Rheumatoid Arthritis Treatment Options and Type 2 Diabetes: Unravelling the Association

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Abstract

Multiple lines of evidence have increasingly suggested a pathogenic connection between rheumatoid arthritis (RA) and the mechanisms of type 2 diabetes (T2D) in a vicious circle perpetuated by glucose derangement and inflammatory mediators. These findings have been further reinforced by clinical studies showing that the inhibition of interleukin (IL)-1 and IL-6 may allow the treatment of RA and concomitant T2D at the same time. Interestingly, IL-1 inhibition induced a more evident reduction of glycated haemoglobin (HbA1c) in patients with concomitant RA and T2D than in previous studies on IL-1 inhibition in patients with this metabolic disease alone. Thus, the inflammatory pathogenic mechanisms of T2D could be exaggerated in the context of a rheumatic disease, possibly explaining these findings. In fact, IL-1 inhibition could not only palliate glycaemia, but also decrease the progressive decline in insulin secretion associated with T2D, interfering with apoptosis of β-cells, improving their function, and ameliorating the peripheral insulin resistance. Moreover, the maintenance of clinical remission of rheumatic disease could further improve the glucose derangement and reduce the occurrence of T2D in RA. On these bases, the presence of T2D may allow the physicians to perform a better profile of patients with RA according to the principles of precision medicine, tailoring the medical treatment to the individual characteristics. In this context, the benefits of targeting the inflammatory process, mainly by IL-1 inhibition, may be suggested in patients with RA and concomitant T2D.

Key Points

- Multiple lines of evidence have increasingly suggested a pathogenic connection between the RA process and the mechanisms of T2D in a vicious circle perpetuated by glucose derangement and inflammatory mediators.
- Some clinical studies showed that the inhibition of inflammatory cytokines, mostly IL-1, may allow the treatment of RA and concomitant T2D at the same time.
- The presence of T2D may allow the physicians to perform a better profile of patients with RA according to the principles of precision medicine, tailoring the medical treatment to the individual characteristics.

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by synovitis, cartilage damage, and bone erosions, which is associated with an increased morbidity and mortality compared with the general population [1]. Patients with RA are burdened by an increased risk of accelerated atherosclerosis and cardiovascular disease (CVD) [2–5]. This finding is partially explained by the enhanced prevalence of “traditional” cardiovascular (CV) risk factors, including smoking habit, overweight, lipid metabolism alterations, high blood pressure, and glucose derangement. The underlying systemic rheumatoid inflammatory process, along with genetic factors, and therapies, may play an important role in synergising with “traditional” CV risk to enhance the risk of CVD. In this context, glucose metabolism abnormalities, insulin resistance (IR), and type 2 diabetes (T2D), are frequently observed in patients with RA [6–9]. Insulin resistance is defined as an altered biologic response to insulin in target tissues associated with the necessity for an enhanced release of this hormone to obtain a quantitatively normal response to glucose [10]. Thus, IR results in a compensatory increase
of insulin production, leading to hyperinsulinaemia. The latter predicts the development of T2D [10], which occurs when pancreatic β-cell function fails to compensate for IR, with a consequent hyperglycaemia, due to either impaired synthesis or impaired insulin function [11]. Patients with RA have an increased prevalence of IR, about 40 %, in respect to the general population [12–15]. Furthermore, an increased prevalence, of almost 15 %, of T2D is reported in those patients [16]. A recent meta-analysis also showed that patients with RA have an approximately 1.5-fold higher risk of developing T2D than the general population [16]. Interestingly, a poorly controlled RA disease activity has been reported to predict the occurrence of T2D in these patients [6, 17]. Conversely, the achievement and maintenance of the clinical remission, underlying the abrogation of the inflammatory process, is associated with a low probability to develop this comorbidity [2]. These findings may lead to hypothesise that the inflammatory process of RA may be implicated in the development of concomitant metabolic diseases [15, 18]. On these bases, multiple lines of evidence have proposed the role of the immune system in contributing to the pathogenesis of IR and T2D; thus, suggesting the possible efficacy of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in treating the glucose derangement [19, 20]. The bDMARDs are immunosuppressive drugs successfully used in patients with RA leading to a significant clinical improvement and reduction of the joint damage in the long term. Interestingly, a systematic review and meta-analysis found that the administration of bDMARDs may be associated with a reduced incidence of T2D in patients with RA than those treated with other drugs [21]. Therefore, common therapeutic targets may exist in patients with RA and concomitant T2D proposing a possible “bidirectional” treatment [22, 23]. In this context, some studies have recently reported that some bDMARDs may have a beneficial role in improving the glucose derangement of patients with RA [24–26]. In this work we aimed to discuss the available evidence, from pathogenic mechanisms to treatment, about the influence of therapeutic options in RA on glucose derangement in patients with concomitant T2D.

2 Pathogenic Links Between RA and T2D

2.1 The Pathogenic Role of Insulin in the Context of Rheumatic Diseases

Insulin is the main hormone regulating glucose homeostasis and it acts through the transmembrane insulin receptors. The latter are expressed on multiple target cells including hepatocytes, adipocytes, synoviocytes and muscle cells [27]. Intriguingly, these receptors may also be found on the surface membrane of immune cells [27, 28]. In fact, these cells need glucose to produce energy, and through its receptors, insulin exerts its hypoglycaemic function and behaves as a growth-like factor as well as a cytokine regulator [29, 30]. Therefore, this hormone may also exert immunomodulatory effects on the immune system in addition to well-known metabolic effects [31, 32]. In this context, it has been shown that hyperglycaemia has negative effects on the immune cells leading to the production of advanced glycation end products and reactive oxygen species, which in turn may stimulate the generation of various pro-inflammatory mediators [33]. Thus, insulin may have a role in reducing the “glucose toxicity” and cell stress, exerting an anti-inflammatory effect [28]. Other evidence performed in healthy non-diabetic subjects explored the effects of insulin on polymorphonuclear leukocytes functions [34]. On those cells, this hormone has shown to have the ability to induce the production of pro-inflammatory mediators. Taking together these findings, a possible role of insulin in contributing to the induction of an aberrant immune response may be speculated during rheumatic diseases [28].

2.2 Inflammatory Pathogenic Mechanisms of T2D may be Exacerbated by RA

Multiple features may be associated with occurrence of T2D in the context of RA [5, 15, 16]. Inactivity, disability, sedentary behaviour, obesity, and glucocorticoid (GC) therapy are known to negatively affect the glucose metabolism and to favour the occurrence of T2D [35]. A recent study demonstrated a strong association between some RA pathogenic mediators and the risk of incident T2D [6]. Interleukin (IL)-1α, IL-1β, and IL-6 predicted the occurrence of this comorbidity during the follow-up in patients with RA [6], suggesting that inflammatory mediators may contribute to the development of the metabolic disease [18]. In fact, as reported in Fig. 1, these molecules may contribute to altering blood lipid levels, inducing endothelial dysfunction, and enhancing oxidative stress; thus, increasing the risk of CVD and metabolic diseases [36, 37]. In this context, it has been shown that the pancreatic β-cell has a high density of IL-1β receptors [38]. On the basis of an overexpression of IL-1β, as observed in RA, β-cells may become more susceptible to the negative effects of this cytokine but also of other inflammatory mediators, such as IL-6 and tumour necrosis factor (TNF) [39]. In turn, these molecules may also attract macrophages and additional immune cells, which infiltrate the pancreatic islets [39]. These alterations may first lead to β-cell dysfunction and consequently to their apoptosis, resulting in a progressive glucose derangement and the consequent occurrence of T2D [40]. Furthermore, β-cells and other insulin-sensitive tissues, stressed by the high glucose
levels, may produce elevated levels of IL-1β via the hyper-expression of nucleotide-binding domain and leucine-rich repeat containing family pyrin 3 (NLRP3) inflammasome in perpetuating this pathogenic vicious circle [39, 41]. Moreover, high levels of glucose may strongly influence the pro-inflammatory status of monocytes derived from patients with RA and concomitant T2D, leading to the production of IL-1β [39]. A work by Almeida-Santiago et al. has shown a direct relationship between IL-1RA, the receptor antagonist of IL-1β, and β-cell function, thus further reinforcing the role of this pathway in glucose derangement during RA [42].

In addition, a pathogenic role of TNF and IL-6 has been also proposed in this setting. Tumour necrosis factor is of crucial importance in the pathogenesis of RA [43]. In fact, it is implicated in the development of arthritis by activation of other cytokines, chemokine and endothelial-cell adhesion molecule expression, promotion of angiogenesis, suppression of regulatory T cells, and amplification of osteoclast differentiation and activation [37, 44]. Tumour necrosis factor may be of some relevance in the development of both IR and T2D since it is produced in the adipose tissue [45]. This cytokine may reduce the expression of glucose transporter type 4 (GLUT4), an insulin-regulated glucose transporter mainly located in adipocytes, skeletal and cardiac muscles, thereby reducing glucose uptake [46]. Moreover, serine phosphorylation of insulin receptor substrate-1 (IRS-1) induced by TNF may inhibit insulin receptor and may antagonise its signal [47]. This mediator is also able to decrease the fatty acid oxidation leading to increase of plasma free fatty acid levels [48]. Furthermore, TNF together with IL-6 may have a negative effect on insulin signalling, thus promoting IR [49–53]. Interleukin-6 is produced by adipocytes and macrophages within adipose tissues, skeletal muscle, and liver, and it is hyper-activated in RA [54]. In addition, hyperinsulinaemia may lead to an increase in IL-6 blood levels [55, 56]; thus, leading to an additional vicious cycle involving a pro-inflammatory molecule and glucose abnormalities [56–58]. In fact, IL-6 values are correlated with obesity grade, and negatively with IR [59]. In contrast, some studies have shown some possible favourable effects of this cytokine on IR, stimulating the production of glucose derangement may be exacerbated by rheumatoid arthritis (RA). Interleukin (IL)-1β, IL-6, and TNF may contribute to the development of glucose derangement and type 2 diabetes (T2D). β-cell has a high density of IL-1β receptors; based on the overexpression of IL-1β, as observed in RA, β-cells may become more susceptible to the negative effects of this cytokine but also of other inflammatory mediators, such as IL-6 and TNF. In turn, these other molecules may also attract macrophages and other immune cells, which infiltrate the pancreatic islets. The consequent inflammatory infiltration is characterised largely by macrophages. These alterations may first lead to β-cell dysfunction and consequently to their apoptosis, with the result of a progressive glucose derangement and the consequent occurrence of T2D. Furthermore, β-cells and other insulin-sensitive tissues, stressed by the high glucose levels, may produce elevated amounts of IL-1β via the hyper-expression of nucleotide-binding domain and leucine-rich repeat containing family pyrin 3 (NLRP3) inflammasome in perpetuating this pathogenic vicious circle. Tumour necrosis factor (TNF) may be of some relevance in the development of both insulin resistance (IR) and of T2D since it is produced in the adipose tissue. This cytokine may reduce the expression of glucose transporter type 4 (GLUT4), an insulin-regulated glucose transporter mainly located in adipocytes, skeletal and cardiac muscles, thereby reducing glucose uptake. Moreover, serine phosphorylation of insulin receptor substrate-1 (IRS-1) induced by TNF may inhibit the insulin receptor and may antagonise its signal. Interleukin-6 is produced by both adipocytes and macrophages within adipose tissues, skeletal muscle, and liver, and it is hyper-activated in RA. Furthermore, hyperinsulinemia may lead to an increase in IL-6 blood levels, thus leading an additional vicious cycle involving a pro-inflammatory molecule and glucose abnormalities.
of glucagon-like peptide-1 from the gut and pancreas [60, 61]. Furthermore, IL-6-deficient mice may develop mature-onset obesity [61]. This controversial role of IL-6 on metabolic processes may be explained by its complex signalling pathways and different experimental conditions. Additionally, activated T cells, which play a central role in the pathogenesis of RA, may also be involved in the development of IR and T2D [62–65]. Interestingly, during T2D, a higher percentage of memory, whereas lower naive CD4+ T cells may be observed [66]. Furthermore, another study identified higher blood percentage of CD4+ memory T cells in T2D patients with CVD, compared with those without [67]. In addition, the rheumatoid pro-inflammatory environment is amplified by the JAnus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signalling pathway [68]. These enzymes have a crucial role in the intracellular signalling transduction of several cytokines, contributing to joint inflammation and damage in RA [69]. Interestingly, hyperglycaemia seems to activate this pathway and dysregulation of the leptin-induced JAK/STAT signalling pathways could play a key role in IR in T2D [70–72]. Moreover, adipocytes produce some molecules acting on JAK/STAT signalling pathway in target tissues further contributing to glucose derangement [73].

Taking together the findings about the inflammatory contribution to the pathogenesis of T2D, it is possible to hypothesise that these mechanisms may be exacerbated in the context of RA, thus proposing possible common therapeutic targets for patients affected by arthritis and T2D.

3 The Effects of RA Therapeutic Agents on Glucose Abnormalities

3.1 Glucocorticoids

During RA, GCs are widely used since they rapidly provide symptomatic relief, suppress disease activity, and significantly slow the progression of progressive radiological damage in these patients [74, 75]. However, the cumulative exposure to GCs is associated with an increased occurrence of CVD [14, 76–78]. These drugs may alter lipid and glucose metabolism, increase blood pressure, and lead to endothelial dysfunction, especially considering the cumulative dosages in the long term [79]. As far as T2D is concerned, many studies found a high cumulative or daily GC dosage could reduce the glucose tolerance due to IR and pancreatic cells dysfunction in patients with RA [8, 13, 14, 80–82]. Although the exact underlying mechanisms are still unknown, genetic disposition, age, and obesity, as well as chronic inflammation, are recognised as risk factors for the development of IR/T2D, and GCs represent an additional factor in patients with RA [83–87]. However, it must be pointed out that the negative effects of GCs may be balanced by the positive effects on inflammation [80, 88]. In fact, GCs could positively affect the rheumatoid inflammatory process associated with the occurrence of CVD and metabolic disease [88]. In this regard, a study evaluated the dose-related effects of GCs on glucose metabolism parameters and RA disease activity [80]. Short-term treatment with high-dose prednisone did not deteriorate glycaemic parameters, but was associated with an improvement [80]. Furthermore, a prospective cohort study evaluated the risk of developing CV disease in patients with RA exposed to GCs [88]. The adjustments for disease activity and disability revealed no relationship between GC and CVD [88]. Based on these observations, GCs could be associated with positive effects on glucose abnormalities due to rheumatoid inflammatory process, but predictable side effects should be carefully considered and monitored when administering these drugs in patients with RA in the long term.

3.2 Methotrexate

Methotrexate (MTX) is one of the most widely used drugs in patients with RA [89, 90]; this is an anti-folate cellular immunosuppressant mainly inhibiting dihydrofolate reductase [91]. Methotrexate mechanisms of action may result in a variety of anti-inflammatory effects, inhibiting the proliferation and inducing apoptosis of activated immune cells, decreasing the release of pro-inflammatory cytokines, like IL-1β, IL-6, and TNF, and simultaneously increasing those anti-inflammatories, mainly IL-4 and IL-10 [92]. Recently, direct effects of MTX on glucose metabolism have been proposed [93]. A prolonged treatment with MTX increased skeletal muscle GLUT-4 expression in T2D murine models, and was also related to a significant reduction of glucose and insulin serum concentrations [93]. In addition, treatment with MTX, compared with other drugs, may be able to reduce the levels of glycated haemoglobin (HbA1c) [94]. In particular, an association between higher levels of erythrocyte MTX polyglutamate, the intracellular form of MTX, and the reduced levels of HbA1c [95] has been
observed, thus, suggesting a possible beneficial effect of this drug on glucose derangement in patients with RA.

### 3.3 IL-1 Inhibitors

In recent years, based on its pathogenic contribution, multiple lines of evidence have suggested the role of IL-1 inhibition in improving glucose metabolism abnormalities (Table 1) [22, 96]. Anakinra is a recombinant form of human IL-1 receptor antagonist, and it works as a competitive inhibitor of IL-1β. Many studies analysed its clinical role in improving glycemic control in T2D reporting the possible usefulness in these patients [97–100]. In a placebo-controlled study, anakinra induced a significant improvement of glucose metabolism, as demonstrated by the significant reduction of HbA1c [97]. The same group also demonstrated that this improvement could be maintained after anakinra withdrawal in a 39-week follow-up [100]. More recently, the clinical efficacy of canakinumab, a monoclonal antibody against IL-1β, has been proposed on CVD, reducing inflammatory markers and CV events in patients characterised by a high risk [101, 102]. In this context, the possibility that canakinumab could decrease the occurrence of T2D has been also tested [103]. Although the incidence of T2D was not prevented, canakinumab reduced values of HbA1c during the first 6–9 months of treatment, despite no consistent long-term benefits on this parameter. Taking together these findings and the well-known pathogenic role of IL-1β in rheumatic diseases, the potential clinical usability of IL-1 inhibition has been tested in RA patients with T2D as a possible “bidirectional” therapy [104–106]. In a clinical trial, patients with RA and concomitant T2D were randomised to receive anakinra or TNF inhibitors (TNFis) to evaluate a differential efficacy on HbA1c [104]. Patients in the anakinra group had a significant and marked reduction of HbA1c%, which has not been observed in the TNFi group after 6 months of follow-up (crude difference 0.93 HbA1c% between groups) [104]. Concerning RA, a progressive reduction of disease activity was observed in both groups without significant differences. Therefore, a benefit of IL-1 inhibition in patients with RA and T2D has been reported, reaching the therapeutic targets of both diseases [104]. In addition, data derived from the long-term extension of this study, including patients with RA and T2D, suggested that the benefits of IL-1 inhibition on metabolic and inflammatory parameters could last longer than the first 6 months of follow-up [105]. Interestingly, a reduction of anti-diabetic drugs was also observed in anakinra-treated patients whereas an increase of anti-diabetic therapies was needed in TNFi-treated patients to reach a reduction of HbA1c [105]. In this trial [104, 105], a persistent good clinical response has been observed in patients randomised to anakinra in regard to RA disease activity. These findings may appear to be in conflict with previous results about the efficacy of this drug in RA [106, 107]. However, it must be pointed out that patients enrolled in this trial showed a short disease duration and were codified according to 2010 ACR/EULAR criteria [104]. Different from those fulfilling 1987 criteria, these patients may have a less severe disease course, developing a less severe radiological joint damage, and more often achieving clinical remission [108]. However, it must be pointed out that future studies are needed to fully clarify the efficacy of anakinra in RA.

Finally, in patients with RA and T2D, anakinra has been shown to improve both IR and IS, suggesting some possible mechanisms of action underlying the improvement of glucose abnormalities. Furthermore, IL-1 inhibition was positively associated with a reduction of some adipokines in patients with RA and T2D [109].

### 3.4 TNF Inhibitors

Tumour necrosis factor has been implicated in the development of IR and T2D, despite conflicting results of antagonising this cytokine in patients with this metabolic disease [110, 111]. In the context of RA, several studies analysed the effects of TNFis (i.e., adalimumab, etanercept, and infliximab) on glucose metabolism, mostly assessing IR and IS by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Quantitative Insulin sensitivity Check Index (QUICKI), respectively [112–117]. In these studies, TNFis were associated with a positive effect on both HOMA-IR and QUICKI, mainly in those patients who were more insulin resistant than others [24, 112–118]. Furthermore, these positive effects were observed in the short term—within a few weeks following the administration of such drugs [24, 112–118].

In addition, it has been shown that a rapid reduction of IR together with improvement of IS may be observed in non-diabetic patients with RA who underwent a single infusion of infliximab [119]. Therefore, the short-term effect of the anti-TNF therapy on IR may be suggested in RA [119]. Although these studies have been limited by a relatively small sample size, all showed the potential beneficial role of inhibiting TNF in IR and IS, implicating this molecule in the development of glucose metabolism derangement in RA. Therefore, TNFi could have a role in the initial phases of IR before the development of T2D, as highlighted by the reduction of the incidence of T2D in patients with RA treated with such drugs [21, 120]. In fact, Lin et al [21], observed that new-onset T2D could be less frequent in patients treated by TNFi, with no differences among specific drugs, synthesising data from 22 randomised controlled trials and 3 cohort studies [21].
| First author, year | Type of study | Number of participants | Disease | Type of drug, dose, frequency | Follow-up | Outcome of interest | Value of assessment measure at baseline | Value of assessment measure at final observation | Difference between baseline and final observation |
|-------------------|---------------|------------------------|---------|--------------------------------|-----------|--------------------|----------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Larsen et al, 2007 [97] | Clinical trial | 67 | T2D | Anakinra, 100 mg, once daily | 13 weeks | HbA1c reduction | 8.7% | 8.4% | − 0.3% |
| Ridker et al, 2012 [101] | Clinical trial | 551 | T2D | Canakinumab, 150 mg, every 4 weeks | 4 months | HbA1c reduction | 7.4% | 7.1% | − 0.3% |
| Everett et al, 2018 [103] | Clinical trial | 10061 | Prior MI, with or without prediabetes or T2D | Canakinumab, 50 mg, every 12 weeks | 48 months | HbA1c reduction | 7.0% | 7.1% | +0.1% |
| Ruscitti et al, 2019 [104] | Clinical trial | 39 | RA and T2D | Anakinra, 100 mg, once daily | 6 months | HbA1c reduction | 7.7% | 6.7% | − 1.0% |
| Tam et al, 2007 [113] | Clinical trial | 19 | RA and T2D | Infliximab, 3 mg/kg, at Week 0, Weeks 2, 6 and 14 | 14 weeks | HOMA-IR reduction | 1.3 | 0.6 | − 0.7 |
| Stavropoulos-Kalinoglou et al, 2012 [114] | Observational study | 32 | RA and T2D | Infliximab, 3 mg/kg, every 8 weeks | 6 months | HOMA-IR reduction | 2.6 | 2.4 | − 0.2 |
| Stagakis et al, 2012 [117] | Prospective study | 61 | RA and T2D | Infliximab, 3 mg/kg, every 8 weeks | 12 weeks | HOMA-IR reduction | 7.0 | − 5.7 | − 12.7 |
3.5 IL-6 Inhibitors

In the past decade, extensive clinical experience has established the efficacy of IL-6 inhibition in patients with RA, by tocilizumab or sarilumab, which are antagonists of IL-6 receptor. In this context, some studies investigated the efficacy of IL-6 inhibition on IR and T2D in patients with RA [121–126]. Tocilizumab showed a positive effect on IR as per reduction of HOMA-IR observed in these studies [124]. Furthermore, the improvement of leptin/adiponectin ratio, a measure of IR, has been reported following the administration of this drug [124]. Additionally, the effect of the administration of TNFi or tocilizumab and HbA1c has been investigated in patients with RA [122]. A significant reduction in HbA1c after starting these drugs has been observed, even if a more pronounced decrease was observed in those treated with tocilizumab rather than TNFi [122]. Another study analysed the correlation between the administration of tocilizumab and the improvement of IR in patients with RA, by using HOMA-IR and QUICKI [121]. A decrease of IR together with an improvement of IS in patients with RA has been observed, especially in those who were more insulin resistant [121]. However, other experiences failed to report this positive effect of tocilizumab on glucose derangement, advising the need of further studies to fully clarify the efficacy of this drug in this context [127, 128]. The efficacy of sarilumab on improving glucose metabolism was assessed in a post hoc analysis [129] of three randomised clinical trials in patients with RA with or without concomitant T2D [130–132]. This study aimed to assess the effect of sarilumab as monotherapy or in combination with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) on HbA1c, after 24 months, compared with either placebo or adalimumab monotherapy. The authors found that sarilumab as monotherapy or in combination may significantly reduce HbA1c than adalimumab monotherapy or placebo + MTX/csDMARDs, particularly in patients with T2D. Moreover, a more relevant reduction of HbA1c was reported in patients treated with sarilumab whose baseline HbA1c was ≥ 7 % [129].

3.6 Other bDMARDs and tsDMARDs

In the large background of RA therapies, other drugs with different mechanisms of action are presently available to treat these patients [89, 133].

Abatacept is a recombinant fusion protein formed by the extracellular domain of human cytotoxic T-lymphocyte-associated protein 4 and the modified Fc region of a human IgG1.
This drug has been studied in patients with type 1 diabetes and T2D [134–137]. A recent study reported an increased activation of T cells in the bone marrow of T2D patients [135]. These authors showed that abatacept reduced this overactivation of immune cells in a murine model of diabetes [135]. In patients with RA, an improvement of IS has been observed following the administration of abatacept by an evaluation of an insulin sensitivity index in a 6-month follow-up study [25]. The authors also reported a concomitant reduction of HaA1c [25]. Conversely, in another study, no effect of abatacept on IR, assessed using HOMA-IR, has been observed [117]. In a large observational cohort study [136], the use of this drug was associated with a lower risk of developing T2D in patients with RA, than the administration of TNFi in a mean follow-up of 368 days [136]. This result mirrored a previous study in which the incidence of T2D in RA patients was lower in patients treated with abatacept than MTX [137].

Rituximab is a chimeric monoclonal antibody to the cell surface antigen cluster differentiation 20 (CD20), which is found on mature B cells. The binding of rituximab with CD20 leads to circulating and tissue B cell depletion with a concurrent decrease in immunoglobulin (IgG and IgM levels. Chen et al evaluated the risk of T2D treatment intensification in patients with RA and concomitant T2D initiating a bDMARD [138]. In the univariate analysis, the rate of T2D treatment intensification was higher in patients treated with rituximab. However, in a multivariable-adjusted analysis, there was no difference between rituximab and other drugs. In this study, the administration of tofacitinib, a JAK-inhibitor, recently approved for patients RA, was also assessed. The rate of treatment intensification was lower in patients treated with tofacitinib than other drugs and was associated with a reduced administration of insulin to manage these patients [138]. Another JAK-inhibitor, which has been introduced in the treatment of RA, is baricitinib. The latter has been recently tested in decreasing diabetic kidney disease progression in patients with T2D in a Phase 2 clinical trial [139]. Baricitinib has been shown to reduce the albuminuria in these patients but also to decrease HbA1c after 24 weeks [139]. Its potential use in metabolic alterations has been also analysed in a murine high-fat/high-sugar diet model [140]. Interestingly, the use of the baricitinib showed a multi-organ protection against the deleterious effects of the high-fat/high-sugar diet exposure [140].

4 The Presence of T2D May Contribute to a Personalised Therapeutic Approach in Patients with RA

As shown in Fig. 1, multiple lines of evidence have increasingly suggested a pathogenic connection between the rheumatoid process and the mechanisms of T2D in a vicious circle perpetuated by glucose derangement and inflammatory mediators [22, 23]. These findings have been further reinforced by some clinical studies showing that the inhibition of IL-1 and IL-6 may simultaneously enable the therapeutic targeting of patients with RA and concomitant T2D [104, 129]. Interestingly, comparing these findings to the previous studies on T2D following administration of bDMARDs [97, 98, 100, 101], a more evident reduction of HbA1c has been observed in patients with RA and concomitant T2D (Table 1), mainly considering results about IL-1 inhibition. Thus, the inflammatory pathogenic mechanisms of the metabolic disease could be exaggerated in the context of a rheumatic disease possibly explaining these findings. In addition, IL-1 inhibition has been proposed to have disease modifying effects on T2D in this setting considering the reduction and the stoppage of the antidiabetic therapies, which have been observed in patients with RA [105]. In fact, despite the latest improvement of the antidiabetic therapeutic strategies, a percentage of patients with T2D, around 30 %, is still treated with insulin after failing a dual oral therapy [141, 142]. Contrarily, IL-1 inhibition could not only palliate glycaemia, but also decrease the progressive decline in insulin secretion associated with T2D, interfering with apoptosis of β-cells, improving their function, and improving the peripheral IR [96]. Moreover, the maintenance of clinical remission of the rheumatic disease could further improve the glucose derangement and reduce the occurrence of T2D in RA [2]. On these bases, the presence of T2D may allow physicians to perform a better profile of patients with RA according to the principles of precision medicine, tailoring the medical treatment to the individual characteristics [143–145]. In addition, in patients with RA and concomitant T2D, IL-1 inhibition could be considered a targeted therapeutic strategy, leading to a simultaneous improvement of both metabolic parameters and inflammatory signs. Furthermore, considering the effects of IL-1 inhibition in the prevention of CVD [102], it is possible to suggest that this therapeutic strategy may decrease the burden of CV risk in RA targeting the synergy between the inflammation and the glucose derangement. These findings may open the way for subsequent confirmatory studies to entirely elucidate the clinical role of IL-1 inhibition in patients with RA and concomitant T2D. However, it must be pointed out that further studies are needed to fully clarify the possible usefulness of additional therapeutic strategies, such as IL-6 and JAK inhibitors, which have also shown some efficacy in this context [146, 147].

5 Conclusions

In conclusion, the benefits of targeting the inflammatory process, mainly by IL-1 inhibition, may be suggested in patients with RA and concomitant T2D. Considering the pronounced
decrease of HbA1c, it could be possible to hypothesise that the pro-inflammatory mechanisms of T2D could be exaggerated by RA in a pathogenic vicious circle perpetuated by glucose derangement and inflammation. Thus, the presence of T2D could identify a subset of RA possibly benefitting by IL-1 inhibition, although further studies are needed to elucidate this topic stratifying the patients according to their clinical picture and associated comorbidities.

**Declarations**

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