN, dyslipidaemia and GC | 6 |

*(Table 1b) contd.....*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dessein (2002) [24] South Africa | 79[†]/39 matched controls | 8.5 years (95% CI, 6.6–10.4 years) | 52 (95% CI, 49–55 years)) | NR | Patients on lipid-lowering agents were excluded | • DM more frequent in RA than non-RA (OA patients) (P<0.05)<br>• CV risk assessment revealed that RA patients exercised more frequently, but they had DM more often and the IS and HDL cholesterol concentrations were lower than those of the OA patients | 7 |
| Gonzalez (2008) [30] USA | 603[†]/603 matched controls RA duration not reported | NR | 58 | 15 | 7.0 | • DM incidence rates for new cases per 100 person years was 0.79 for RA patients and 1.02 for non-RA (Rate ratio 0.78 (0.57–1.06)<br>• The mean follow-up period was 15 and 17 years for RA and non-RA patients, respectively | 7 |
| Solomon (2010) [49] Canada | 48,718[§]/ 442,033 | NR | 58±16 | NR | NR | • DM incidence rate was 8.6 per 1000 (8.5–8.7) and 5.8 (5.8–5.8) for non-rheumatic controls<br>• Adjusted HR for DM compared with non-rheumatic controls was 1.5 (1.4–1.5)<br>• Adjusted for age, gender and medication use | 8 |
| Wasko (2007) [53] US | 4905[†] | 13.0±11.7 years never HCQ, 8.4±9.4 years ever HCQ | 53.7–58.2 | 21.5 | T2D excluded at baseline | • T2D incidence per 1000 person years was 5.2 for HCQ users versus 8.9 not HCQ non-users (P<0.001) over a follow-up period of 21,5 years | 6 |

**Abbreviations**: [†]RA defined using ACR 1987 criteria; [‡]RA defined using 2010 ACR/EULAR classification; [§]RA defined using International Classification of Diseases ICD-9 or IC-D10 codes; [¶]≥1 RA read code; [¥]ICPC code for RA L88 or L88.01; [$]rheumatologists who confirmed the diagnosis.

ACR, American College of Rheumatology; BMI, body mass index; CI, confidence interval; CM, clinical modification; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; CVD, CV disease; DMARD, disease-modifying anti-rheumatic drugs; EULAR, European League Against Rheumatism; FG, fasting glucose; FPG, fasting plasma glucose; GC, glucocorticoid; HbA1c, glycosylated haemoglobin; HCQ, hydrochloroquine; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment for Insulin resistance; HR, hazard ratio; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; IR, incidence rate; IRR, incidence rate ratio; KPSC, Kaiser Permanente Southern California; NOS, Newcastle-Ottawa scale; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; OR, odds ratio; PsA, psoriatic arthritis; PsO, psoriasis; QUICKI, Quantitative Insulin Sensitivity Check Index; RA, rheumatoid arthritis; RR, relative risk; T2D, type 2 diabetes; TBC, to be completed; Anti-TNF, tumour necrosis factor inhibitor.

Studies were heterogeneous in terms of study design, inclusion criteria, and variable definition and reporting. DM prevalence ranged between 1% and 20% in RA patients, which was similar to controls (1–29%).

Out of 5 studies reporting on the relative risk of DM in RA patients, 3 reported a significant odds ratio (OR) of 2.54 [47] and risk ratios (RR) of 1.4 and 2.2 [28, 32] while 2 population-based studies – including the relatively large population-based survey within NHANES III [48]– reported no significant correlation [21, 48]. No clear distinction could be made between studies performed before and after 2010.

### 3.3. Incidence of DM in RA Patients

Eighteen cohort studies [14, 16 - 18, 20, 23, 24, 27, 30, 31, 34, 35, 41, 42, 46, 49, 50, 53] reported DM incidence in RA and are presented in Table **1**.

Studies reporting DM incidence included large retrospective cohorts of insurance data or medical files, in addition to prospective cohorts. Participant numbers ranged from 10s to 100,000s, again with a large degree of heterogeneity in population inclusion criteria between studies. The mean age of participants with RA was typically 50–60 years, and as expected, most RA participants were female, typically ranging from 70% to 80%. DM incidence was reported variably, the number of cases, DM per 100–10,000 patient years, % cumulative incidence, and hazard ratio (HR).

The cumulative incidence of DM in RA patients ranged between 1.3% and 11.7% over different time frames. DM incidence rates in patients with RA per 1000 person-years ranged from 5.2 to 16.7 [27, 30, 34, 41, 42, 49, 53]. Six studies reported a significantly higher relative risk of incident DM [16, 24, 27, 34, 49, 50] compared with the general population, while 3 studies reported no significant increase [14, 30, 35]. One study reported the increased incidence of insulin resistance [31]. Five studies reported the adjusted HR, ranging from 1.1 to 2.2 [20, 27, 34, 49, 50], suggesting a correlation, however, they lacked a clear adjustment for the main confounders.

### 3.4. Traditional Risk Factors for Developing DM in RA Patients

Data on the baseline characteristics and traditional risk factors for DM development in patients with RA *versus* non-RA (where possible) is summarised in Table **2**.

Risk factors were reported using various measures. Mean/median BMI was typically in the overweight range (25–30) in both RA and non-RA populations. Smoking rates were also similar in RA patients (7.6–49.0%) and non-RA patients (9.1–30%. Several studies reported that ~40% of RA patients had hypertension [14, 16, 42, 46] and that was significantly more severe in RA *vs* non-RA. Otherwise, a family history of DM and metabolic syndrome was not accounted for when assessing DM prevalence and incidence.

Table **3** includes details on the reported associations between DM risk factors and RA, however, where statistical

inference is made on the relationship between the risk of RA and CV disease or CV outcome, these values are not included.

**Table 2. Traditional risk factors for diabetes mellitus in patients with RA *versus* non-RA**

| Study | Population RA/non-RA) (n/n) | Mean Disease Duration | Mean/ Median RA Age (years) | Female, % | DM, % | Ethnicity | HTN | Smoking | Dyslipidaemia | BMI | NOS Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Studies Post 2010** | | | | | | | | | | | |
| Agca (2020) [13] | 326[†]/1,869 | 7 (4–10) years | 63±7 RA *vs* 62±7 non-RA | 65 RA *vs* 52 non-RA (P≤0.05) | 5.0 RA *vs* 9.0 non-RA | Dutch Caucasian | Systolic BP in RA 142±20 *vs* 135 (±20) non-RA (P≤0.05) Diastolic BP in RA 81 (±8)[†]*vs* 82 (±10) non-RA (P≤0.05) | Former: 159 RA (49)[†]*vs* non-RA 666 (36) (P≤0.05) Current: 96 (29)[†] RA *vs* 562 (30) in non-RA (P≤0.05) | TG, mmol/L: 1.32 (0.96–1.84) in RA In 1.40 (1.00–1.90) in non-RA NS TC mmol/L: 5.79±1.13[†] for RA *vs* 6.63±1.16 for non-RA (P≤0.05) | For RA 26.7±4.8 *vs* 26.5±3.4 for non-RA | 7 |
| Agarwal (2013) [12] | 56[†]/31 normal controls | NR | Median 50.4 | 67 | 17.9 RA *vs* 19.4 non-RA | Study performed in India, though ethnicity not reported | 26.8% RA *vs* 19.4% non-RA (P=0.43) | 5.4% RA *vs* 9.7% non-RA (P=0.44) | LDL: 111.13 RA *vs* 93.04 non-RA (P=0.01) TG: 114.55 RA *vs* 125.03 non-RA (P=0.399) | RA 25.53 *vs* non-RA 23.49 (P=0.013) | 5 |
| Alemao (2016) [14] | 24,859[#]/ 87,304 | NR | Mean 60.0±15.1 | 69.2 | 7.0 RA *vs* 8.0 non-RA (P<0.0001) | NR | 39.4% RA *vs* 38.2% non-RA (P=0.001) | RA & DM: 28.1% (current) Non-RA: 27.6% (current) (P=0.175) | 27.2% RA *vs* 27.7% non-RA(P=0.103) | 11.6% RA *vs* 10.9% non-RA (P=0.003) Obese | 7 |
| Alten (2019) [15] | 2,350[†] 30-month follow up | | BN 59.9 BF 57.0 | NR | 12.3 (BN) 12.6 (BF) | NR | 38.2% (BN) 39.1% (BF) | NR | NR | >25 in 58.8% (BN) 59.4% (BF) | 5 |
| An (2016) [16] | 9,440[#]/ 31,009 | | 56.8±14.1 | 76.5 | 13.5 DM defined as ICD-9 250 (diabetes), ≥2 outpatient DM diagnoses, or an anti-DM prescription | White 47.7%, Hispanic 31.7%, African American 12.2%, Asian 7.7%, | 44.9% | RA: 11.6% (current) *vs*: 10.5% non-RA (current) | 30.2% (N.B. non-RA significantly more likely to have dyslipidaemia, 35.8% P<0.0001) | ≥30 in 22.9% | 7 |
| Antohe (2012) [17] | 1,587[§] | | 57 (46–68) | 72 | 5.7 T2D defined as ICD-9 250 (diabetes) or random serum glucose ≥200 mg/dL or HbA1c ≥6.5%, or ever use of hypoglycaemic/antidiabetic medications | White: 95% | NR | NR | NR | Median, 28.8 (25.0–33.1) | 6 |
| Bili (2011) [18] | 1127[§] | NR | 60.7 | 73 | T2D excluded at baseline T2D defined as ICD-9 250 (diabetes) or random serum glucose ≥200 mg/dL or HbA1c ≥6.5%, or ever use of hypoglycaemic/antidiabetic medications | White: 97% | NR | NR | NR | Mean, 29.1 | 6 |
| Chung (2012) [21] | 197[†]/274 frequency matched controls Not significantly associated with risk of DM | NR | 59.4±8.7 | 60 | 7.0 *vs* 9.0 (P=0.41) | Caucasian: 86% RA *vs* 85% non-RA (P=0.9) | 57% RA *vs* 42% non-RA (P=0.001) SBP: 128.1±18.6 RA *vs* 122.1±19.2 non-RA (P<0.001) DPB: 75.7±8.9 RA *vs* 70.9±9.7 non-RA (P <0.001) | 12% RA *vs* non-RA 14% (P=0.58) | LDL: 45% RA *vs* 51% non-RA (P=0.22) | 35% in RA and non-RA (P=0.92) | 6 |
| Dregan (2014) [25] | 27,358[#] | | 57 | 69 | 4.0 | NR | 35% | 22% | 8% | BMI ≥30: 21% | 7 |

*(Table 2) contd.....*

| Study | Population RA/non-RA) (n/n) | Mean Disease Duration | Mean/ Median RA Age (years) | Female, % | DM, % | Ethnicity | HTN | Smoking | Dyslipidaemia | BMI | NOS Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gomes (2018) [29] | 338[‡]/84 age and gender matched controls | 12.2±8.7 years | 53.5±12 *vs* 50.3±12.3 OR for MetS = 1.04 (1.01–1.06) | 90.8 | 18.8 *vs* 6.2 | | 46.7% RA *vs* 23.5% non-RA (P<0.001) | 5.6% RA *vs* 13.4% non-RA (P=0.14) | 42.2% RA *vs* 49.4% non-RA (P=0.241) OR for MetS =1.89 (95% CI 1.03–3.47) P=0.040 | 27.4±4.8 RA *vs* 25.9±3.7 non-RA (P=0.11) OR for MetS = 1.12, 95% CI 1.05–1.20; P<0.001 | 5 |
| Guin (2019) [31] | 50[†]/23 | 0.46±0.36 years <1 year RA, 9.6±3.3 years >5 years RA | RA< 1 yr = 38.8±11.4 RA >5 yr = 41.2±6.8 non-RA = 36.58±4.6 | 67 | T2D excluded at baseline | Indian | NR | NR | NR | RA < 1 yr = 21.8±3.2 RA > 5 yr = 21.5±3.6 non-RA = 23.7±2.9 | 6 |
| Hoes (2011) [33] | 140[ǁ]/50 | 13±8 years RA with disease duration of >2 years | 57 RA-GC 59 RA+GC 56 non-RA | 71 | 14 RA+GC 9 RA-GA | | non-RA 10% RA-GC 23% RA+GC 26% (P=0.6 for non-RAs *vs* RA-GC; P=0.3 for non-RAs *vs* RA+GC) | | non-RA 50% RA-GC 82% RA+GC 62% (P<0.001 for non-RA *vs* RA-GC; P=0.3 for non-RA *vs* RA+GC) | non-RA 29±4 RA-GC 25±4 RA+GC 26±6 (P<0.001 for non-RA *vs* RA-GC; P=0.008 for non-RA *vs* RA+GC) | 5 |
| Jafri (2017) [34] | 53,215[#]/389,263 | | RA: 60.73 Non-RA: 51.33 | RA: 70.3 Non-RA: 55.9 | RA: 8.6 non-RA: 6.2 | NR | RA: 29.3% Non-RA: 21.1% | NR | RA: 10.9 non-RA: 9.1 | RA: mean, 26.66 non-RA. mean, 26.39 | 7 |
| Li (2019) [37] | 276[†]/261 (RA+T2D: 151) | 36 months | 61.1 | 84.1 | 55 were diagnosed with T2D if they met ≥1 of the following conditions: (1) previously diagnosed T2D; (2) prescriptions for antidiabetic drugs; (3) newly diagnosed T2D according to laboratory tests (FPG >7.0 mmol/L, random glucose level >11.1 mmol/L, or a GTT >11.1 mmol/L) | NR | 32.97 | 7.64 | TC (>5.2 mmol/L): 15.22 OR for T2D=1.53 (0.86–1.03), P=0.26 TG (>1.7 mmol/L): 19.93 OR for T2D=1.23 (0.74–12.06), P=0.42 HDL-C (<1.0 mmol/L): 43.84 LDL-C (>3.4 mmol/L): 17.03 OR for T2D=1.11 (0.54–2.25), P-0.78 TC/HDL-C (>4.5): 34.42 | NR RF for T2D not measured | 5 |
| Lillegraven (2019) [38] | 21,775[#] | 10±9.8 years | 58.2±13.4 | 76.4 | T2D excluded at baseline | NR | NR | 16% | RF for T2D not measured | Mean, 28.7 HR for incident DM=6.27, (95% CI 2.97, 13.25) | 9 |
| Ozen (2017) [42] | 13,669[#] | 14.4±12.4 years | 58.6±13.4 | 80.3 | DM excluded at baseline; 8.3% after follow-up DM defined as patient report of new DM diagnosis or initiating use of an antidiabetic medication | Non-Hispanic Caucasian: 93.4% | 43.3% (with DM: 53.6%) | Current: 11.7% Past: 30.4% (with DM – Current: 11.3 Past: 35.7) | RF for DM not measured | Mean, 27.8 (with DM: 30.8) | 9 |
| Pieringer (2012) [43] | 203[†]/208 sex matched controls | 12.8±9.3 years | 56.3±12.2 | 83.7 | 3.4 *vs* 29, P<0.001 (T1D and T2D grouped together) | NR | Anti-hypertensive medication 25.6% RA *vs* 32.2% non-RAs (P=0.14) | Current: 18.2 RA *vs* 26.9% non-RAs (P=0.05) Former: 24.1 RA *vs* 16.3% non-RAs (P=0.05) | TC: 217.2 ±44.1 RA *vs* 191.6 ± 47.8 non-RA (P<0.001) TG: 119.9 (57.9) RA *vs* 135.7 (110.7) non-RA (P=0.13) | 25.9 (4.8) RA *vs* 26.3 non-RAs (6.0) (P=0.58) | 6 |

*(Table 2) contd.....*

| Study | Population RA/non-RA) (n/n) | Mean Disease Duration | Mean/ Median RA Age (years) | Female, % | DM, % | Ethnicity | HTN | Smoking | Dyslipidaemia | BMI | NOS Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ruscitti (2017) [46] | 439† | 5.1±3.8 years OR for T2D is NS | 58.38±13.5 | 61 | T2D excluded at baseline; 7.1% at follow-up FPG ≥126 mg/dL patients were classified as having T2D | NR | 37.1% OR for T2D=6.8 (95% CI 2.2–21.3) P<0.001 Adjusted for IFG and high blood pressure | 29.8% OR for T2D is NS | RF for T2D not measured | <18.5, 3.9% 18.5–<25: 50.9% 25–<30: 24.1% ≥30: 7.7% OR for T2D is NS | 6 |
| Ruscitti (2017) [45] | 500†‡/500 age, sex matched controls | 10.1±7.1 years OR for T2D=1.09 (95% CI 1.05–1.13) P<0.001 Adjusted for IFG and high blood pressure | 59.3±13.6 | 86.6 | 13.6 RA *vs* 8.4 non-RA (P=0.01) | NR | 38.4% RA *vs* 27.0% non-RA OR for T2D=1.86 (95% CI 1.11–3.22) P=0.02 | 34.2 RA *vs* 30.8 non-RA (P=0.28) OR for T2D is NS | TC: 195.9±54.9 RA *vs* 203.3±40 non-RA (P=0.007) TG: 112.7±38.8 RA *vs* 115.8±75.1 non-RA (P=0.42) OR for T2DM is NS | Obesity 23.8 RA *vs* 20.2 non-RA (P=0.17) OR for T2D is NS | 7 |
| Ursini (2016) [51] | 100‡/100 age and sex matched controls | 32.9±24.7 months OR for prediabetes =1.90 (95% CI 1.2–2.9) P=0.005 In 1 year | 56.6±11.3 OR for prediabetes = 1.13, (95% CI 1.028–1.245, P =0.01) | 61 | 10 *vs* 2 | NR | SBP: 131+17 RA *vs* 124+12 (P<0.001) DBP: 82+11 RA *vs* 76+9 non-RA (P<0.001) | NR | TC (mg/dL): 203.2+45.7 RA *vs* 208.4+35.4 0.36 non-RA (P=0.36) TG (mg/dL): 106.6+51.8 RA *vs* 119.0+68.5 non-RA (P=0.15) OR for T2D is NS | 28.8+6.1 RA *vs* 27.5+3.8 non-RA (P=0.09) | 8 |
| Ursini (2015) [52] | 15† | 52.1±38.3 months | 52.7±10.5 | 46.7 | DM excluded at baseline | NR | 33.3% | NR | NR | Mean, 26.5±5.9 | 8 |
| Studies Pre 2010 | | | | | | | | | | | |
| del Rincon 2005 [22] | 234†/102 | NR | 59 (40–84) | 90 | 17% RA *vs* 1% non-RA (P<0.001) | NR | SBP: 139 (94–240) RA *vs* 136 (98–202) non-RA (P=0.7) DBP: 74 (46–150) RA *vs* 77 (52–124) non-RA (P=0.3) | No smokers | Hypercholesteremia 118 (50) RA *vs* 57 (56) non-RA (P=0.4) | 28.2 (14.2–56.4) RA *vs* 25.8 (18.4–43.3) non-RA (P<0.001) | 5 |
| Dessein (2004) [23] | 92† | 11 years, 95% CI 9–13 years | 56 (54–58 years) | 80 | DM at baseline 12 (13%) (FPG ≥7 mmol/L) | 80 Caucasian, 9 Asian, 2 of mixed ancestry, and 1 Black | 57 (62%) | Normal IS 5 (25%); decreased IS: 21 (29%) | LDL cholesterol >3 mmol/l n=65 (71%) Low HDL-C and/or high TG n=55 (60%) | BMI>27.5 53 (58%) Normal IS: 5 (25%); decreased IS: 21 (29%) | 6 |
| Dessein (2002) [24] | 79†/39 age and sex matched controls | 8.5 years (95% CI, 6.6–10.4 years) | 52 (95% CI, 49–55 years) | 83.5 | IS was estimated using the QUICKI with the formula: 1/log insulin (uU/ml) x log glucose (mg/dl) | 69 Caucasian, 10 Asian | 39 (50%) | 18 (23%) | NR | 26.4 (25.6–28.2) | 7 |
| Gonzalez (2008) [30] | 603†/603 | NR | 58 | 73 | Baseline: (FPG ≥7 mmol/L) 44 (7%) RA *vs* 41 (7%) non-RA Incidence: 0.79 (66) RA *vs* 1.02 (98) for non-RA rate ratio; (95% CI) 0.78 (0.57–1.06) | NR | Baseline:312 (52%) for RA *vs* 298 (49%) for non-RA Incidence: 3.67 (179) RA *vs* 3.59 (215) non-RA; rate ratio 1.02 (0.84–1.25) NS | Former: 148 (25%) for RA *vs* 118 (19%) non-RA Current: 170 (28%) for RA *vs* 144 (24%) non-RA P<0.001 | Baseline: 163 (49%) for RA *vs* 169 (52%) for non-RA Incidence: 2.71 (158) RA *vs* 3.64 (228) non-RA; rate ratio 0.75 (0.61–0.91) NS | Baseline High BMI: 71 (13%) RA *vs* 68 (13%) non-RA Low BMI: 73 (13%) RA *vs* 63 (12%) non-RA Incidence: High BMI: 0.47 (35) RA *vs* 0.63 (54) non-RA; rate ratio 0.75 (0.48–1.13) Low BMI: 1.17 (83) RA *vs* 0.65 (53) non-RA; rate ratio 1.79 (1.28–2.54) NS | 7 |

*(Table 2) contd.....*

| Study | Population RA/non-RA) (n/n) | Mean Disease Duration | Mean/ Median RA Age (years) | Female, % | DM, % | Ethnicity | HTN | Smoking | Dyslipidaemia | BMI | NOS Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| McEntegart (2001) [40] | 76[†]/641 | 12.5 years | 57 | 82 | 1% RA *vs* 3% non-RA (P=0.7) | | | Ever: 80% RA *vs* 75% non-RA (P=0.003) | TC (m/mol/l): 5.3 (4.6–6.3) RA *vs* 6.2 (5.4–7.0) non-RA (P<0.0001) TG (m/mol/l): 1.5 (1.0–2.3) RA *vs* 1.7 (1.2–2.4) P=0.57 | 25.7 (22–29) RA *vs* 25.7 (23–29) (P=0.91) | 6 |
| Simard (2007) [48] | 144[†]/ 5,152 | NR | 72.9±8.4 | 59 | 17% RA *vs* 16% non-RA (P=0.46) | Non-Hispanic White 58% RA *vs* 57% non-RA; Non-Hispanic Black 19% *vs* 20% controls; Mexican American 22% RA *vs* 19% controls | SBP: 138.2±22.5 RA *vs* 139±23.3 non-RA (P= 0.41) DBP: 74.2±11.5 RA *vs* 72.6±11.8 non-RA (P=0.65) | Current: 12% RA *vs* 15% non-RA Former:37% RA *vs* 38% non-RA (P=0.44) | TC: 215±49 RA *vs* 222.1±45.2 non-RA (P=0.56) | 26.8±5.6 RA *vs* 27±5.2 non-RA (P=0.6) | 6 |
| Rho (2009) [44] | 169[†]/ 92 Disease duration not noted | NR | 54.2±11.8 | 69.2% | 11.2% (T2D not defined) | Caucasian 88.2% | HTN: 53.3% SBP: 133.3±20.3 DBP: 74.9±10.8 | | HDL: 46.6 + 13.9 LDL: 112.7 + 33.4 TG: 144.6 + 178.5 | NR | 6 |
| Wasko (2007) [53] | 4905† | 13.0±11.7 years NH 8.4±9.4 years ever HCQ (EH) | 58.2 (EH) *vs* 53.7 (NH) | 80.4 (EH) *vs* 75 (NH) | Newly reported disease or new use of hypoglycaemic medication(s) | White 2778 (89.7) *vs* for NH 1613 (89.2) for EH (NS) | NR | NR | NR | 27.7 (5.8) for NH *vs* 28.0 (6.3) for EH | 6 |

**Note**: [†]RA defined using ACR 1987 criteria; [‡]RA defined using 2010 ACR/EULAR classification; [§]RA defined using ICD-9 or IC-D10 codes; [¶]≥1 RA read code; [¥]ICPC code for RA L88 or L88.01; [$]rheumatologists who confirmed the diagnosis; [#]RA database; Ⅱnot defined.

**Abbreviations**: ACR, American College of Rheumatology; BMI, body mass index; BF, biologic failure; BN, biologic naïve; BP, blood pressure; CI, confidence interval; CM, clinical modification; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; EH, ever HCQ; EULAR, European League Against Rheumatism; FG, fasting glucose; FPG, fasting plasma glucose; GTT, glucose tolerance test; HbA1c, glycosylated haemoglobin; HCQ, hydrochloroquine; HDL-C, high-density lipoprotein cholesterol; ICD, International Classification of Diseases; IQR, interquartile range; IS, insulin sensitivity; KPSC, Kaiser Permanente Southern California; LDL-C, low-density lipoprotein cholesterol; NH, never HCQ; NOS, Newcastle-Ottawa scale; NR, not reported; NS, non-significant; OA, osteoarthritis; RA, rheumatoid arthritis; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides; THIN, The UK Health Improvement Network.

## Table 3. RA treatment impact on diabetes mellitus and diabetes mellitus risk factors.

| Study RA (n) | RA Characteristics | Current Treatment | Previous Treatment | Comparator | Adjustment Variables | Main Outcome | Key Findings | NOS Score |
|---|---|---|---|---|---|---|---|---|
| Antohe (2012) [17] N=1,587 RA NT (n=1,065) ET (n=522) | RF and anti-CCP were positive in 77% and 58%, respectively | Anti-TNF • The median duration of Anti-TNF exposure was 16.9 months (IQR 7.6–35.3 months) | Hydroxychloroquine 609 (38); NT 402 (38); ET 207 (40) NS NSAIDs 1,139 (72); NT 745 (70); ET 394 (76) NS GCs 1,350 (85); NT 865 (81); ET 485 (93) P<0.001 MTX 993 (63); ET 592 (56); 401 (77) P<0.001 | Never users of Anti-TNF | Sex, age, race, BMI, RD, anti-CRP, ESR, NSAID, GCs, HCQ, MTX T2D excluded at baseline | Anti-TNF use was associated with a 51% reduction in risk of developing T2D | Incident T2D was found in 91 patients (5.7%) The median follow-up time (from RA diagnosis date to T2D diagnosis date or censor date) for ET and NT was 44.9 months (IQR 23.7–73.0 months) and 37.1 months (IQR 16.3– 65.1 months), respectively (P<0.001) Adjusting for covariates, HR for incident T2D in Anti-TNF users was 0.49 (95% CI 0.24–0.99, P=0.049) *vs* the never users | 6 |

*(Table 3) contd.....*

| Study<br>RA (n) | RA<br>Characteristics | Current Treatment | Previous<br>Treatment | Comparator | Adjustment<br>Variables | Main Outcome | Key Findings | NOS<br>Score |
|---|---|---|---|---|---|---|---|---|
| Bili (2011) [18]<br>N=1127 RA<br>NH (n=794)<br>EH (n=333) | RF and anti-CCP were positive in 78% and 53%, respectively | cDMARD<br>• HCQ (typical dose,6.5 mg/kg or 400 mg/d; HCQ dose remained stable throughout the study) | NSAIDs 750 (67); EH 243 (73); NH 507 (64) P=0.003<br>GCs 864 (77); EH 256 (77); NH 608 (77) NS<br>MTX 640 (57); EH 158 (48); NH 482 (61) P<0.001<br>Anti-TNF 319 (28); EH 79 (24); NH 240 (30) P=0.027 | Never users of HCQ | (1) Sex, Age, and Race, and (2) BMI, RF, Anti-CCP NSAID GC, MTX, anti-TNF, MTX, and (3) for ESR<br>T2D excluded at baseline | 48 cases developing T2D during observation, 3 were EH at time of development and 45 were NH, yielding IRs of 6.2 and 22.0 per 1000 per year (P=0.03), respectively | HR for incident T2D among EH users was:<br>• (1) 0.31 (95% CI, 0.10–1.00; P=0.049) *vs* non-users<br>• (2) 0.27 (95% CI 0.08–0.90) P=0.033<br>• (3) 029 (95% CI 0.09–0.95) P=0.041 | 6 |
| Dessein (2004) [23]<br>Full RA cohort, N=92 | RF positive in 79% | GC<br>• All patients had received pulsed (intraarticular, intramuscular, and/or intravenous) methylprednisolone [cumulative dose 2.0 (1.6–2.6) g) from 1 month up to a year<br>o Pulses per patient 8.8 (1–39)<br>o Yearly frequency of pulses 1.9 (0–8)<br>o Mean pulse doses, mg 230 (60–665)<br>• Currently using DMARD 1.7 (0–3) | 37 (40%) patients had received oral prednisone [cumulative dose 4.8 (2.0–8.5) g; duration 1 month to 20 years]<br>Total number of DMARD used 3.5 (1–8) | Control | None | Previous exposure to oral prednisone and high doses of pulsed GCs was associated with decreased insulin sensitivity in RA (P<0.05) | The mean (95% CI) fasting insulin concentrations were 12.4 (8.9–16.0) and 8.6 (6.4–10.8) (P=0.026) in patients having received oral GCs and patients who had never used oral GCs, respectively.<br>By comparison, the mean (95% CI) fasting insulin level in control subjects was 4.6 (4.2–5.0) | 6 |
| Hoes (2011) [33]<br>(N=140)<br>(13±8 years)<br>GE, n=58<br>GN, n=82<br>Non-RA controls, n=50 | RA with disease duration of >2 years<br>The RA groups had similar anthropometrics, but RA+GC had higher disease activity than RA−GC<br>2.8±1.3 for GN *vs* 3.5±1.2 for GE P=0.002; Anti-CCP positivity 71 for GN and GE | GC, cDMARD, biological<br>• cDMARD<br>o EG: 78%<br>o NG: 89% (P=0.07 NG *vs* control)<br>• Biological<br>o EG: 55%<br>o NG: 21% (P<0.001 *vs* control) | Historic DMARD use<br>Synthetic (%/n) 71/1.9 71/2.8 1.0<br>• cDMARD<br>o EG: 71%<br>o NG: 71% (P=0.07 NG *vs* control)<br>• Biological<br>o EG: 24%<br>o NG: 7% (P=0.05 *vs* control) | Non-RA control | HTN, smoking, BMI, WC and MetS effect of GC use<br>T2D excluded at baseline | T2D prevalence (FPG>7.1 mmol/l or a 2 h glucose value >11.1 mmol/l) and other risk factors | • T2D was comparable between the 2 RA groups (RA-GC 9% *vs* RA±GC 14%, P=0.3). If those patients with RA who were excluded because of known T2D would have been included, then prevalence would have been 19% (RA-GC 18% *vs* RA+GC 21%, P=0.9)<br>• Prednisolone dose was associated with T2D in univariate analysis, and the effect from cumulative dosing this was sustained (P=0.03) after adjusting for disease activity and patient characteristics | 5 |
| Lillegraven (2019) [38]<br>(N=21,775)<br>Anti-TNF n=9880<br>Biologic n=1756<br>MTX n=7441<br>Hydroxychloroquine n=1496<br>cDMARD n=1202 | Mean disease duration 10.0 (9.8) years<br>Mean CDAI score 13.4 (12.4) (moderate disease activity) | Anti-TNF, biologics, cDMARDs and GC<br>• Peroral GC use, n (%)<br>o Anti-TNF: 2706 (27.4)<br>o Biologic: 712 (40.5)<br>o MTX: 2331 (31.3)<br>o Hydroxychloroquine: 404 (27.0)<br>o cDMARD: 385 (32.0) | N/A | Inter-group comparison | Propensity score models included CDAI, pain VAS, disease duration, age, BMI, gender, white *vs*. non-white, subcutaneous nodules, GC, bDMARD use, nbDMARD use.<br>T2D excluded at baseline | HR (95% CI) for T2D was significantly reduced in patients receiving TNF inhibitors, HR 0.35 (0.13, 0.91), *vs* patients treated with non-biologic DMARDs other than HCQ and MTX | Adjusted HR for incident T2D (95% CI)<br>• Anti-TNF *vs* other non-biologic DMARDs: 0.35 (0.13–0.91) P= 0.03 | 9 |

*(Table 3) contd.....*

| Study<br>RA (n) | RA<br>Characteristics | Current Treatment | Previous<br>Treatment | Comparator | Adjustment<br>Variables | Main Outcome | Key Findings | NOS<br>Score |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | • Biologic *vs* cDMARD: 0.44 (0.08–2.57) P=0.36<br>• MTX *vs* other cDMARD 0.67 (0.44–1.02) P=0.34<br>• Hydroxychloroquine *vs* other cDMARD 0.45 (0.13–1.53) P=0.21 | |
| Mazzantini *et al* (2010) [39] | GC users more frequently tested positive for RF (P<0.05) and anti-CCP (P<0.01) | GC<br>• 14.2±4.0 yrs of GC use | The number of DMARD used was significantly higher in GC users 3.2±1.5 (1–6) versus GC non-users 1.8±1.3 (1–4) (P< 0.01) reflecting more active disease in GC users | Never users of GC | None | T2D prevalence was not significantly different between GC users (12.1%) and nonusers (13.4%) | HTN was significantly increased in GC users *vs* GC nonusers | 6 |
| Movahedi (2016) [41]<br>CRPD and NDB<br>CRPD (N= 21,962)<br>NG (n =12,066)<br>EG (n=9,896)<br>NDB (N=12,657)<br>NG (n=6,658)<br>EG (n=5,999) | Disease duration 2 (CPRD) –13/14 (NDB) years | GC<br>• Percentage of time receiving GCs for those using GCs in the 3 years prior to cohort entry, mean + SD<br>o CRPD: 28+31; NG 11+17; EG 33+31<br>o NDB: 26+39 NG 9+22; EG 47+44 | N/A | Never users of GC | Sex, age, HTN, NSAID, time-varying use during follow-up of 4 main disease-modifying antirheumatic drugs, duration of RA, GCs in the 3 years prior to cohort entry T2D excluded at baseline | GC use was a clinically important and quantifiable risk factor for T2D Risk was influenced by the dosage and treatment duration, although only for GC use within the last 6 months | Incident cases of T2D<br>• CRPD: 2,260; NG 1,209; EG 1,051<br>• NDB: 861; NG 402; EG 459<br>Incidence per 1,000 person-years, person-years (95% CI)<br>• CRPD: 16.7 (16.1–17.4); NG 13.9 (13.2–14.8) EG 21.8 (20.5–2: 3.1)<br>• NBD: 14.2 (13.3–15.2); NG 12.0 (10.9–13.3); EG 16.9 (15.4–18.6)<br>• HR for DM in GC ever used was 1.35 (95%CI 1.22–1.48) for CPRD and 1.42 (95%CI 1.221.66) for NDB | |
| Ozen (2017) [42]<br>Full RA cohort, N=13,669 | Disease duration 14.5 years | Anti-TNF, cDMARDs and GC<br>Crude IRs per 100 person-years (95% CI)/and Standardised incidence ratio (95% CI) of T2D in RA by disease activity<br>• Any GC 1.99 (1.81–2.20) 1.72 (1.56–1.91)<br>• Any HCQ 1.03 (0.88–1.20) 0.91 (0.78–1.07)<br>• DMARD<br>o MTX monotherapy 1.46 (1.26–1.68) 1.21 (1.04–1.42)<br>o Any abatacept 1.14 (0.71–1.83) 0.96 (0.58–1.59)<br>o Any other DMARD with MTX 1.47 (1.29–1.67) 1.27 (1.10–1.45)<br>o Other or no DMARDs 2.08 (1.91–2.26) 1.82 (1.67–1.99) | MTX-ever, 71.1%<br>Anti-TNF -ever, 27.0%<br>Biologics-ever, 6.1%<br>• Abatacept-ever, 3.6%<br>• Rituximab-ever, 1.7%<br>• Tocilizumab-ever, 0.4%<br>• EG, 54.9% | Intergroup comparison | Age, sex, disease duration, socioeconomic status ethnicity, smoking, HTN, comorbidity index, BMI, HAQ, NSAID usage and year of entry. | Other synthetic/biologic DMARDs were not associated with any risk change.<br>Concomitant use of GCs did not alter T2D risk reduction with HCQ (HR 0.69 (0.51 to 0.93)) | Adjusted HR (95% CI) for T2D were:<br>• HCQ: 0.67 (0.57–0.80) P<0.001<br>• Any abatacept: 0.52 (0.31–0.89) P=0.017<br>• GC: 1.31 (1.15–1.49) P<0.001 | 9 |

*(Table 3) contd.....*

| Study<br>RA (n) | RA<br>Characteristics | Current Treatment | Previous<br>Treatment | Comparator | Adjustment<br>Variables | Main Outcome | Key Findings | NOS<br>Score |
|---|---|---|---|---|---|---|---|---|
| Rho (2009) [44]<br>N=169 RA | - | Range of treatments<br>• Anti-TNF 20.7%<br>• CCS 54.4%<br>• MTX 71.0%<br>• HCQ 24.9%<br>• NSAIDs 33.1%<br>• COX-2 inhibitors 30.2%<br>• Leflunomide 18.3% | Steroids 34.3%<br>MTX 20.1%<br>HCQ 13.0%<br>NSAIDs 18.9%<br>COX-2 inhibitors 36.7%<br>Anti-TNF 6.5% | Never users and intergroup comparison | To exclude the potential confounding effects of co-therapies additional statistical models for each drug that were constructed, to adjust for the other drugs | RA did not have major adverse effects on CV risk factors and use of HCQ was associated with beneficial lipid profiles | • No CV risk factor differed significantly among current users and non-users of NSAIDs, COX-2 inhibitors, MTX and Anti-TNF<br>• Serum HDL cholesterol concentrations were significantly higher in patients receiving GC (42.2±10.5 *vs* 50.2±15.3 mg/dL, adjusted P<0.001)<br>• DBP (75.9±11.2 *vs* 72.0±9.1 mmHg, adjusted P=0.02), serum LDL cholesterol (115.6±34.7 *vs* 103.7±27.8 mg/dL, adjusted P=0.03) and TG concentrations (157.7±202.6 *vs* 105.5±50.5 mg/dL, adjusted P=0.03) were significantly lower in patients taking HCQ<br>• Plasma glucose was significantly lower in current leflunomide users (93.0±19.2 *vs* 83.6±13.4 mg/dL, adjusted P=0.006) | 6 |
| Ruscitti (2017) [45]<br>RA (n=500); non-RA controls (n=500) | 70.2% with RA had seropositive disease with a mean duration of 10.1±7.1 years<br>The presence of extra-articular manifestations was observed in 15% of patients and 7% underwent RA-related joint surgery | Range of treatments<br>• Anti-TNF 41.8%<br>• MTX 84.8%<br>• GC 80.4%<br>• Biologic (other) 12.7% | N/A | Control | T2D excluded at baseline | GC exposure was significantly associated with an increased likelihood of being classified as T2D | Univariate regression analyses of predictors of T2D in RA patients: OR (95% CI)<br>• MTX 1.63 (0.72–3.72) P=0.24 NS<br>• Anti-TNF 1.28 (0.77–2.14) P=0.34 NS<br>• Biologics (other) 0.40 (0.14–1.15) P=0.09<br>• GC 2.77 (1.16–6.60) P=0.02 | 7 |
| Su (2013) [50]<br>Full RA cohort, N=4193 | - | GC | N/A | None | Age, sex, RA, HTN, DLM, and GC<br>T2D prior o diagnosis of RA | GC use is a strong risk factor for T2D in patients with RA, based on results from both univariate and multivariate models | HR (95% CI) for T2D from GC usage<br>• Unadjusted: 1.31 (1.28–1.35) P<0.0001<br>• Adjusted:1.34 (1.22–1.47) P<0.0001<br>• The multivariate model revealed that GC use has significant interactions with HTN and age | 8 |

*(Table 3) contd.....*

| Study<br>RA (n) | RA<br>Characteristics | Current Treatment | Previous<br>Treatment | Comparator | Adjustment<br>Variables | Main Outcome | Key Findings | NOS<br>Score |
|---|---|---|---|---|---|---|---|---|
| Wasko (2007) [53]<br>4905 adults with RA<br>EH (n=1808)<br>NH (n= 3097) | Duration of disease EH 13.0 years, NH 8.4 years (P<0.001) | cDMARD, GC n, % of observation time<br>• Prednisone NH 1797 (58); EH: 1298 (72) P<0.001<br>• MTX NH 1520 (49); 1155 (64) P<0.001 | N/A | Never users of HCQ | Sex, age, year of study entry, education, ethnicity, duration of RA at study entry, maximum BMI<br>T2D excluded at baseline | In Poisson regression, the risk of incident T2D was significantly reduced with increased duration of HCQ use (P<0.001 for trend); among those taking HCQ for >4 years (n=384) | Incident T2D per 1000 person-years: NH 8.9 *vs* EH 5.2, P<0.001<br>Risk of Developing T2D in RA patients by duration of HCQ use (years) (RR)<br>• <1 year: 0.83 (0.51–1.34) NS<br>• 1–2 years: 0.71 (0.39–1.29) NS<br>• 2–3 years: 0.65 (0.38–1.10) NS<br>• >4 years: 0.23 (0.11–0.50) P<0.001 | 6 |
| Wilson (2019) [54]<br>GC treatment (n=13,770)<br>No GC (n=20,280) | - | GC | N/A | Never users of GC | Age, sex, and GC use | GCs were associated with an elevated risk of T2D (adjusted OR 1.33 [1.14–1.56]) | T2D IRs per 1,000 person-years and IRRs (95% CI)<br>• All cohort: 1,462 (person-time years 248,690.4) and 5.88 (5.59–6.19)<br>• No GC prescription 908 (person-time years 146,058.1) and 6.22 (5.83–6.63)<br>• GC prescription 554 (person-time years 102,632.3) and 5.40 (4.97–5.87) | 7 |

**Abbreviations**: BF, biologic failure; BN, biologic naïve; CCP, cyclic citrullinated peptide; CCS, corticosteroids; CDAI, Clinical Disease Activity Index; cDMARD, conventional disease-modifying anti-rheumatic drug; CI, confidence interval; COX-2, cyclo-oxygenase-2; CV, cardiovascular; DBP, diastolic blood pressure; DMARD, disease-modifying anti-rheumatic drugs; EG, ever used GC therapy; EH, ever taken HCQ; ET, ever taken Anti-TNF; GC, glucocorticoid; HCQ, hydrochloroquine; HDL, high-density lipoprotein; HR, hazard ratio; ICPC, International Classification of Primary Care; IQR, interquartile range; IR, incidence rate; IRR, incidence rate ratio; LDL, low density lipoprotein; MTX, methotrexate; N/A, not available; NDB, National Data Bank for Rheumatic Diseases; NG, not yet used GC therapy; NH, never taken HCQ; NOS, Newcastle-Ottawa scale; NS, non-significant; NSAID, nonsteroidal anti-inflammatory drug; NT, never taken Anti-TNF; OR, odds ratio; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, risk ratio; T2D, type 2 diabetes; TBC, to be completed; TG, triglyceride; Anti-TNF, tumour necrosis factor inhibitor.

### 3.5. Effect of RA Treatment on the Development of DM in RA Patients

Fourteen studies reporting on the association of DM prevalence or incidence with RA treatments are presented in Table **3** [15, 17, 18, 23, 33, 38, 39, 41, 42, 44, 45, 50, 53, 54].

Anti-tumour necrosis factor (TNF) treatment was associated with reduced risk of DM (HR=0.49, 95% confidence intervals [CI] 0.24–0.99, P=0.049) [17] as was abatacept (HR=0.61; 95% CI 0.38–0.99, P=0.043) [15] and hydroxychloroquine (HCQ) (HR=0.27, 95% CI 0.08–0.90, P=0.033) [18] and this was also observed when these treatments compared with conventional DMARDs (other than HCQ) [38]. Compared with nonusers, GC users were reported to have a significantly increased risk of DM in most studies addressing that question (HR=1.31; 95% CI=1.15–1.49) [42] and (HR=1.34; 95% CI=1.22–1.47; P<0.0001) [50] and in current GC users compared with nonusers in the CPRD and NDB databases (HR=1.35; 95% CI=1.22–1.48; and HR=1.42; 95% CI=1.22–1.66) [41]. GC exposure may also increase the likelihood of DM (OR=2.77; 95% CI=1.16–6.60; P=0.02) and OR=1.33; 95% CI=1.1–1.56) [45, 54], reduce insulin sensitivity (P<0.05) [23] and elevate lipid levels [44]. GC use was also associated with incident T2DM (OR cumulative dose (1.04 g) p=0.002 and daily dose (1.13 mg) p=0.048 [33]); in this study, both GC cumulative dose (1.04 g) p=0.002 and daily dose (1.13 mg) p=0.048 [33] were significantly associated with incident DM. A single study reported no difference in DM prevalence between GC users and non-users [39].

In contrast to the above observations, Chen *et al*. (2017) [20] reported that early prednisolone therapy provided a protective effect against the development of DM, as disease activity was rapidly controlled and eventually required a lower cumulative doses. Besides, the study population combined RA, ankylosing spondylitis and psoriasis/psoriatic arthritis, limiting the interpretation of these data since CV risk may substantially differ across this spectrum of diseases.

## 4. DISCUSSION

DM is an important risk factor that both worsens CV outcomes and increases CV-related mortality in patients with RA [10]. In this systematic review of studies including patients with RA, we found that DM incidence may be increased in patients with RA and this may be driven by concomitant traditional risk factors such as elevated BMI and metabolic syndrome, as well as RA-related risk factors such as inflammation, disease duration and GC therapy.

Similar to previous SLRs [10, 55], we found that the risk of DM may be increased in patients with RA, although unlike these studies we did not pool data to determine the overall risk.

It remains unclear whether DM occurs more frequently in RA patients than in the general population, as the prevalence data were nonconclusive. Despite the great strides in RA patient management and treatment in the last decade, no clear signal could be captured in terms of DM incidence in RA studies performed before and after 2010 when the treat-to-target treatment approach and improved RA diagnostic criteria and several new treatments became available [7]. Owing to study heterogeneity, the correlation between RA and DM varied significantly between studies and risk factors for DM were not similarly accounted for.

RA treatment may differentially influence the incidence and progression of DM. In agreement with the SLR and metanalyses by Xie *et al*. (2020) [56], GCs were found to be associated with an increased risk of DM [41, 42, 45, 54], reduced insulin sensitivity and elevated lipid levels [23, 44]. GC use has been previously associated with poorer outcomes in RA patients, including GC-mediated deterioration of glucose tolerance [57 - 59] and higher mortality rates in patients with comorbid DM compared with those without DM [60]. Again, in line with a previous SLR [56], anti-TNF agents, abatacept and hydroxychloroquine may reduce the risk of DM [15, 17, 18, 38, 42, 53] and this may occur either directly *via* moderation of the inflammatory response or improved glucose metabolism [61, 62] or simply GC-sparing. Despite being widely prescribed GCs drugs, their toxicity is well understood and the most recent ACR/EULAR management recommendations advocate GCs as adjunctive treatment to DMARDs [63, 64], for the shortest duration and at the lowest dose possible, with stricter GC recommendations on the horizon.

This SLR builds upon other studies in which particular aspects of risk in RA have been evaluated, such as the risk of DM [10, 55] or treatment effects [56]. Nevertheless, the wide-ranging objectives of this study represent a novel and holistic approach to evaluating DM in terms of prevalence, incidence, as well as traditional and treatment-related risk factors.

### 4.1. Shared Inflammatory Mechanisms in RA and DM

Links between the activation of the innate immune system and obesity, metabolic syndrome, and diabetes suggest the existence of shared disease mechanisms [65], but whether systemic inflammation and potential downstream effects on glucose metabolism lead to DM requires elucidation.

It is thought that inflammatory mechanisms bridging the association between RA and DM may include interleukin (IL)-1, as evidenced by its inhibition leading to improved outcomes for patients with both diseases [66]. These proinflammatory cytokines participate in the bone destruction observed around affected joints RA [67], as well as the defining beta-cell dysfunction of T2D [68]. The increased levels of inflammatory mediators such as TNFα and IL-6 [69] that characterise RA may inhibit insulin function leading to insulin resistance, in turn resulting in DM development [70, 71].

The majority of the studies in this report include RA patients with a disease duration above 10 years and therefore it can be assumed that these patients are on long-term RA treatment. Few studies provide information on RA treatment, inflammatory status, or concomitant risk factors when reporting on DM occurrence, which precludes us from establishing whether RA alters glucose metabolism per se, with the ultimate occurrence of DM.

Large prospective cohorts with systematic collection on RA disease activity, concomitant DM risk factors, and RA therapy are needed to evaluate whether RA is an actual risk factor for DM that may be modified by GC and DMARDs.

## 5. LIMITATIONS

The selected observational studies demonstrate significant heterogeneity, as has been reported in a previous systematic review [55]. The variation in study design and subject selection, choice and definition of DM, risk factors, reporting of RA, disease duration, severity, and treatment are all potentially linked to DM occurrence. The studies also vary largely in how results and analyses were presented, which prevents meta-analysis and restricts the conclusions that can be drawn.

## CONCLUSION

This SLR shows that DM incidence among RA patients may be driven by a higher incidence of concomitant traditional risk factors for DM and higher exposure to GC among RA patients as compared with the general population. It does not provide enough evidence for an increased risk of DM as a result of RA disease activity or a different effect of the various DMARDs. Properly designed prospective studies are required to adequately address the question along with other relevant CV risk factors before conclusions could be made on whether RA persistent inflammation is a driver of glucose metabolism impairment.

## AUTHORS' CONTRIBUTIONS

Authors JO, FF, RB, OAT, KA, MG, NS, and EM contributed to the conceptualization of the manuscript. All the authors helped with data curation, writing- review and editing. All authors read and approved the final manuscript.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| **DM** | = | Diabetes Mellitus |
| **RA** | = | Rheumatoid Arthritis |
| **SLR** | = | Systematic Literature Review |
| **GC** | = | glucocorticoids |
| **DMARDs** | = | Disease-modifying Anti-rheumatic Treatments |
| **CV** | = | cardiovascular |
| **TNF** | = | Anti-tumour necrosis factor |
| **HCQ** | = | hydroxychloroquine |

## CONSENT FOR PUBLICATION

Not applicable.

## STANDARDS OF REPORTING

PRISMA guidelines and methodology were followed.

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## CONFLICT OF INTEREST

Marcelle Ghoubar and Nancy Sunna are employees of Pfizer, and no other authors have any conflicts of interest to declare.

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## APPENDIX 1: EMBASE SEARCH STRING

EMBASE: (('rheumatoid arthritis'/exp OR 'arthritis deformans' OR 'arthritis, rheumatoid' OR 'arthrosis deformans' OR 'beauvais disease' OR 'chronic polyarthritis' OR 'chronic progressive poly arthritis' OR 'chronic progressive polyarthritis' OR 'chronic rheumatoid arthritis' OR 'disease, beauvais' OR 'infantile rheumatoid arthritis' OR 'inflammatory arthritis' OR 'polyarthritis, primary chronic' OR 'primary chronic polyarthritis' OR 'progressive polyarthritis, chronic' OR 'rheumarthritis' OR 'rheumatic arthritis' OR 'rheumatic polyarthritis' OR 'rheumatism, chronic articular' OR 'rheumatoid arthritis') NOT ('juvenile rheumatoid arthritis'/exp OR 'arthritis deformans juvenilis' OR 'arthritis, juvenile' OR 'arthritis, juvenile rheumatoid' OR 'arthropathy, juvenile' OR 'chronic arthritis, juvenile' OR 'chronic juvenile arthritis' OR 'juvenile arthritis' OR 'juvenile arthritis deformans' OR 'juvenile arthropathy' OR 'juvenile chronic arthritis' OR 'juvenile idiopathic arthritis' OR 'juvenile polyarthritis' OR 'juvenile rheumatoid arthritis' OR 'juvenile rheumatoid polyarthritis' OR 'polyarthritis, progressive splenoadenomegalic' OR 'rheumatoid arthritis, juvenile') AND ('diabetes mellitus'/exp OR 'diabetes' OR 'diabetes mellitus' OR 'diabetic')) AND (('risk factor'/exp OR 'risk factor') OR (('tumor necrosis factor inhibitor'/exp OR 'tnf alpha inhibitor' OR 'tnf inhibitor' OR 'anti tnf agent' OR 'anti tnf alpha agent' OR 'anti tumor necrosis factor agent' OR 'anti tumour necrosis factor agent' OR 'tumor necrosis factor alpha inhibitor' OR 'tumor necrosis factor inhibitor' OR 'tumor necrosis factor inhibitors' OR 'tumour necrosis factor alpha inhibitor' OR 'tumour necrosis factor inhibitor') AND ('biological product'/exp OR 'biologic' OR 'biologic agent' OR 'biologic agents' OR 'biologic product' OR 'biologic products' OR 'biological' OR 'biological agent' OR 'biological agents' OR 'biological product' OR 'biological products' OR 'biologicals' OR 'biologics') AND ('disease modifying antirheumatic drug'/exp OR 'disease modifying antirheumatic agent' OR 'disease modifying antirheumatic drug' OR 'disease modifying antirheumatic drugs')))).

## APPENDIX 2: PUBMED SEARCH STRING

PubMed: ((“arthritis, rheumatoid”[MeSH Terms] OR (“arthritis”[All Fields] AND “rheumatoid”[All Fields]) OR “rheumatoid arthritis”[All Fields] OR (“rheumatoid”[All Fields] AND “arthritis”[All Fields])) AND (“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields])) AND (((((((“risk factors”[MeSH Terms] OR (“risk”[All Fields] AND “factors”[All Fields]) OR “risk factors”[All Fields] OR (“risk”[All Fields] AND “factor”[All Fields]) OR “risk factor”[All Fields]) AND (“risk factors”[MeSH Terms] OR (“risk”[All Fields] AND “factors”[All Fields]) OR “risk factors”[All Fields] OR (“risk”[All Fields] AND “factor”[All Fields]) OR “risk factor”[All Fields])) OR “risk factors”[MeSH Terms]) OR (“antirheumatic agents”[Pharmacological Action] OR “antirheumatic agents”[MeSH Terms] OR (“antirheumatic”[All Fields] AND “agents”[All Fields]) OR “antirheumatic agents”[All Fields] OR “dmard”[All Fields])) OR (“antirheumatic agents”[Pharmacological Action] OR “antirheumatic agents”[MeSH Terms] OR (“antirheumatic”[All Fields] AND “agents”[All Fields]) OR “antirheumatic agents”[All Fields] OR (“disease”[All Fields] AND “modifying”[All Fields] AND “antirheumatic”[All Fields] AND “drug”[All Fields]) OR “disease modifying antirheumatic drug”[All Fields])) OR ((“tumour necrosis factor”[All Fields] OR “tumor necrosis factor-alpha”[MeSH Terms] OR (“tumor”[All Fields] AND “necrosis”[All Fields] AND “factor-alpha”[All Fields]) OR “tumor necrosis factor-alpha”[All Fields] OR (“tumor”[All Fields] AND “necrosis”[All Fields] AND “factor”[All Fields]) OR “tumor necrosis factor”[All Fields]) AND inhibitor[All Fields]) OR (“biology”[MeSH Terms] OR “biology”[All Fields] OR “biologic”[All Fields])) OR (“adrenal cortex hormones”[MeSH Terms] OR (“adrenal”[All Fields] AND “cortex”[All Fields] AND “hormones”[All Fields]) OR “adrenal cortex hormones”[All Fields] OR “corticosteroid”[All Fields])) AND (“0001/01/01”[PDAT]: “2020/03/12”[PDAT]).

## SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher’s website along with the published article.

## REFERENCES

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