

# Association of Rheumatoid Arthritis with Diabetic Comorbidity: Correlating Accelerated Insulin Resistance to Inflammatory Responses in Patients

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**Abstract:** Over the past two decades, with advancement of medical research and technology, treatments of many diseases including chronic disorders like rheumatoid arthritis (RA) have been revolutionized. Treatment and management of RA has been refined by advances in understanding its pathologic mechanisms, the development of drugs which target them and its association with various other chronic comorbidities like diabetes. Diabetes prevalence is closely associated with RA since elevated insulin resistance have been observed with RA. It is also associated with inflammation caused due to pro-inflammatory cytokines like tumour necrosis factor  $\alpha$  and interleukin 6. Inflammation encourages insulin resistance and also stimulates other factors like a high level of rheumatoid factor in the blood leading to positivity of rheumatoid factor in RA patients. The degree of RA inflammation also tends to influence the criticality of insulin resistance, which increases with high activity of RA and vice versa. Markers of glucose metabolism appear to be improved by DMARDs like methotrexate, hydroxychloroquine, interleukin 1 antagonists and TNF antagonist while glucocorticoids adversely affect glycemic control especially when administered chronically. The intent of the present review paper is to understand the association between RA, insulin resistance and diabetes; the degree to which both can influence the other along with the plausible impact of RA medications on diabetes and insulin resistance.

**Keywords:** rheumatoid arthritis, diabetes, myocardial infarction, tumor necrosis factor  $\alpha$ , interleukin 6

## Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory and chronic autoimmune disorder that causes symmetrical polyarthritis of small as well as large joints, usually between the ages of 30 and 50 years.<sup>1</sup> Various genetic and environment risk factors have been found to influence the disease susceptibility. Researchers have demonstrated that genetic variation accounts for 50 to 60% of the RA risk development.<sup>2</sup>

While RA affects nearly 1% of the world's adults,<sup>3</sup> its association with other chronic disorders like diabetes has been widely explored upon in recent years with the advancement in medical research and technology. Dougados et al performed the first population-based cross-sectional observational study (n=4586) to evaluate various comorbidities in RA patients from five distinct continents and confirmed the high prevalence of comorbidities in RA patients.<sup>4</sup> Studies reported that RA enhances the atherosclerotic cardiovascular disorder risk among RA patients.<sup>5-7</sup>

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Adipokines also play a key role in cardiovascular and atherosclerosis risk among patients with RA.<sup>8</sup> Although the number of people with diabetes is much more than RA (463 million in 2019) and continues to increase due to the challenges of modern lifestyle,<sup>9</sup> however their interdependence cannot be rejected. In fact, around 90% of all diabetes cases related to type 2 diabetes (T2D)<sup>10</sup> and recent research reveals the progression of RA with insulin resistance, advancing into T2D. Further, diabetes being a chronic disease has been found to be associated with the increased risk and complication of several cardiovascular diseases, chronic kidney disease, and other diseases like blindness resulting in an increase in morbidity and mortality among diabetic patients.<sup>11</sup>

The association of RA with diabetes has been identified in several cases, and anomalies are linked with RA in the metabolism of glucose, primarily insulin resistance which may develop into T2D.<sup>12</sup> Numerous findings supported a higher chance of diabetic prevalence in people with RA, whereas some studies reported conflicting results in their association.<sup>13–15</sup> Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL6) were observed to be associated with pathogenesis of diabetes, insulin resistance and RA.<sup>15</sup> The intent of the present review paper is to understand the association between RA, insulin resistance and diabetes; the degree to which they can influence each other along with the plausible impact of RA medications on diabetes and insulin resistance.

## Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a chronic disorder and the strongest genetic risk factor linked to its onset and progression are (HLA)-DRB1\*01, \*04, and \*10 alleles, particularly for anti-citrullinated protein antibody (ACPA) positive RA.<sup>16</sup> Mostly *HLA-DRB1* gene variants linked with RA have indistinguishable sequence of amino acids among peptide binding groove, known as shared epitope (SE).<sup>17</sup> Environmental factors like smoking and infection can also have an impact on the development, progression and severity of RA.<sup>18,19</sup> RA patients have higher rheumatoid factor (RF) titers, that are auto-antibodies against Fc portion of immunoglobulin G (IgG), expected to have extra articular manifestations involving rheumatoid vasculitis, rheumatoid nodules, and hematologic, cardiovascular, pleuropulmonary, digestive, neurologic, cutaneous, and ocular complications.<sup>20–22</sup> RA may become more complex by vasculitis with systemic manifestations.<sup>23,24</sup>

In the pathophysiology of RA, B lymphocytes, T lymphocytes, and coordinated communication of pro-inflammatory cytokines play significant roles.<sup>25,26</sup> Pro-inflammatory cytokines such as TNF- $\alpha$  and IL6 influenced RA pathogenesis.<sup>27,28</sup> Vascular endothelial growth factor (VEGF), IL1 and IL17 also have an important influence on RA. The multifaceted interaction of cytokines and effector cells results in joint damage which is initiated at synovium or synovial membrane. Local activation and/or recruitment of plasma cells, macrophages, mastocytes, B lymphocytes, T lymphocytes, and angiogenesis causes synovitis. Synovial lining turns to hyperplastic and synovial membrane enlarges and create villi structures. Pannus or osteoclast-rich area of synovium damages the bone and cartilage degrades over time by the enzymes released by chondrocytes, neutrophils, and synoviocytes.<sup>25</sup>

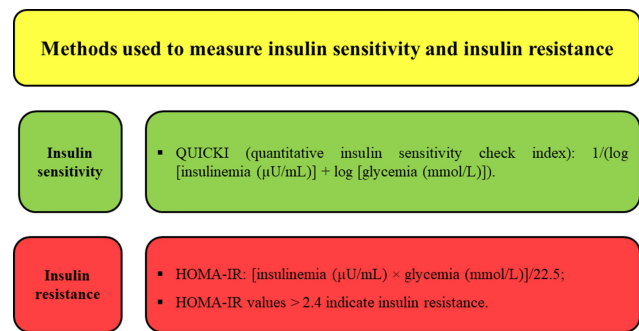
## Rheumatoid Arthritis and Insulin Resistance

### Insulin Resistance

Insulin sensitivity occurs due to biological effects in the insulin responsive tissue mainly adipose, liver, and striated muscle tissue. Decreased insulin sensitivity is also called insulin resistance (IR) and it is usually classified as decreased suppression of hepatic glucose production, reduced lipolysis rate among adipose or fat tissue and impaired clearance of glucose in striated muscle or through reduced joint action on complete body glucose disposal.<sup>29</sup> IR plays a key role in metabolic syndrome's pathophysiology and it is linked with a twofold increase in cardiovascular disease risk.<sup>30</sup> There are several methods present which depict the relationship between insulin and fasting blood sugar. Among all methods, homeostatic model assessment for insulin resistance (HOMA-IR) is a low cost, fast, and accurate method and it is based on statistics for assessing IR and function of  $\beta$  cells (Figure 1).<sup>31</sup>

### Association of IR and RA

IR prevalence has been observed to be greater in people with RA (58% and 51% in long-standing and early RA, respectively) in comparison with normal people (19%).<sup>32–34</sup> Insulin resistance in RA partially causes obesity by increasing fat mass, disease activities, and occurrence of RF. Insulin resistance can also be linked significantly with some inflammation markers such as C-reactive protein (CRP) and TNF (Figure 2).<sup>32,35</sup>



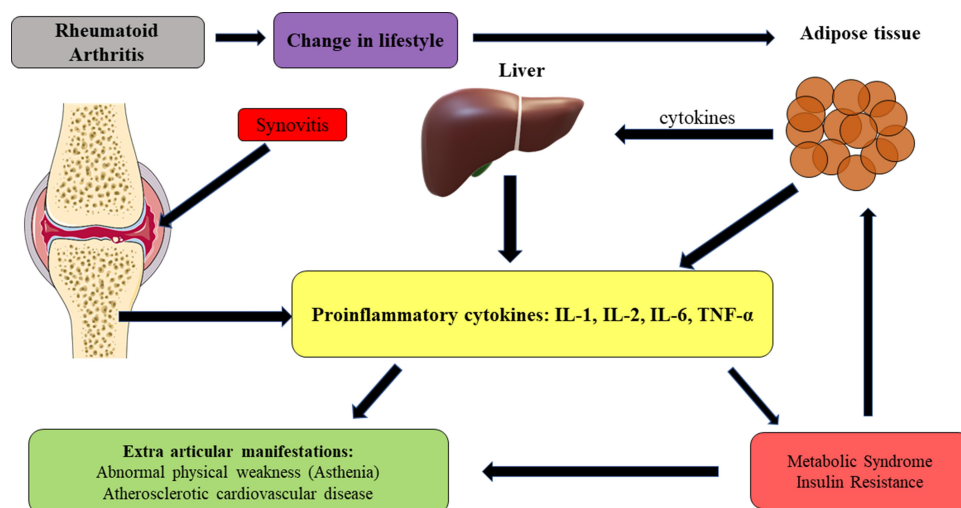
**Figure 1** Processes applied to determine insulin sensitivity and insulin resistance.  
**Notes:** Data from Nicolau et al.<sup>127</sup>

According to a study by Shahin et al, insulin resistance is more serious and critical in people experiencing high disease activity than in people experiencing medium disease activity. Measured disease activity by disease activity score 28 (DAS28), people with DAS28  $> 5.5$  exhibit high disease activity and people with DAS28  $\geq 3.6$  or DAS28  $\leq 5.5$  exhibit medium disease activity.<sup>36</sup> Insulin resistance is not associated with all rheumatic disease or all inflammatory cytokines.<sup>34,37</sup> For example, insulin resistance is not associated with inflammation severity among individuals with systemic lupus erythematosus (SLE), regardless of alike concentration of TNF serum that is observed in people with RA.<sup>37</sup> Obesity was the main factor for insulin resistance in the case of SLE and serum IL6 in the case of RA.<sup>37</sup> Giles et al reported that insulin resistance in RA was correlated with prednisone therapeutic technique, level of

CRP and positivity of RF. However, it was not correlated with serum IL6 determined at a particular time.<sup>34</sup> People having a low level of IL6 exhibited higher insulin resistance in comparison with sex and age coordinated study controls having a similar level of IL6. The inconsistency between high insulin resistance and a low level of IL6 indicates that the main factors that are responsible for insulin resistance are incidence of noninflammatory factors.<sup>34</sup> Other researchers also reported that longterm exposure to increased IL6 level induced insulin resistance, which suggests different processes responsible for insulin resistance in RA and SLE. Hence, inflammation can encourage insulin resistance and also stimulate other factors like positivity of RF.<sup>38</sup>

## Association of RA and Diabetes

The worldwide diabetes prevalence is 463 million (9.3% in 2019), predicted to increase more than 10% by 2045.<sup>39</sup> In a British cohort study, 11,158 RA patients were tracked for 24 years (1986–2010), rate of incidence of diabetes was 6.3 per 1000 person-years.<sup>40</sup> After adjusting body mass index (BMI), age, sex, consumption of alcohol, history of smoking, glucocorticoid therapeutic technique and related comorbidities, HR of development of diabetes in people with RA in comparison with gender and age matched healthy controls was 0.94 with 95%CI: 0.84–1.06. Therefore, lifestyle factors such as smoking, alcohol consumption, and high BMI (or obesity) were found to be mainly responsible in developing diabetes among RA



**Figure 2** Commonality between pathophysiology of rheumatoid arthritis and insulin resistance.

**Notes:** Adapted from Wasko MC, Kay J, Hsia EC, Rahman MU. Diabetes mellitus and insulin resistance in patients with rheumatoid arthritis: risk reduction in a chronic inflammatory disease. © 2011 the American College of Rheumatology.<sup>15</sup>

**Abbreviations:** TNF, tumor necrosis factor; IL, interleukin.

patients.<sup>40</sup> Su et al reported that the main reason for mortality in RA patients is cardiovascular disease. Along with diabetes, hyperlipidemia and hypertension are important and the main cardiovascular disease risk factors. Their study revealed that hyperlipidemia or hypertension elevates the diabetes risk among RA patients. Presence of both hyperlipidemia and hypertension increase the hazard rate of diabetes by 23-fold. All these risk factors can also be associated with a sedentary lifestyle.<sup>41</sup> Crepaldi et al reported that diabetes was associated with higher disease activity in RA patients whereas hyperlipidemia was associated with lower disease activity.<sup>42</sup> A study projected that T1D approximately affects 2.8% of total RA patients. High prevalence of T1D was found among people with RA having ACPA with OR: 7.3 and 95%CI: 2.7–20.2.<sup>43</sup> The correlation between T1D and RA recommends the presence of common susceptible genes like T cell activation RhoGTPase activating protein (*TAGAP*) gene, protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*) gene, *HLA-DRB1* gene, *KIAA1109/TENR/IL2/IL21* genes and cytotoxic T lymphocyte associated protein 4 (*CTLA-4*) gene.<sup>44–48</sup> But no polymorphism with *IL6* gene is linked with T1D or RA.<sup>49</sup> Association of T2D and RA is very complex and debatable high levels of *IL6* or CRP encourage T2D development.<sup>50</sup> Study of 114,342 US women did not observe a difference in T2D incidence among women with RA and without RA.<sup>51</sup>

In another prevalent study, significance of T2D was moderately higher among 28,208 RA patients (10.4%) in comparison to healthy individuals (7.6%) with  $P$ -value=0.01.<sup>14</sup> Data comparison of people with and without RA taken from the ORALE (Outcome of Rheumatoid Arthritis Longitudinal Evaluation) and (SAHS) San Antonio Heart Study, demonstrated the higher significance of T2D in people with RA (16.1%) compared to people without RA (9.5%),  $P$ -value <0.001. But, in age-stratifying sampling this variation between data was eliminated (age  $\geq 55$  years; 22.8% vs 20.1%;  $P=0.7$  and age <55 years; 8.3% vs 6.7%;  $p=0.5$ ).<sup>52</sup> Moreover, after adjusting for age, sex, glucocorticoid treatment, the cohort study from Canada of 490,751 individuals reported that T2D risk was higher in RA patients ( $n=48,718$ ) in comparison with controls (442,033) with HR: 1.5; 95%CI: 1.4–1.5.<sup>51</sup> Another study also reported the significant risk of T2D in patients with RA and association of glucose metabolism imbalance and uncontrolled disease activity. This study found that out of 439 RA patients, 31 developed T2D after 12 months of prospective follow-up.<sup>53</sup> Ruscitti et al performed a cross-

sectional study and found elevated prevalence of impaired fasting glucose and T2D among RA patients in Italian population in comparison with gender and age-matched controls. They also observed that cardiovascular risk factors like high blood pressure and RA-specific characteristics like duration of disease, and exposure to corticosteroids were considerably associated with abnormal glucose metabolism whereas disease activity, increasing erythrocyte sedimentation rate, and serum triglyceride levels were not associated with impaired fasting glucose among RA patients.<sup>54</sup>

A case-controlled study from Taiwan highlighted the chances of development of RA in diabetes patients. In 1416 RA patients and 7080 controls it was found that the odds ratio of development of RA after diagnosis of diabetes was higher in females with OR: 1.46 and 95%CI: 1.24–1.72 but not in males with OR: 1 and 95%CI: 0.72–1.37.<sup>55</sup> In contrast, another case-control study from Taiwan with 600,695 participants reported that the T2D risk was greater in males with RA (OR: 1.68; 95%CI: 1.53–1.84) in comparison to females with RA (OR: 1.46; 95%CI: 1.39–1.54).<sup>41</sup> In a cohort study with 48,718 RA patients, RA was shown to be associated with increased diabetes risk.<sup>13</sup>

People with RA showed association with several other diabetes risk factors like obesity, lifestyle, glucocorticoid therapeutic technique which encourage T2D development in RA patients. Several research-based results support the correlation of diabetes and RA, and their associated impact on development, progression, and the severity of both.

## Effect of RA Medication on Insulin Resistance

### RA Medications and Diabetes:

#### Glucocorticoids

Glucocorticoids (GC) deteriorate glucose tolerance through various pathways by inhibiting glucose uptake in the adipose tissue and increasing hepatic gluconeogenesis.<sup>56</sup> GCs were found to be associated with different levels of dysfunction of  $\beta$  cells, decrease in the insulin sensitivity as well as reduced  $\beta$  cell function as they function through the GC receptors found on pancreatic  $\beta$  cells (Table 1).<sup>57</sup> Patients with RA cured by oral GC therapy is a vital risk factor of diabetes. Every 5 mg rise in current dose of oral GC was found to be linked with 25–30% increased diabetes risk. It was also found that GC dosages, which were within the preceding six-months were related to current diabetes risk.<sup>58</sup> In a cross-sectional analysis of patients with RA, treatment with GCs decreased fasting



**Table I** Effect of RA Medication on Diabetes and Insulin Resistance

Name of Drug	Insulin Resistance	HbA <sub>1c</sub>	Diabetes Risk	Insulin Sensitivity	References
Glucocorticoid	↑	↑	↑	↓	60,61,64,100,101
Hydroxychloroquine	–	↓↓	↓	↑	95,96,98,102
Methotrexate	↓	↓	–	↑	96,98,103
TNF antagonists	↓	↓	↓	↑	15,78,104
Interleukin-1 $\beta$ antagonist	↑	↓	↓	-	83,105
Interleukin-6 antagonist	↓	↓	↓	-	106

**Note:** Arrows significant the association of drug with insulin resistance, HbA<sub>1c</sub>, diabetes risk, insulin sensitivity.

**Abbreviations:** ↑, increase; ↓, decrease; ↓↓, larger decrease; HbA<sub>1c</sub>, glycosylated hemoglobin.

insulin sensitivity<sup>59,60</sup> and likely to project development of T2D.<sup>61,62</sup> A single blind randomized controlled study was performed among 41 early active RA patients who were administered prednisolone 60 or 30 mg/day for seven days. In active RA patients, improvement in disease activity was observed in short periods of treatment with 30 or 60 mg/day prednisolone and this treatment did not deteriorate glucose tolerance.<sup>63</sup> Lillegraven et al<sup>12</sup> reported that patients with RA having prescribed doses of GCs (7.5 mg daily or more) had a hazard ratio of 2.33 95%CI: 1.68–3.22 incidence of diabetes than in patients without oral GC prescription. Short-term GC therapy, even in high doses in active RA patients does not tend to have an adverse effect on glucose tolerance. Whereas chronic GC therapy is linked with impaired glucose tolerance and with a non-negligible risk of T2D development. Thus, the European League Against Rheumatism (EULAR) suggests that patients be weaned off GC therapy as soon as possible to avoid IR worsening and ultimately T2D developing.<sup>64</sup>

## Diseasemodifying Antirheumatic Drugs (DMARDs)

DMARDs are immunomodulators and immunosuppressants and classified either as biological DMARDs (bDMARDs) or conventional DMARDs (cDMARDs).<sup>65</sup> Radner et al showed that out of 3920 multimorbid patients with RA, 59.9% received synthetic DMARDs (sDMARDs), 32.7% bDMARDs only, 54.8% used corticosteroids and 51.1% used concomitant non-steroidal anti-inflammatory drugs (NSAIDs).<sup>66</sup>

### Biological Disease-modifying Antirheumatic Drugs (bDMARDs)

bDMARDs are very specific and target particular pathways of the immune system.<sup>65</sup>

### TNF Antagonists

TNF antagonists decreases pro-inflammatory cytokines levels in synovial membrane and systemic circulation.<sup>67</sup> TNF antagonists reduce C-reactive protein in RA patients and also modify the well-known cardiovascular risk factors, involving lipid metabolism and insulin resistance.<sup>68–70</sup> Insulin sensitivity is improved with TNF antagonists in animal studies.<sup>71</sup> TNF antagonist's treatment in RA patients improves insulin sensitivity<sup>68,70,72–76</sup> and changes the lipid profile.<sup>70</sup> TNF inhibitors significantly reduced the diabetes risk in RA patients when adjusted for covariates like BMI and disease activity.<sup>12</sup>

Stagakis et al<sup>77</sup> performed a cohort analysis in patients with RA with anti-TNF agents (etanercept, n=1; adalimumab, n=11; infliximab, n=49), and found that 12 weeks after the anti-TNF treatment, patients having high IR displayed considerable decrease in HOMA-IR with  $P<0.001$  and rise in quantitative insulin sensitivity check index (QUICKI) ( $P<0.001$ ). Lillegraven et al<sup>78</sup> examined the relationship of exposure of DMARDs with incidence diabetes in a large multicenter prospective cohort study of 21,775 patients with RA and found reduction in the risk of developing diabetes in patients with RA treated by TNF-inhibitors after controlling for disease activity, BMI and steroid use.

### Interleukin 1 $\beta$ Antagonist

Interleukin 1 $\beta$  (IL1 $\beta$ ) is a pro-inflammatory cytokine, which is involved in chronic inflammatory disease like RA, cardiovascular disease and T2D.<sup>79</sup> Diabetes incidences were reduced by IL1 antagonist in animal models,<sup>80,81</sup> as this cytokine plays a modulatory role either in insulin sensitivity, function of pancreatic  $\beta$  cell, or immune system function. Larsen et al<sup>82</sup> demonstrated that blocking with anakinra

(recombinant human IL1 receptor antagonist) leads to improvement in secretory function of  $\beta$  cells and glycemia and decreased markers of systemic inflammation in double-blind, placebo-controlled, parallel-group analysis with 70 people with T2D, who were given either once-daily 100 mg anakinra (Kineret®) or placebo in the morning for 13 weeks. Several studies confirmed the vital role of IL1 in the  $\beta$ -cell mass maintenance, suggesting the processes lead to improvement of glucose after anakinra treatment are complex and possibly mediated by a double effect on both  $\beta$ -cell function and IR.<sup>82–88</sup> Ruscitti et al performed an open-label, randomized, parallel-group trial in RA patients with T2D and suggested that IL1 inhibition by anakinra may facilitate therapeutic targeting of RA as well as T2D and use of only a single agent may be beneficial in management of both metabolic and inflammatory disorder.<sup>89</sup> Studies suggested that inflammatory mechanisms of T2D could be exaggerated by RA and on this basis, single therapy/treatment that manages both disorders RA and T2D seems to be a promising treatment for enhancing the care of patients with T2D and RA.<sup>85,90,91</sup>

### Interleukin 6 Antagonist

IL6 is an important component in chronic inflammation, and it is excessively expressed at inflammation sites. Similar to TNF and IL1, IL6 triggers the production of acute phase protein.<sup>92,93</sup> It stimulates particular antibody-mediated immune response like differentiation of B lymphocytes and activation of T lymphocytes.<sup>94</sup> Many evidences have recommended that IL6 is an important component in rheumatoid inflammation.<sup>95</sup> Studies reported that acute infusion of IL6 elevates the muscle sensitivity to insulin through AMP-activated protein kinase activation.<sup>96</sup> Chronic increase of circulating IL6 level, higher than acute secretion of IL6, has null or weak effect in vivo in muscle, while it can contribute to whole body IR, mainly in adipose and liver tissue. IL6 can also be indirectly engaged in IR through its effect on metabolism of lipids. IL6 also encourages lipolysis in the culture of adipose and adipocyte tissue.<sup>97–99</sup> In mice, chronic overexpression of levels of IL6 in skeletal muscle cause reduced body weight, inflammation of liver, hypoglycemia, incongruous hyperinsulinemia, hypoadiponectinemia, and reduced insulin stimulated glucose transfer to muscles.<sup>100</sup>

Tocilizumab (TCZ) (humanized monoclonal antibody against IL6 receptor) is an efficient therapy for RA.<sup>101,102</sup> Schultz et al conducted a study on 11 RA patients without diabetes, where intravenous TCZ (8 mg per kg of body

weight) was administered every four weeks to study insulin sensitivity and significant decrease was found in HOMA-IR after three months of treatment.<sup>103</sup> In another study on 24 RA patients, when treated with intravenous TCZ dose (4 mg/kg) once monthly for the first three months and then 8 mg/kg once monthly, they observed significant decrease in HOMA-IR at week 24.<sup>104</sup> Inhibition of IL6 can be a helpful strategy in reducing IR and decreasing the risk of T2D development.

## Conventional DMARDs (cDMARDs)

### Hydroxychloroquine

Initially hydroxychloroquine (HCQ) was used as antimalarial drug, but now it is extensively used in treating systemic inflammatory conditions like RA and SLE. HCQ decreases diabetes risk through improving the function of pancreatic  $\beta$  cells and insulin sensitivity,<sup>105,106</sup> which can be independent of anti-inflammatory activities. A large US-wide observational cohort analysis performed by Ozen et al<sup>107</sup> found that diabetes incidences were increased in RA patients and HCQ was linked with decreased risk of diabetes among RA patients. Several studies found that HCQ reduced incidence of diabetes risk among RA patients.<sup>108–110</sup> Earlier observational findings showed that HCQ ever use was associated with 38–71% decrease in diabetes risk in comparison with never used<sup>108,110</sup> and current use was related to a 46% decrease in diabetes risk in comparison to any nonbiological non-MTX DMARD use.<sup>109</sup> Mean decrease was observed in HbA1c of 0.66% (95%CI: 0.26–1.05) between pre-HCQ use and post-HCQ use.<sup>111</sup> Findings of Desai et al<sup>112</sup> showed a 33% decrease in incidences of diabetes risk with HCQ monotherapy (HR: 0.66; 95%CI: 0.45–0.98). Most of the previous studies advocate the positive effects of HCQ on glucose metabolism with favorable alterations in insulin clearance, release, and sensitivity.

### Methotrexate

Methotrexate (MTX) is suggested as first-line drug by EULAR and American College of Rheumatology (ACR) in early and established RA management.<sup>113,114</sup> In a cross-sectional analysis of 387 patients with RA, it was found that metabolic syndrome was uncommon in patients with MTX therapy. However, risk of metabolic syndrome is not affected by preceding use of MTX and current use of GCs, other biologic agents and DMARDs. Use of MTX was observed to be related to lower fasting blood sugar level.<sup>115</sup> A study by Dessein et al<sup>116</sup> demonstrated that

MTX had a beneficial impact on insulin sensitivity and in insulin resistance through QUICKI and HOMA and suggested this effect may be caused due its anti-inflammatory activity. Although they also suggested that the chances of this effect are partly arbitrated by other activities of classical drugs which encourage lipid profile remission or other areas cannot be excluded. Other study also revealed negative association between metabolic syndrome and use of MTX.<sup>117</sup> Solomon et al<sup>109</sup> conducted a retrospective cohort analysis on patients with RA and found that risk of T2D was not lower with MTX therapy in comparison to other DMARDs, after adjusting for confounders.

A new guideline formulated by the ACR for RA treatment, addressed use of biologicals in the clinical management of high risk populations and vaccine usage for infections such as herpes zoster, influenza and hepatitis B among patients receiving or starting antirheumatic drugs.<sup>118</sup> The patients in which monotherapy with conventional DMARDs fails and those who were having continuous medium to high disease activity should be given treatment with combination therapy.<sup>119</sup> EULAR recommended suggestions for management of CVD risk among RA patients.<sup>64</sup> These recommendations consisted of the necessity of cardiovascular examination among RA patients and insufficiency of classic tables for CVD risk stratification when utilized in RA patients, particularly those having long-term disease (>10 years).<sup>120</sup> Current evidence proposed that testing persons for high diabetes risk may decrease cardiovascular mortality.<sup>121</sup>

## Janus Kinase Inhibitors

Janus kinase inhibitors (JAKi) are a novel category of oral medications counteracting JAK activation and JAKs are cytoplasmic enzymes which have control of several biological functions such as inflammatory cascade activation among cells of the immune system.<sup>122</sup> They play a vital role in immune responses and are associated with various receptors of cytokine. Hence, JAKinhibition seemed to be a potential therapeutic strategy in autoimmune disorders like RA.<sup>123</sup> Several oral JAKi like upadacitinib, tofacitinib, peficitinib, and baricitinib have been approved for the treatment of immune mediated disorders such as RA.<sup>124</sup> Fujita et al observed that the JAKi drug baricitinib was efficient in the treatment of RA complicated by T1D and systemic sclerosis.<sup>125</sup> Trivedi et al reported that JAKi drugs like baricitinib and ruxolitinib were effective for human consumption for the treatment and prevention of T1D.<sup>126</sup>

## Conclusion

RA is an inflammatory chronic autoimmune disorder that may be linked with several abnormalities in glucose metabolism, primarily insulin resistance, which may develop into T2D. Environmental factors like smoking and infections may affect the progression, development, and severity of RA and onset of T2D in RA-affected persons. Numerous studies report that insulin resistance prevalence is greater in people with RA in comparison to normal people. Insulin resistance in RA partially causes obesity by increasing fat mass, disease activities and occurrence of factors of RA. Similarly, lifestyle factors such as smoking, alcohol consumption and high BMI (or obesity) are mainly responsible in the development of diabetes among RA patients. RA patients showcased association with several other diabetes risk factors like obesity, lifestyle, glucocorticoid therapeutic technique, which encourage T2D development in RA patients. Several studies reported significant association between development of T2D and RA whereas in contrast, some studies did not find any considerable association with T2D development and RA. Markers of glucose metabolism appear to be improved by DMARDs like methotrexate, hydroxychloroquine, IL1 antagonists and TNF antagonist while glucocorticoids adversely affect glycemic control, especially when administered chronically. Therefore, optimal drug selection for RA treatment may be helpful in attaining the treatment targets for diabetes to reduce the incidence of diabetes risk among RA patients. Although many studies reveal the chance of diabetes onset among people with RA. However, studies also suggest, administering combination drug therapy to RA patients, vaccine usage for treating infections among patients taking antirheumatic drugs, examining and monitoring cardiovascular conditions among RA patients with high diabetic risk may reduce the onset of diabetes risk and morbidity among patients.

## Abbreviations

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28, disease activity score including 28-joints; EULAR, European League Against Rheumatism; IL6, interleukin-6; RA, rheumatoid arthritis; RF, rheumatoid factor; T2D, type 2 diabetes; TNF, tumor necrosis factor; IR, insulin resistance; HOMA, homeostatic model assessment; SLE, systemic lupus erythematosus; ORALE, outcome of rheumatoid arthritis longitudinal evaluation; SAHS, San Antonio heart

study; GC, glucocorticoids; HCQ, hydroxychloroquine; TCZ, tocilizumab; MTX, methotrexate; HLA, human leukocyte antigen; SE, shared epitope; VEGF, vascular endothelial growth factor; T1D, type 1 diabetes; TAGAP, T cell activation RhoGTPase activating protein; PTPN22, protein tyrosine phosphatase nonreceptor type 22; CTLA-4, cytotoxic T lymphocyte associated protein 4; IL1 $\beta$ , interleukin 1 $\beta$ ; QUICKI, quantitative insulin sensitivity check index.

## Ethics Approval

The current review does not require ethical approval.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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