

## Review Article

# Interrelationship between rheumatoid arthritis and diabetes mellitus: current insights and perspectives

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## ABSTRACT

Rheumatoid arthritis (RA) and diabetes mellitus (DM) are chronic, systemic conditions with significant global health burdens. Emerging evidence suggests a bidirectional relationship between these diseases, with shared pathophysiological mechanisms, including chronic inflammation, immune dysregulation, and metabolic disturbances. This review explores the current insights into the interrelationship between RA and DM, emphasizing the role of pro-inflammatory cytokines, insulin resistance, and genetic predispositions. Additionally, it examines the impact of therapeutic interventions for RA on glycemic control and vice versa, highlighting challenges and opportunities in clinical management. Understanding these interactions is crucial for developing integrated treatment strategies, improving patient outcomes, and addressing the broader implications of coexisting RA and DM. This review article aims to provide a comprehensive perspective on the evolving knowledge in this field and to identify areas for future research.

**Keywords:** Rheumatoid arthritis, Diabetes mellitus, Insulin resistance, Cytokines, Interrelationship

## INTRODUCTION

Rheumatoid arthritis (RA) and diabetes mellitus (DM) are chronic systemic diseases that significantly impact global health. RA is an autoimmune disorder characterized by persistent joint inflammation, leading to pain, deformity, and disability. DM, primarily classified into type 1 and type 2, is a metabolic condition marked by hyperglycemia due to impaired insulin production or action. Both conditions independently contribute to increased morbidity and mortality and share overlapping inflammatory and metabolic pathways.<sup>1</sup>

Recent studies have highlighted a bidirectional relationship between RA and DM. Chronic inflammation, a hallmark of RA, has been implicated in the development of insulin resistance, a precursor to type 2 DM. Conversely, hyperglycemia in DM exacerbates systemic

inflammation, potentially aggravating RA symptoms. Additionally, shared genetic predispositions, lifestyle factors, and co-morbidities such as obesity and cardiovascular disease further complicate the clinical interplay between these conditions. Understanding this interrelationship is crucial for optimizing management strategies and improving patient outcomes.<sup>2,3</sup>

Despite the growing body of evidence linking RA and DM, significant gaps remain in understanding their shared patho-physiology, the impact of one condition on the progression of the other, and the influence of pharmacological treatments.

Exploring these connections is vital for developing integrated therapeutic approaches, reducing disease burden, and addressing the unique challenges faced by patients with coexisting RA and DM.<sup>4,5</sup>

## **Objectives**

The aim of this review is to provide a comprehensive review of the interrelationship between RA and DM, focusing on current insights and emerging perspectives. The specific objectives include: analyzing the shared inflammatory and metabolic pathways underlying RA and DM, evaluating the impact of RA treatments on glycemic control and the influence of DM management on RA progression, identifying clinical challenges in managing patients with coexisting RA and DM, and highlighting potential areas for future research to advance understanding and improve therapeutic outcomes.

This review aims to bridge existing knowledge gaps and provide a foundation for a more holistic approach to managing these interconnected conditions.

## **REVIEW OF LITERATURE**

RA and DM are chronic conditions that often coexist, sharing common inflammatory pathways and risk factors. Recent studies have explored the bidirectional relationship between these diseases, shedding light on their interconnected pathophysiology.<sup>6</sup>

### ***Prevalence and risk association***

A systematic review and meta-analysis by Jin et al found that individuals with RA have a 23% increased risk of developing DM compared to the general population, suggesting that inflammatory pathways in RA may contribute to DM pathogenesis.<sup>7</sup> Similarly, an analysis by Xie et al reported a 43% increased risk of DM in RA patients, with a more pronounced association with T1DM than type 2 diabetes mellitus (T2DM).<sup>8</sup>

### ***Inflammatory pathways and shared mechanisms***

Both RA and DM are characterized by systemic inflammation. Pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 play pivotal roles in the pathogenesis of both diseases, contributing to insulin resistance in DM and joint inflammation in RA. This shared inflammatory milieu suggests a common pathophysiological link.<sup>9</sup>

### ***Impact of RA treatment on DM risk***

The use of glucocorticoids (GC) in RA management has been associated with an increased risk of DM due to their hyperglycemic effects. Conversely, treatments like hydroxychloroquine and certain biologic DMARDs may reduce DM risk by modulating inflammatory pathways and improving insulin sensitivity.<sup>10</sup>

### ***Genetic predisposition***

Emerging research indicates a genetic overlap between RA and DM. A study published in *International Journal of Obesity* (2024) found that the prevalence of arthritis was

almost twice as high in diabetic patients compared to non-diabetic patients, indicating a potential genetic and observational nexus between these conditions.<sup>11</sup>

## **Clinical implications**

The coexistence of RA and DM poses significant challenges in clinical management. The presence of one condition can exacerbate the other, leading to increased morbidity and complicating treatment strategies. Therefore, a comprehensive approach that addresses both conditions simultaneously is essential for optimal patient outcomes.<sup>12</sup>

The interrelationship between RA and DM is complex, involving shared inflammatory pathways, genetic predispositions, and the impact of therapeutic interventions. Understanding this interplay is crucial for developing integrated treatment strategies and improving patient care. Further research is needed to elucidate the mechanisms linking these diseases and to identify effective interventions that can address both conditions concurrently.<sup>13</sup>

## **INCLUSION AND EXCLUSION CRITERIA**

For a comprehensive and focused review article on the interrelationship between RA and DM, the following inclusion and exclusion criteria are established.<sup>14,15</sup>

### ***Inclusion criteria***

#### ***Publication type***

Peer-reviewed journal articles, meta-analyses, systematic reviews, and clinical trials.

Articles published in reputable databases like PubMed, Scopus, Web of Science, and Google Scholar.<sup>15</sup>

#### ***Timeframe***

Studies published within the last 10 years (2014–2024) to ensure relevance and recency.

#### ***Focus***

Research explicitly addressing the pathophysiological, genetic, or clinical relationship between RA and DM. Studies exploring the impact of RA treatments on glycemic control or the effect of DM management on RA progression. Articles examining shared inflammatory pathways, such as cytokine involvement, and metabolic interactions.

#### ***Population***

Studies involving adult human populations diagnosed with RA, DM, or both.

Research including diverse demographics and geographic regions to ensure generalizability.

#### *Language*

Articles published in English to ensure accessibility and accurate interpretation.

#### **Exclusion criteria**

##### *Publication type*

Non-peer-reviewed articles, opinion pieces, editorials, or conference abstracts without detailed data.<sup>16</sup>

Studies published in predatory journals or with questionable credibility.

##### *Timeframe*

Articles published before 2014 unless they are seminal works directly relevant to the topic.

##### *Focus*

Studies that do not specifically address the interrelationship between RA and DM. Research limited to animal models or in vitro studies without clinical correlation. Articles focusing solely on either RA or DM without discussing their interaction.

##### *Population*

Studies involving pediatric populations or rare forms of RA or DM not relevant to the general adult population.

##### *Language*

Articles published in languages other than English.<sup>17</sup>

This inclusion and exclusion framework ensures that the review article is based on high-quality, recent, and clinically relevant evidence, providing valuable insights into the interrelationship between RA and DM.<sup>18</sup>

## **PATHO-PHYSIOLOGICAL CORRELATION**

RA and DM share overlapping pathophysiological mechanisms that contribute to their bidirectional relationship. These mechanisms include shared inflammatory pathways, the role of cytokines, insulin resistance, and the impact of chronic inflammation.

### **Shared pathways**

#### *Chronic inflammation*

Both RA and DM are characterized by systemic inflammation. In RA, immune-mediated joint

inflammation is driven by an autoimmune response, while in DM, particularly T2DM, low-grade inflammation contributes to insulin resistance and metabolic dysregulation.<sup>19</sup>

#### *Oxidative stress*

Excessive production of reactive oxygen species (ROS) is a common feature in both diseases, leading to cellular damage and exacerbation of inflammatory responses.

#### *Endothelial dysfunction*

Persistent inflammation in RA and DM damages the vascular endothelium, increasing the risk of cardiovascular co-morbidities.

### **Role of cytokines**

#### *Tumor necrosis factor-alpha (TNF-α)*

TNF-α is a key pro-inflammatory cytokine in RA, promoting joint inflammation and destruction.

In DM, TNF-α impairs insulin signaling, contributing to insulin resistance.<sup>20</sup>

TNF-α inhibitors used in RA treatment have shown potential in improving insulin sensitivity.

#### *Interleukin-6 (IL-6)*

IL-6 levels are elevated in both RA and DM, driving inflammation and metabolic dysregulation.

IL-6 contributes to the hepatic production of glucose, worsening hyperglycemia in DM.

#### *Interleukin-1β (IL-1β)*

IL-1β exacerbates joint inflammation in RA and promotes beta-cell dysfunction and apoptosis in the pancreas, leading to impaired insulin secretion in DM.

### **Insulin resistance**

#### *Mechanism*

Chronic inflammation in RA promotes the release of cytokines such as TNF-α and IL-6, which interfere with insulin receptor signaling pathways.<sup>21</sup>

This results in decreased glucose uptake by muscle and adipose tissues, contributing to hyperglycemia.

#### *Impact of medications*

Glucocorticoids, commonly used in RA, exacerbate insulin resistance by increasing hepatic gluconeogenesis

and reducing peripheral glucose uptake.<sup>22</sup> Conversely, some DMARDs (e.g., hydroxychloroquine) may improve insulin sensitivity.

### **Impact of chronic inflammation**

#### *Systemic effects*

In RA, systemic inflammation extends beyond joints, affecting metabolic and vascular health. Chronic inflammation in DM worsens insulin resistance and accelerates complications such as neuropathy and nephropathy.<sup>23</sup>

#### *Immune dysregulation*

Dysregulated immune responses in RA contribute to the activation of macrophages and T-cells, which secrete pro-inflammatory cytokines that also impair insulin action.<sup>24</sup>

#### *Clinical implications*

The shared inflammatory and metabolic pathways between RA and DM highlight the need for integrated management strategies.

Anti-inflammatory therapies targeting cytokines may offer dual benefits by alleviating RA symptoms and improving glycemic control in DM.

Further research is required to develop personalized treatment approaches addressing the unique challenges posed by coexisting RA and DM.<sup>25</sup>

Understanding the pathophysiological correlation between RA and DM is crucial for improving patient outcomes and mitigating the burden of these chronic diseases.

## **EPIDEMIOLOGICAL EVIDENCE**

### **Prevalence of DM in RA patients**

#### *Increased risk of diabetes in RA*

Studies indicate that individuals with RA have a higher prevalence of DM, particularly T2DM.

A meta-analysis by Jin et al reported that RA patients have a 23% increased risk of developing DM compared to the general population.

The chronic inflammation in RA is believed to contribute significantly to insulin resistance and subsequent diabetes.<sup>26</sup>

#### *Type 1 diabetes mellitus*

Though less common, T1DM and RA occasionally coexist due to shared autoimmune mechanisms.

The prevalence of T1DM in RA patients is relatively lower but still noteworthy due to overlapping genetic predispositions.

### **Prevalence of RA in DM patients**

#### *Higher incidence of RA in DM*

The prevalence of RA in patients with DM is also elevated. Chronic hyperglycemia in DM may exacerbate systemic inflammation, potentially triggering autoimmune responses.<sup>27</sup>

A study by Xie et al reported that DM patients had a 43% higher likelihood of developing RA compared to non-diabetic individuals.

### **Influence of gender**

#### *Rheumatoid arthritis*

RA is more prevalent in women, with a female-to-male ratio of approximately 3:1. Hormonal factors, particularly estrogen, are thought to play a role in immune modulation, influencing RA susceptibility.<sup>28</sup>

#### *Diabetes mellitus*

The prevalence of T2DM is slightly higher in men, but women with RA are more likely to develop DM than men with RA. This may be due to differences in adiposity, hormonal changes, and inflammation-related factors.

### **Influence of age**

#### *Rheumatoid arthritis*

RA typically manifests between the ages of 30 and 60, but the risk increases with age, particularly for seronegative RA.<sup>29</sup>

#### *Diabetes mellitus*

The prevalence of T2DM increases with age, particularly in individuals over 45 years.

Older RA patients are at a higher risk of developing T2DM due to prolonged exposure to systemic inflammation and the use of glucocorticoids.

### **Genetic predispositions**

#### *Shared genetic factors*

Certain genetic markers, such as variations in the HLA-DRB1 gene, are associated with both RA and DM.<sup>30</sup> Polymorphisms in genes related to cytokine production, such as TNF- $\alpha$  and IL-6, have been implicated in the pathogenesis of both conditions.

### *Autoimmune susceptibility*

Both RA and T1DM share autoimmune predispositions, with associations observed in genes like PTPN22 and CTLA4, which regulate immune tolerance.

### **Key observations**

The bidirectional relationship between RA and DM underscores the need for vigilance in monitoring patients with either condition for signs of the other. Gender and age significantly influence disease prevalence and progression, while genetic predispositions highlight the shared autoimmune and inflammatory underpinnings.

Understanding these epidemiological patterns is crucial for tailoring preventive strategies, early detection, and effective management of coexisting RA and DM.

## **CLINICAL IMPLICATIONS**

### **Diagnostic challenges**

The coexistence of RA and DM poses significant diagnostic challenges due to overlapping symptoms, shared inflammatory markers, and the impact of treatment modalities on clinical presentations.<sup>31</sup>

### **Overlapping symptoms**

#### *Fatigue and joint pain*

Both RA and DM can cause fatigue, making it difficult to attribute this symptom to one condition. Joint pain and stiffness, hallmark features of RA, may also occur in diabetic patients with diabetic arthropathy or neuropathy.

#### *Peripheral neuropathy*

Peripheral neuropathy is common in long-standing DM but can also result from RA-related vasculitis, leading to diagnostic confusion.

### **Shared inflammatory markers**

#### *C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)*

Elevated CRP and ESR are markers of inflammation seen in both RA and DM, especially in poorly controlled diabetes. These markers may not reliably differentiate between disease activity in RA and systemic inflammation in DM.

#### *Cytokines*

Pro-inflammatory cytokines like TNF- $\alpha$  and IL-6 are elevated in both conditions, complicating the identification of the primary driver of inflammation.

### **Impact of RA treatments on DM diagnosis**

#### *Glucocorticoids*

Glucocorticoids used in RA management can induce hyperglycemia, mimicking or exacerbating DM symptoms. Chronic steroid use may mask the onset of DM by delaying diagnosis until complications arise.

#### *Biologic DMARDs*

Biologic therapies targeting cytokines like TNF- $\alpha$  or IL-6 may improve glycemic control, potentially masking early signs of DM.<sup>32</sup>

### **Impact of DM on RA diagnosis**

#### *Masking joint symptoms*

Diabetic complications like Charcot joint or limited joint mobility syndrome can mimic RA symptoms, delaying an accurate RA diagnosis.

#### *Confounding imaging findings*

Diabetic arthropathy may cause joint deformities visible on imaging, leading to misdiagnosis as RA or obscuring RA-specific erosions.

### **Comorbidities and multisystem involvement**

#### *Cardiovascular risk*

Both RA and DM increase cardiovascular disease risk, and overlapping symptoms like chest pain or dyspnea may complicate differential diagnosis.

#### *Kidney function*

Diabetic nephropathy and RA-associated kidney involvement (e.g., amyloidosis) can present similarly, complicating diagnostic clarity.<sup>33</sup>

### **Gender and age factors**

Women with RA are at a higher risk of developing DM, and symptoms may be dismissed as age-related or hormonal changes, delaying diagnosis. Older adults with DM may develop atypical RA presentations, such as less pronounced joint inflammation, further complicating diagnosis.

### **Strategies to overcome diagnostic challenges**

#### *Comprehensive clinical evaluation*

Detailed patient history and physical examination focusing on the sequence of symptom onset.

### *Targeted biomarkers*

Utilizing disease-specific markers like anti-cyclic citrullinated peptide (anti-CCP) antibodies for RA and HbA1c for DM to confirm diagnoses.

### *Multidisciplinary approach*

Collaboration between rheumatologists, endocrinologists, and primary care physicians to ensure accurate diagnosis and management.

### *Regular monitoring*

Routine screening for DM in RA patients and vice versa, particularly in high-risk populations. The coexistence of RA and DM requires heightened clinical awareness and a tailored diagnostic approach to address overlapping features and ensure timely and accurate identification of both conditions.

## **MANAGEMENT**

### ***Impact of RA treatments on glucose metabolism***

The treatment of RA often involves medications that can significantly influence glucose metabolism, particularly in patients with coexisting DM. Understanding these effects is crucial for optimizing therapeutic strategies and minimizing adverse metabolic outcomes.

### ***Corticosteroids***

#### *Mechanism of action*

Corticosteroids like prednisone are potent anti-inflammatory agents used to control RA symptoms. They act by suppressing pro-inflammatory cytokines and modulating immune responses.

#### *Impact on glucose metabolism*

#### *Hyperglycemia*

Corticosteroids increase hepatic gluconeogenesis, reduce peripheral glucose uptake, and impair insulin secretion, leading to hyperglycemia.

#### *Insulin resistance*

Prolonged corticosteroid use exacerbates insulin resistance, making blood glucose levels harder to control in diabetic patients.

#### *Risk of new-onset diabetes*

Chronic corticosteroid therapy in RA patients can lead to glucocorticoid-induced diabetes mellitus (GIDM), particularly in individuals with predisposing risk factors.<sup>34</sup>

### *Clinical implications*

Blood glucose levels should be closely monitored in RA patients receiving corticosteroids.

Strategies like tapering doses, using alternate-day regimens, or switching to steroid-sparing agents can help mitigate metabolic side effects.

### ***Biologic DMARDs***

#### *Tumor necrosis factor-alpha (TNF-α) inhibitors*

Examples include infliximab, adalimumab, and etanercept.

#### *Effect on glucose metabolism*

TNF-α inhibitors improve insulin sensitivity by reducing systemic inflammation and cytokine-induced insulin resistance.

#### *Clinical evidence*

Studies have shown improved glycemic control (e.g., reduced HbA1c levels) in RA patients with DM treated with TNF-α inhibitors.

#### *Interleukin-6 (IL-6) inhibitors*

Examples include tocilizumab and sarilumab.

#### *Effect on glucose metabolism*

IL-6 inhibitors decrease hepatic glucose production and improve peripheral insulin sensitivity, benefiting glycemic control.

#### *Considerations*

These agents may be particularly useful in RA patients with poorly controlled DM.

#### *Interleukin-1 (IL-1) inhibitors*

Example include anakinra.

#### *Effect on glucose metabolism*

IL-1 inhibitors have been shown to improve beta-cell function and reduce systemic inflammation, aiding glycemic control in RA patients with DM.<sup>35</sup>

### ***Methotrexate***

#### *Mechanism of action*

Methotrexate (MTX), a conventional DMARD, reduces inflammation by inhibiting dihydrofolate reductase and modulating cytokine production.

### *Impact on glucose metabolism*

MTX indirectly improves insulin sensitivity by reducing systemic inflammation.

Studies suggest that MTX may lower the risk of developing DM in RA patients.

### **Hydroxychloroquine**

#### *Mechanism of action*

Hydroxychloroquine (HCQ) modulates immune responses and has anti-inflammatory properties.

#### *Impact on glucose metabolism*

HCQ enhances insulin sensitivity and reduces blood glucose levels by improving insulin receptor function and reducing inflammation.

Clinical trials have demonstrated a significant reduction in HbA1c levels in diabetic patients treated with HCQ.

#### **Janus kinase inhibitors**

Examples include tofacitinib and baricitinib.

#### *Impact on glucose metabolism*

Janus kinase (JAK) inhibitors target cytokine signaling pathways, reducing inflammation and potentially improving insulin sensitivity.

However, long-term effects on glucose metabolism require further investigation.

### **Non-pharmacological considerations**

#### *Lifestyle modifications*

Patients with RA and DM should be encouraged to adopt anti-inflammatory diets, engage in regular physical activity, and manage stress to improve glucose metabolism.

#### *Weight management*

Obesity exacerbates insulin resistance and inflammation, complicating the management of both RA and DM. Weight loss can significantly improve outcomes.<sup>36</sup>

## **KEY CLINICAL RECOMMENDATIONS**

### **Individualized therapy**

Tailor RA treatment regimens to minimize adverse effects on glucose metabolism, especially in patients with preexisting DM.

### **Monitoring**

Regularly monitor blood glucose levels and HbA1c in RA patients, particularly those on corticosteroids or with risk factors for DM.

### **Interdisciplinary care**

Collaboration between rheumatologists, endocrinologists, and primary care providers is essential for optimizing management in patients with RA and DM.

Effective management of RA and DM requires a delicate balance between controlling inflammation and maintaining glycemic stability, emphasizing the need for an integrated and patient-centered approach.

## **COMORBIDITIES IN RA AND DM**

It includes cardiovascular risks, neuropathy, and joint deformities.

RA and DM are chronic inflammatory conditions that often coexist, sharing common pathophysiological pathways and contributing to significant comorbidities. These include cardiovascular risks, neuropathy, and joint deformities, which complicate the clinical management of affected patients.

### **Cardiovascular risks**

#### *Shared mechanisms*

Chronic systemic inflammation in both RA and DM accelerates atherosclerosis and endothelial dysfunction.<sup>37</sup>

Pro-inflammatory cytokines like TNF- $\alpha$  and IL-6, elevated in both conditions, contribute to plaque formation and instability.

#### *Increased risk in coexisting RA and DM*

RA and DM individually double the risk of cardiovascular disease (CVD); their coexistence significantly amplifies this risk.

Patients are at higher risk of myocardial infarction, stroke, and heart failure.

#### *Key factors*

#### *Insulin resistance*

Exacerbated by systemic inflammation in RA.

#### *Dyslipidemia*

Common in both conditions, with RA patients often presenting with an atherogenic lipid profile.

## *Hypertension*

Frequently observed in RA and DM due to vascular inflammation and metabolic disturbances.

### *Clinical implications*

Aggressive management of traditional CVD risk factors (e.g., hypertension, dyslipidemia).

Use of anti-inflammatory therapies (e.g., TNF- $\alpha$  inhibitors) may reduce CVD risk in RA patients.

## **Neuropathy**

### *Diabetic neuropathy*

A common complication of DM, resulting from chronic hyperglycemia-induced nerve damage.

Symptoms include numbness, tingling, burning sensations, and loss of sensation, typically in a "glove and stocking" distribution.

### *RA-associated neuropathy*

Peripheral neuropathy in RA may result from vasculitis, inflammation of the peripheral nerves, or compression due to joint deformities (e.g., carpal tunnel syndrome).<sup>38</sup>

### *Overlap and challenges*

Neuropathy in RA-DM patients can be multifactorial, complicating diagnosis and treatment.

RA-related vasculitis may mimic diabetic neuropathy, requiring careful differentiation.

### *Clinical implications*

Regular neurological assessments in patients with coexisting RA and DM. Optimize glycemic control in DM and manage RA inflammation to prevent progression.

## **Joint deformities**

### *RA-related joint deformities*

RA causes progressive joint damage and deformities due to chronic synovitis, cartilage destruction, and bone erosion. Common deformities include ulnar deviation, swan-neck deformities, and boutonnière deformities.

### *DM-related joint conditions*

### *Diabetic arthropathy*

It includes conditions like Charcot joint, where neuropathy leads to joint destruction and deformity.

Limited joint mobility syndrome: Also known as diabetic cheiroarthropathy, characterized by stiffness and contractures, particularly in the hands.

### *Impact of coexistence*

DM-related complications like Charcot joint can mimic or exacerbate RA deformities.

Joint damage in RA may be accelerated by poor glycemic control in DM.

### *Clinical implications*

Early diagnosis and intervention to prevent irreversible joint damage.

Use of imaging modalities (e.g., MRI, ultrasound) to differentiate between RA and DM-related joint pathology.

## **MANAGEMENT STRATEGIES**

### *Integrated approach*

Collaboration between rheumatologists, endocrinologists, and primary care providers is essential.

### *Monitoring*

Regular screening for CVD, neuropathy, and joint complications in patients with RA and DM.

### *Lifestyle modifications*

Encourage anti-inflammatory diets, regular exercise, and smoking cessation to reduce comorbid risks.

### *Targeted therapies*

Use of biologics (e.g., TNF- $\alpha$  or IL-6 inhibitors) in RA may reduce systemic inflammation and improve comorbid outcomes.

Optimize glycemic control in DM to prevent neuropathy and joint complications.

The coexistence of RA and DM significantly increases the risk of cardiovascular complications, neuropathy, and joint deformities. A proactive, multidisciplinary approach is essential to mitigate these risks, improve patient outcomes, and enhance quality of life.

## **CURRENT TREATMENT APPROACHES**

Current treatment approaches include DM management in RA, RA management in DM, and integrated approaches.

The coexistence of RA and DM presents unique challenges in management due to overlapping pathophysiological

mechanisms, medication interactions, and the impact of inflammation on glycemic control. Treatment strategies must be tailored to address both conditions effectively while minimizing adverse effects.<sup>39</sup>

### ***DM management in RA***

RA-associated systemic inflammation can worsen glycemic control in DM patients. Conversely, some RA treatments can either improve or exacerbate glucose metabolism.

#### *Goals*

Maintain optimal glycemic control.

Reduce systemic inflammation to improve insulin sensitivity.

Minimize the metabolic side effects of RA therapies.

#### *Approaches*

##### *Anti-inflammatory treatments*

TNF- $\alpha$  inhibitors improve insulin sensitivity by reducing inflammation. IL-6 inhibitors decrease hepatic glucose production and improve peripheral insulin sensitivity.

##### *Steroid-sparing strategies*

Minimize or avoid glucocorticoids, as they can induce hyperglycemia.

Use DMARDs (e.g., methotrexate) or biologics as alternatives to control RA.

##### *Lifestyle interventions*

Anti-inflammatory diets, regular physical activity, and weight management to improve both RA symptoms and glycemic control.

##### *Monitoring*

Regular glucose monitoring in RA patients, especially during corticosteroid therapy.

### ***RA management in DM***

Managing RA in DM patients requires balancing effective inflammation control with the potential impact of RA therapies on glucose metabolism.

#### *Goals*

Control RA disease activity, avoid therapies that exacerbate hyperglycemia, and monitor and mitigate cardiovascular risks.

#### *Approaches*

##### ***Glucose-friendly RA therapies***

MTX reduces systemic inflammation without adversely affecting glucose metabolism.

HCQ improves glycemic control by enhancing insulin sensitivity.

Biologics like TNF- $\alpha$  and IL-6 inhibitors are effective in RA and may improve glucose metabolism.

##### ***Avoiding high-risk medications***

Minimize glucocorticoid use to prevent hyperglycemia.

Avoid non-steroidal anti-inflammatory drugs (NSAIDs) in patients with renal complications from DM.

##### ***Management of comorbidities***

Address cardiovascular risks, neuropathy, and joint deformities common in both RA and DM.

##### ***Integrated approaches***

Given the shared pathophysiology and overlapping comorbidities, an integrated approach is essential for managing RA and DM concurrently.

##### ***Principles***

Holistic patient assessment, including metabolic, inflammatory, and cardiovascular profiles.

Multidisciplinary collaboration between rheumatologists, endocrinologists, and primary care providers.

Personalized treatment plans based on disease severity, comorbidities, and patient preferences.

##### ***Strategies***

###### *Inflammation control and glycemic optimization*

Use biologics to target shared inflammatory pathways (e.g., TNF- $\alpha$ , IL-6) to benefit both RA and DM.

Incorporate insulin sensitizers (e.g., metformin) in DM management.

###### *Lifestyle modifications*

Promote anti-inflammatory diets (e.g., Mediterranean diet) to improve both RA symptoms and glucose control.

Encourage low-impact exercises (e.g., swimming, yoga) to reduce joint stress and enhance insulin sensitivity.

### *Monitoring and prevention*

Screen for cardiovascular risks, neuropathy, and renal complications regularly. Monitor medication side effects, especially hyperglycemia with corticosteroids or renal issues with NSAIDs.

### *Patient education*

Empower patients with knowledge about the interplay between RA and DM. Encourage adherence to treatment plans and lifestyle changes.

### **Future directions**

#### *Research on dual-target therapies*

Development of drugs targeting both RA inflammation and DM metabolic pathways.

#### *Biomarker identification*

Advanced biomarkers to personalize therapy and predict treatment responses.

#### *Digital health tools*

Use of wearable devices and apps for monitoring disease activity, glucose levels, and treatment adherence.

The effective management of RA and DM requires an integrated approach that addresses shared inflammatory mechanisms, minimizes treatment-related adverse effects, and prioritizes patient-centered care. Collaboration across specialties and ongoing research into dual-target therapies will further enhance outcomes for patients with these chronic conditions.

## **RECENT ADVANCES**

Recent advances in RA and DM include biomarkers, therapeutic innovations, and personalized medicine.

The complex interrelationship between RA and DM has spurred research into shared mechanisms, novel biomarkers, and innovative therapeutic strategies. Recent advancements focus on improving diagnostic accuracy, enhancing treatment efficacy, and tailoring interventions through personalized medicine.<sup>40</sup>

### **Biomarkers in RA and DM**

#### *Emerging biomarkers*

#### *Inflammatory cytokines*

TNF- $\alpha$ , IL-6, and IL-1 $\beta$  are elevated in both RA and DM, linking chronic inflammation to insulin resistance and joint damage.

Their levels can guide disease activity and therapeutic response.

#### *Adipokines*

Adiponectin and leptin, secreted by adipose tissue, play roles in RA inflammation and insulin sensitivity.

Elevated leptin levels are associated with worse outcomes in both RA and DM.

#### *Autoantibodies*

Anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) are specific to RA but may also be associated with metabolic disturbances in DM.

#### *Metabolic biomarkers*

Glycated hemoglobin (HbA1c) and advanced glycation end products (AGEs) provide insights into glucose metabolism and its impact on RA progression.

#### *Clinical utility*

Biomarkers are being integrated into risk prediction models for early detection and stratification of RA and DM patients.

They enable monitoring of treatment responses and disease progression.

### **Therapeutic innovations**

#### *Advances in RA therapies*

#### *Targeted biologics*

IL-6 inhibitors (e.g., tocilizumab) reduce systemic inflammation and improve glucose metabolism in DM. JAK inhibitors (e.g., baricitinib) provide effective RA control with potential benefits for insulin sensitivity.

#### *Small molecule therapies*

Tyrosine kinase inhibitors are under investigation for dual anti-inflammatory and metabolic effects.

#### *Advances in DM therapies*

#### *Anti-inflammatory diabetes drugs*

GLP-1 receptor agonists (e.g., liraglutide) improve glucose control and exhibit anti-inflammatory properties beneficial for RA.

SGLT2 inhibitors (e.g., empagliflozin) reduce cardiovascular risks, a common comorbidity in RA-DM overlap.

### *Adjunctive therapies*

Hydroxychloroquine (HCQ), traditionally used in RA, has shown benefits in improving glycemic control in DM.

### *Combination approaches*

Combining biologics for RA with glucose-lowering agents for DM is being explored to address shared pathways effectively.

## **Personalized medicine**

### *Precision diagnostics*

Genomic studies have identified shared genetic predispositions (e.g., HLA-DRB1 alleles) in RA and DM, aiding in risk stratification. Advanced imaging techniques (e.g., PET-MRI) provide insights into joint inflammation and metabolic disturbances.

### *Individualized treatment plans*

#### *Pharmacogenomics*

Genetic testing is guiding the selection of biologics and DMARDs in RA based on individual responses.

In DM, genetic markers predict responsiveness to insulin sensitizers and other therapies.

#### *Lifestyle personalization*

Diet and exercise regimens are being tailored based on inflammatory and metabolic profiles. Anti-inflammatory diets (e.g., Mediterranean diet) show promise in improving both RA and DM outcomes.

#### *Digital health tools*

Wearable devices and apps track glucose levels, inflammatory markers, and joint function, enabling real-time adjustments to therapy. Artificial intelligence (AI) algorithms are being used to predict disease flares and optimize treatment schedules.

## **Future directions**

### *Dual-target therapies*

Development of drugs targeting both RA and DM pathways, such as combined IL-6 and glucose metabolism modulators.

### *Microbiome-based interventions*

Gut microbiota alterations influence inflammation and insulin resistance. Probiotics and prebiotics are being studied for their therapeutic potential.

### *Regenerative medicine*

Stem cell therapies are being explored for repairing joint damage in RA and improving pancreatic function in DM.

### *AI-driven insights*

Machine learning models are enhancing the understanding of RA-DM interactions and optimizing personalized treatment plans.

Recent advances in biomarkers, therapeutic innovations, and personalized medicine are transforming the management of RA and DM. These developments promise improved diagnostic precision, targeted treatments, and better quality of life for patients facing the dual burden of these chronic conditions.

## **CHALLENGES AND GAPS**

Challenges and gaps in the interrelationship of RA and DM.

Despite significant advancements in understanding the interrelationship between RA and DM, several challenges and gaps remain. These obstacles hinder optimal management, necessitate interdisciplinary approaches, and emphasize the need for patient-centric care strategies.<sup>41</sup>

### ***Lack of large-scale longitudinal studies***

#### *Challenges*

##### *Limited data on causality*

Most existing studies are cross-sectional, providing associations but not causal relationships between RA and DM.

Longitudinal studies are needed to explore the bidirectional influence of inflammation and metabolic dysfunction over time.

##### *Heterogeneity in study populations*

Variations in genetic, environmental, and lifestyle factors across populations make it difficult to generalize findings.

##### *Insufficient focus on comorbidities*

Comorbidities such as cardiovascular disease, neuropathy, and obesity complicate the RA-DM relationship but are underexplored in existing research.

#### *Opportunities*

Establishing large-scale, multicenter longitudinal cohorts to assess disease progression, shared mechanisms, and treatment outcomes.<sup>42</sup>

Incorporating diverse populations to ensure findings are applicable globally.

### ***Need for interdisciplinary care models***

#### *Challenges*

##### *Fragmented care*

RA and DM are often managed independently by rheumatologists and endocrinologists, leading to a lack of coordinated care.

Overlapping symptoms (e.g., fatigue, joint pain) may be misattributed to one condition, delaying diagnosis and treatment of the other.

##### *Inadequate training*

Healthcare providers may lack expertise in managing the complexities of coexisting RA and DM.

##### *Communication barriers*

Poor communication between specialists can result in conflicting treatment plans and suboptimal outcomes.

#### *Opportunities*

Developing integrated care models that include rheumatologists, endocrinologists, primary care physicians, and allied health professionals. Establishing shared decision-making frameworks to align treatment goals for both conditions. Utilizing digital health tools for real-time communication and coordinated care delivery.

### ***Addressing patient adherence and quality of life***

#### *Challenges*

##### *Complex treatment regimens*

Patients with RA and DM often face polypharmacy, leading to poor adherence due to pill burden, side effects, and financial constraints.

##### *Impact on quality of life*

Chronic pain, fatigue, and functional limitations from RA, combined with the demands of managing DM, significantly affect physical and mental well-being. Depression and anxiety are common, further complicating adherence to treatment and lifestyle modifications.

##### *Health literacy*

Limited understanding of the interplay between RA and DM can hinder patient engagement in self-management.<sup>43</sup>

#### *Opportunities*

Simplifying treatment regimens by prioritizing dual-benefit therapies (e.g., IL-6 inhibitors for RA and improved glycemic control).

Implementing patient education programs to enhance understanding of disease management and the importance of adherence.

Providing psychological support and counseling to address mental health challenges and improve quality of life.

### ***Research and clinical gaps***

#### *Challenges*

##### *Limited understanding of shared pathways*

The exact mechanisms linking chronic inflammation, insulin resistance, and joint damage remain unclear.

##### *Lack of personalized treatment guidelines*

Current guidelines for RA and DM do not adequately address their coexistence or shared management strategies.

##### *Underutilization of biomarkers*

While promising biomarkers exist, their integration into clinical practice is limited.

#### *Opportunities*

Conducting mechanistic studies to unravel shared inflammatory and metabolic pathways.

Developing evidence-based guidelines for managing patients with both RA and DM.

Advancing biomarker research for early detection, risk stratification, and monitoring treatment responses.

Addressing the challenges and gaps in the interrelationship between RA and DM requires a multifaceted approach, including robust research efforts, interdisciplinary care models, and patient-centered strategies. By overcoming these obstacles, healthcare providers can enhance disease management, improve patient outcomes, and elevate the quality of life for those living with these chronic conditions.<sup>44</sup>

### **FUTURE DIRECTIONS**

The intricate interrelationship between RA and DM necessitates a forward-looking approach to enhance understanding, diagnosis, and management. The following areas of focus are critical for advancing research and clinical care.<sup>45</sup>

### **Call for research on molecular mechanisms**

#### *Deepening understanding of shared pathways*

Investigate the molecular links between chronic inflammation, cytokine activity, and insulin resistance to identify key drivers of the RA-DM association.

Explore the role of emerging factors, such as adipokines, oxidative stress, and the gut microbiome, in the pathogenesis of both conditions.

#### *Epigenetics and gene-environment interactions*

Study epigenetic modifications and their influence on the onset and progression of RA and DM.

Examine how environmental factors, such as diet, stress, and infections, interact with genetic predispositions.

### **Exploration of novel therapeutic targets**

#### *Dual-target therapies*

Develop drugs that simultaneously address inflammatory and metabolic pathways, such as combined cytokine inhibitors or metabolic modulators.

#### *Biologic innovations*

Expand research on biologics like IL-6 inhibitors and JAK inhibitors for their dual benefits in controlling inflammation and improving glucose metabolism.

#### *Regenerative medicine*

Investigate the potential of stem cell therapy for repairing joint damage in RA and restoring pancreatic function in DM.

#### *Microbiome-based interventions*

Explore probiotics, prebiotics, and microbiome modulation as therapeutic strategies for both conditions.

### **Advocacy for integrated guidelines**

#### *Developing evidence-based protocols*

Advocate for the creation of clinical guidelines that address the coexistence of RA and DM, focusing on screening, diagnosis, and management.

#### *Personalized treatment approaches*

Promote the integration of biomarkers and pharmacogenomics into treatment plans to tailor therapies to individual patient profiles.

### **Interdisciplinary care models**

Encourage collaboration among rheumatologists, endocrinologists, and primary care providers to ensure comprehensive and coordinated care.

Future directions in understanding and managing RA and DM lie at the intersection of advanced research, innovative therapies, and collaborative care models. By prioritizing molecular studies, exploring novel therapeutic targets, and advocating for integrated guidelines, we can improve outcomes and quality of life for patients affected by these interconnected chronic conditions.<sup>46</sup>

## **CONCLUSION**

The interrelationship between RA and DM highlights a complex interplay of shared pathophysiological mechanisms, overlapping risk factors, and mutual clinical challenges. Chronic inflammation, insulin resistance, and cytokine dysregulation form the cornerstone of this association, underscoring the need for an integrated approach to understanding and managing these conditions.

Key findings from this review reveal the following.

#### **Shared pathways**

The role of inflammatory cytokines and metabolic disturbances in linking RA and DM.

#### **Epidemiological evidence**

A significant prevalence of DM in RA patients and vice versa, influenced by factors such as age, gender, and genetic predispositions.

#### **Clinical implications**

Diagnostic challenges posed by the coexistence of these conditions, often leading to delayed or suboptimal treatment.

#### **Management complexities**

The dual impact of RA treatments on glucose metabolism and the influence of DM therapies on RA progression.

#### **Comorbidities**

Increased cardiovascular risks, neuropathy, and joint deformities in patients with both RA and DM, necessitating holistic care.

#### **Advances in care**

Emerging biomarkers, therapeutic innovations, and personalized medicine approaches hold promise for better outcomes.

Understanding the correlation between RA and DM is crucial for early diagnosis, effective management, and prevention of complications. A multidisciplinary approach, incorporating rheumatology, endocrinology, and primary care, is essential to address the overlapping challenges and optimize patient care.

Future research should focus on large-scale longitudinal studies, development of integrated care models, and exploration of novel therapeutic targets. By bridging the knowledge gaps and implementing evidence-based strategies, we can improve the quality of life for patients living with the dual burden of RA and DM.

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