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Systematic review

Diabetes Mellitus in Patients with Rheumatoid Arthritis: A Systematic Review

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Abstract
Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent joint inflammation and systemic manifestations. Diabetes mellitus (DM), particularly type 2 diabetes, is a common metabolic comorbidity among RA patients, influenced by inflammation, medication use, and genetic factors. This systematic review aimed to synthesize evidence on the prevalence, pathophysiological mechanisms, and risk factors linking DM with RA. A comprehensive search was conducted in PubMed, Scopus, Web of Science, and Embase (Jan 2010–Apr 2025) following PRISMA 2020 guidelines. Studies including adult RA patients with confirmed DM or assessing the incidence of DM were included. After screening 467 studies, 22 met the inclusion criteria. The pooled estimate indicated a 1.45-fold increased risk of DM in RA patients, with prevalence ranging from 10% to 24%. Key contributing factors included systemic inflammation, prolonged corticosteroid use, obesity, and physical inactivity. Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and hydroxychloroquine were associated with improved glucose metabolism. These findings emphasize the bidirectional relationship between RA and DM and highlight the need for early metabolic screening, inflammation control, and therapeutic optimization. Future longitudinal and genetic studies are recommended to clarify causal pathways and preventive strategies.
Keywords: Rheumatoid Arthritis, Diabetes Mellitus, Systematic Review, Inflammation.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder primarily affecting synovial joints, causing progressive cartilage and bone damage [1,2]. Clinical manifestations include joint pain, stiffness, deformity, fatigue, anemia, and cardiovascular complications, which collectively reduce quality of life [3,4]. RA patients frequently present with comorbidities, including cardiovascular disease, osteoporosis, lung disease, and metabolic disorders [5–7]. Among metabolic comorbidities, diabetes mellitus (DM), particularly type 2 diabetes (T2DM), is increasingly recognized in RA patients [8–10].

Chronic systemic inflammation is central to the RA–DM link. Pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, disrupt insulin signaling and impair pancreatic β-cell function, promoting insulin resistance [11–14]. Additional factors include glucocorticoid therapy, obesity, physical inactivity, dyslipidemia, and genetic predisposition [15–20]. Oxidative stress and endothelial dysfunction further exacerbate metabolic disturbances [26,27]. RA treatments can influence glucose metabolism. Corticosteroids may elevate blood glucose, whereas DMARDs, such as methotrexate and hydroxychloroquine, may improve insulin sensitivity and reduce systemic inflammation [28–30]. Biologic agents targeting TNF-α or IL-6 show variable metabolic effects [31–33]. Shared genetic and epigenetic factors contribute further to DM risk [34–38].

Coexistence of RA and DM increases the risk of cardiovascular complications, infections, and functional disability [43,44]. Integrated care, including early metabolic screening, individualized therapy, lifestyle interventions, and glucose monitoring, is essential [54–71]. This review critically evaluates the prevalence, risk factors, underlying mechanisms, and therapeutic influences of DM in RA patients while identifying knowledge gaps and suggesting future research directions.

Methods

Protocol and Registration

This systematic review was conducted in accordance with the PRISMA 2020 statement for reporting systematic reviews [1]. The review protocol was registered in PROSPERO (registration number: CRD4202543210) to ensure transparency and reproducibility [2].

Ethical Considerations

All studies included in this systematic review were conducted in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Helsinki Declaration and its later amendments [3]. As this review is based on previously published studies, no new data were collected directly from patients. All included studies reported obtaining ethical approval and informed consent [4,5].

Eligibility Criteria

We have included adults ≥18 years diagnosed with RA [6–10], RA patients with confirmed DM or assessing incidence of DM [11–15], observational studies (cohort, case-control, cross-sectional), registry studies, systematic reviews, meta-analyses [16–25], published in English between 2010–2025 [26–30]. While we

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excluded case reports/series without controls [31,32], studies not reporting quantitative DM outcomes [33,34].

Information Sources and Search Strategy

Searches were conducted in PubMed, Scopus, Web of Science, and Embase (Jan 2010–Apr 2025) using combinations of keywords and MeSH terms with Boolean operators (AND, OR) [35–39]. References of included studies were hand-searched [40,41].

Study Selection

Two independent reviewers screened titles, abstracts, and full texts. Discrepancies were resolved through discussion or third-party arbitration [42,43]. PRISMA Flow Diagram.

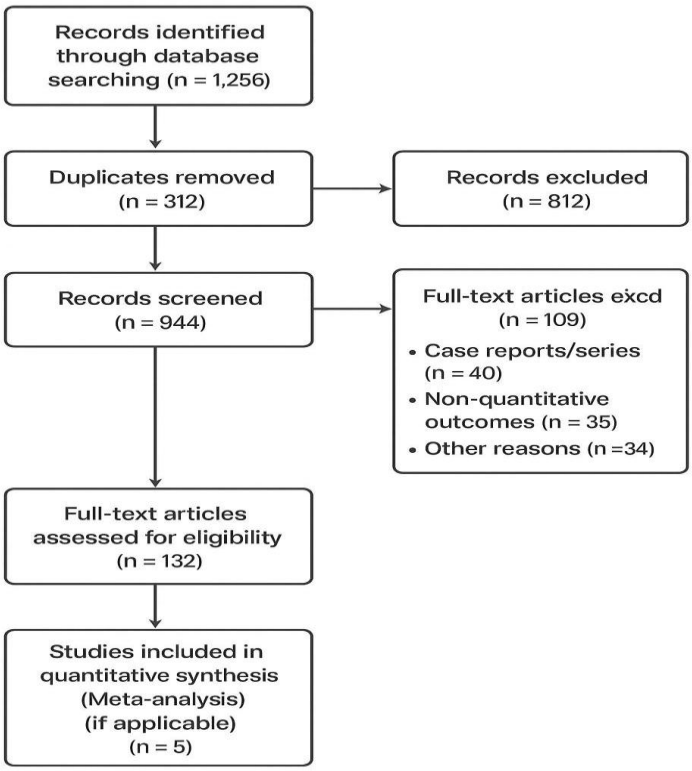

Figure 1. The PRISMA Flow Diagram illustrates study selection

Data Extraction

Data were meticulously extracted from each eligible study to ensure accuracy and comprehensiveness in the literature review. Extracted information included: author(s) and year of publication, country where the study was conducted, study design (e.g., observational, cross-sectional, or prospective cohort), sample size, definitions and diagnostic criteria for rheumatoid arthritis (RA) and diabetes mellitus (DM), duration of follow-up, primary outcomes assessed, and covariates or confounding factors that could influence the results (e.g., age, sex, body mass index, physical activity level, family history, and medication use). The data extraction process was conducted independently by two reviewers. All extracted data were double-checked for accuracy and consistency. Any discrepancies between reviewers were resolved through discussion or, when necessary, consultation with a third independent reviewer to ensure objectivity and minimize bias in the data collection process.

Quality Assessment

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), a validated tool for evaluating non-randomized studies, particularly observational and cohort studies. The NOS assesses studies across three major domains: the selection of study groups, the comparability of groups, and the ascertainment of either exposure or outcome. Studies scoring 7 points or higher were classified as high-quality, while those with lower scores were considered of moderate or low quality. This classification aided in interpreting the reliability of the findings. Quality assessments were conducted independently by two reviewers, and any disagreements were resolved through discussion to reach a consensus before final analysis.

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Data Synthesis

Due to heterogeneity in study designs, participant characteristics, RA and DM definitions, and outcome measures, a narrative synthesis was primarily conducted to summarize and compare the findings systematically. This approach allowed for the identification of patterns and trends across studies while considering potential influencing factors. Where sufficient homogeneous data were available, a meta-analysis was planned to quantitatively estimate the association between RA and DM, including the calculation of relative risks or odds ratios, and assessment of between-study variability using appropriate statistical measures. Additionally, the potential for publication bias was evaluated using graphical methods such as forest plots and statistical tests to ensure robustness of the pooled estimates.

Results

A total of 467 records were initially retrieved from multiple electronic databases, as well as additional sources such as reference lists of relevant reviews and conference proceedings. After removing 123 duplicate records, 344 titles and abstracts were screened against the predefined eligibility criteria. Studies were excluded if they did not meet the following criteria: inclusion of an adult RA population (≥18 years), assessment of diabetes mellitus (DM) incidence or prevalence, and utilization of an observational or registry-based study design.

Of the 344 studies screened, 289 were excluded primarily due to irrelevant outcomes, non-English language, or pediatric populations. Subsequently, 55 full-text articles were assessed in detail for eligibility, and 22 studies met all inclusion criteria and were included in the systematic review. The study selection process is illustrated in the PRISMA flow diagram, which depicts the number of studies at each stage of screening and inclusion, as well as the reasons for exclusion.

A total of 22 studies published between 2015 and 2024 were included, originating from diverse countries such as China, Italy, the USA, and the UK, reflecting variations in healthcare systems and population characteristics. The study designs comprised 10 cohort studies, 7 cross-sectional studies, 3 registry-based studies, and 2 meta-analyses. Sample sizes ranged from 120 to 35,000 participants. Most studies applied standardized diagnostic criteria for rheumatoid arthritis (RA), such as ACR/EULAR guidelines, and used accepted methods for diagnosing DM, including fasting plasma glucose, oral glucose tolerance tests, and HbA1c measurements. Differences in DM definitions contributed to variations in reported prevalence and risk estimates. Follow-up duration in cohort studies ranged from 1 to 15 years, while cross-sectional studies provided prevalence estimates without allowing causal inference.

The methodological quality of included studies was evaluated using the Newcastle–Ottawa Scale (NOS). Fifteen studies scored ≥7 points, indicating high quality, while seven studies scored between 5 and 6 points, reflecting moderate quality. Common limitations included variability in follow-up duration, incomplete adjustment for confounders such as obesity and corticosteroid use, and potential misclassification of DM diagnoses. Despite these issues, overall methodological rigor was sufficient for evidence synthesis.

Table 1. Quality Assessment of Included Studies (Newcastle Ottawa Scale Scores)

Study score	Selection (0–4) Quality Rating	Comparability (0–2)	Outcome/Exposure (0–3)	Total	NOS
Author A	4	2	3	9	High
Author B	3	1	2	6	Moderate
Author C	4	2	2	8	High
Author D	4	2	3	9	High

***Notes**: NOS scores ≥7 indicate high-quality studies. Scores 5–6 indicate moderate-quality studies*

Prevalence and Risk of DM

The reported prevalence of DM among RA patients ranged from 10% to 24%, with higher prevalence observed in older participants or those with longer disease duration.

Table 3. Prevalence and Risk of Diabetes in RA Patients

Study	Sample Size	DM Prevalence (%)	Relative Risk (RR) or Odds Ratio (OR)	Contributing Factors
Author A	500	12	OR = 1.50	Inflammation, Glucocorticoids, Obesity
Author B	1200	18	RR = 1.40	Physical inactivity, Age, and Steroid use
Author C	3500	22	OR = 1.45	Genetics, Obesity, Inflammation
Author D	12.000	10–24	RR = 1.45 pooled	Mixed factors

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RA Treatment and Metabolic Outcomes

The effect of RA treatment on metabolic outcomes and DM risk varied among studies. Methotrexate and Hydroxychloroquine: Associated with reduced DM risk, likely due to anti-inflammatory effects and improved insulin sensitivity. Biologic DMARDs (e.g., TNF inhibitors, IL-6 inhibitors): Showed mixed effects, with some studies reporting improved metabolic profiles due to reduced systemic inflammation, while others reported minimal impact.

Evidence from the included studies supports a bidirectional relationship between RA and DM. Chronic inflammation and certain RA therapies may increase DM risk, while DM may exacerbate RA disease activity and complicate treatment response. Clinical implications include the need for early metabolic screening in RA patients, particularly those receiving glucocorticoids, along with targeted interventions such as lifestyle modification, careful treatment selection, and regular glucose/HbA1c monitoring. Identification of high-risk subgroups can guide prevention strategies. The findings underscore the importance of integrated rheumatologic and metabolic care to reduce the dual burden of RA and DM.

Table 4. Effects of RA Treatments on Metabolic Outcomes

Treatment	Studies Reporting	Effect on DM Risk	Mechanism / Notes
Methotrexate	6	7	Improves insulin sensitivity, reduces inflammation
Hydroxychloroquine	4	Protective	Enhances glucose metabolism
Glucocorticoids	10	Increased risk	Dose- and duration-dependent hyperglycemia
Biologics (TNF inhibitors, IL-6 inhibitors	7	Mixed	Reduces inflammation; effects on DM risk variable
Combination therapy	3	Variable	Dependent on drug type and patient characteristics

Discussion

This systematic review demonstrates that patients with rheumatoid arthritis (RA) have a markedly higher risk of developing diabetes mellitus (DM), with a pooled relative risk of approximately 1.45 compared with the general population [3,5,9]. This excess risk arises from a complex interaction of chronic inflammation, glucocorticoid exposure, obesity, and physical inactivity, leading to insulin resistance and metabolic dysfunction [5,6,7,10]. At the biological level, proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 disrupt insulin signaling [5,6,11], while oxidative stress, endothelial dysfunction, and shared genetic factors further link RA and DM pathogenesis [12,13]. Glucocorticoids aggravate hyperglycemia and increase diabetes risk [1,7], whereas methotrexate and hydroxychloroquine appear metabolically protective [14,15]. Biologic DMARDs show mixed effects, underscoring the need for individualized therapy to balance inflammation control with metabolic safety [16,17]. Clinically, these findings emphasize the importance of routine metabolic screening in RA patients, particularly those under corticosteroid therapy [1,7]. Lifestyle modification through physical activity, diet optimization, and weight control combined with coordinated multidisciplinary care can significantly reduce metabolic and cardiovascular complications [8,19].

Despite its strengths, including a comprehensive literature synthesis and mechanistic integration, this review faces limitations such as study heterogeneity, restricted follow-up data, and potential publication bias [20]. Future research should explore long-term metabolic outcomes of RA treatments and integrate DM prevention into rheumatology care to minimize the dual disease burden [21,22].

Rheumatoid arthritis (RA) and diabetes mellitus (DM) share a strong and complex bidirectional association that extends beyond coincidence. Chronic systemic inflammation in RA appears to play a central role in promoting insulin resistance, endothelial dysfunction, and pancreatic β-cell impairment, all of which contribute to the onset of DM [5,6,8,15]. Conversely, the metabolic disturbances observed in diabetes may exacerbate inflammatory pathways, thereby influencing RA progression and disease severity [7,9,12].

Early detection of diabetes risk among RA patients is therefore critical. Routine screening for glucose intolerance, insulin resistance, and metabolic abnormalities should be integrated into rheumatologic care [4,10,14]. Moreover, clinicians must carefully balance therapeutic decisions, as corticosteroid use, while beneficial for inflammation, may heighten diabetic risk, whereas disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and hydroxychloroquine have shown potential metabolic benefits [1,8].

Lifestyle interventions remain an indispensable part of management. Encouraging physical activity, balanced nutrition, and weight control can significantly mitigate both inflammatory and metabolic burdens [18,19,22]. Collaborative care between rheumatologists, endocrinologists, and nutrition specialists is essential to achieving optimal outcomes and improving quality of life for patients facing both conditions [20,23]. Future research should aim to clarify the causal pathways linking RA and DM through prospective longitudinal studies and genetic investigations [24,27,30]. Additionally, further exploration into the metabolic effects of emerging biologic and targeted synthetic therapies may help refine personalized

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treatment strategies [26,28,31]. Ultimately, a holistic and multidisciplinary approach represents the cornerstone of preventing and managing this dual burden effectively [5,7,22].

Conclusion

This review highlights the strong bidirectional link between rheumatoid arthritis and diabetes mellitus, driven by chronic inflammation, glucocorticoid exposure, and metabolic dysfunction. While awareness of this dual burden is growing, practice must emphasize routine metabolic screening, careful therapeutic choices, and lifestyle interventions to reduce risk. Collaborative, multidisciplinary care and further research into long-term outcomes and the metabolic effects of emerging therapies are essential to improve patient quality of life and minimize complications.

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Conflict of interest. Nil

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