Anti- and non-tumor necrosis factor-α-targeted therapies effects on insulin resistance in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

Chrong-Reen Wang, Hung-Wen Tsai

ORCID number: Chrong-Reen Wang 0000-0001-9881-7024; Hung-Wen Tsai 0000-0001-9223-2535.

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Chrong-Reen Wang, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan 70403, Taiwan

Hung-Wen Tsai, Department of Pathology, National Cheng Kung University Hospital, Tainan 70403, Taiwan

Corresponding author: Chrong-Reen Wang, MD, PhD, Professor, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138 Sheng-Li Road, Tainan 70403, Taiwan. wangcr@mail.ncku.edu.tw

Abstract

In addition to β-cell failure with inadequate insulin secretion, the crucial mechanism leading to establishment of diabetes mellitus (DM) is the resistance of target cells to insulin, i.e. insulin resistance (IR), indicating a requirement of beyond-normal insulin concentrations to maintain euglycemic status and an ineffective strength of transduction signaling from the receptor, downstream to the substrates of insulin action. IR is a common feature of most metabolic disorders, particularly type II DM as well as some cases of type I DM. A variety of human inflammatory disorders with increased levels of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β, have been reported to be associated with an increased risk of IR. Autoimmune-mediated arthritis conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), with the involvement of proinflammatory cytokines as their central pathogenesis, have been demonstrated to be associated with IR, especially during the active disease state. There is an increasing trend towards using biologic agents and small molecule-targeted drugs to treat such disorders. In this review, we focus on the effects of anti-TNF-α- and non-TNF-α-targeted therapies on IR in patients with RA, PsA and AS. Anti-TNF-α therapy, IL-1 blockade, IL-6 antagonist, Janus kinase inhibitor and phosphodiesterase type 4 blocker can reduce IR and improve diabetic hyper-glycemia in autoimmune-mediated arthritis.

Key Words: Insulin resistance; Diabetes mellitus; Tumor necrosis factor-α-targeted therapy; Non-tumor necrosis factor-α-targeted therapy; Rheumatoid arthritis; Psoriatic arthritis
INTRODUCTION

In addition to β-cell failure with inadequate insulin secretion, the central mechanism leading to the development of diabetes mellitus (DM) is the resistance of target cells to insulin, i.e., insulin resistance (IR). Such a pathological condition in the human body indicates resistance to the effects of insulin, with a requirement of beyond-normal insulin concentrations to maintain euglycemic status and ineffective strength of insulin signaling from the receptor, downstream to the final substrates of its action. The intramembrane insulin receptor consists of two extracellular α and two intracellular β subunits linked by disulphide bonds. Binding of insulin to the α subunits can activate the tyrosine kinase in the β subunits. Upon activation, autophosphorylation of the β subunit amplifies the kinase activity, further recruiting the adaptor proteins, insulin receptor substrates (IRSs). This process creates a suitable binding site for an IRS, that is phosphorylated by different insulin-induced kinases, including protein kinase C, salt-inducible kinase 2, protein kinase B (PKB), p70-S6 kinase, mammalian target of rapamycin, extracellular signal-regulated kinase (ERK)1/2, and rho-associated, coiled-coil-containing protein kinase 1.

The phosphorylated IRS can act as a docking protein for various effector molecules possessing the src homology 2 (SH2) domain. The intracellular SH2 domain protein binds to the phosphotyrosine residues of IRSs. These IRS partners include adaptors such as phosphoinositide 3-kinase (PI3K), growth factor receptor-bound protein 2, CT10 regulator of kinase and non-catalytic region of tyrosine kinase adaptor protein 1 (Nck), and enzymes comprising of Fyn, C-terminal Src kinase, SH2 domain-containing inositol polyphosphate 5'-phosphatase and SH2-containing protein tyrosine phosphatase 2. The activated IRS triggers subsequent signals by binding to PI3K and activating it, to catalyze the conversion of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a potent inducer for activating various kinases, PKB in particular, to facilitate the entry of glucose into cells by translocating glucose transporter 4 (GLUT4) to the cell surface and to promote the synthesis of glycogen by suppressing the inhibitory glycogen synthase kinase-3β. Most of the physiological effects of insulin are mediated by the signaling pathway involving the activated IRS and SH2 domain proteins, leading to activation of multiple downstream effectors to regulate cell differentiation, growth, survival, and metabolism via a variety of intracellular pathways.

IR is an impedance of human tissues to the action of insulin on glucose uptake, metabolism or storage, a common feature of most metabolic disorders, including atherosclerosis and hypertension, non-alcoholic fatty liver disorder, hyperlipidemia, metabolic syndrome, obesity and type II DM as well as some cases in type I DM. In hepatocytes, IR increases the circulating levels of glucose due to a reduction of glycogen synthesis, further compounded by the inability of skeletal muscle cells and adipocytes to take up glucose. Although the exact pathogenic mechanisms of IR...
remains to be elucidated, any defects in expression or function of any enzymes and modulatory proteins involved in the insulin signal transduction may impair normal insulin signaling, leading to IR in peripheral tissues.\(^{[14,15]}\) Notably, non-transmembrane protein-tyrosine phosphatase 1B (PTP1B) is a dominant-negative regulator of insulin signaling, which functions by reversing the phosphorylation on IRS-1 tyrosine residues to reduce the insulin signal transduction.\(^{[16]}\) Transgenic mice overexpressing human PTP1B selectively in muscle displayed IR with an impairment in insulin-induced glucose transport into skeletal muscle, whereas mice lacking the PTP1B gene had a reduced risk of IR with higher insulin sensitivity in peripheral tissues.\(^{[17]}\) In human, overexpression of the PTP1B protein has been observed in an obesity-related IR status, implicating reduction of PTP1B levels as a therapeutic strategy for IR.\(^{[18]}\)

Miscellaneous inflammatory disorders in human with increased levels of proinflammatory cytokines, as measured by tumor necrosis factor (TNF-α), interleukin (IL)-1β and IL-6 depending on the study designs, have been reported to be associated with increased risk of developing IR.\(^{[19]}\) There are commonly encountered autoimmune-mediated arthritis conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).\(^{[20-22]}\) Active disease activities in these inflammatory arthritis conditions have been demonstrated to be associated with IR.\(^{[23-25]}\) Recently, there has been an increasing trend towards using biologic agents and small molecule-targeted drugs to treat such disorders. In this review, we focus on the effects of anti-TNF-α and non-TNF-α-targeted therapies on IR in RA, PsA and AS patients.

**ROLE OF TNF-α IN IR**

Upon binding of TNF-α to its receptor, sphingomyelinases can be activated to trigger further interactions with the insulin signaling pathway. Via the action of sphingomyelinases, serine phosphorylation of IRS-1 and reduced tyrosine phosphorylation of the insulin receptor and IRS-1 are induced. The serine-phosphorylated IRS-1 acts in a negative feedback loop to inhibit tyrosine kinase activity of the insulin receptor. An inhibitory kB kinase (IKK)-β has been identified as the cellular kinase responsible for the serine phosphorylation of IRS-1 in response to TNF-α stimulation.\(^{[26]}\) Insulin-targeted cells lacking endogenous IRS-1 were found to be resistant to TNF-α-mediated inhibition of insulin receptor signaling, while transfecting IRS-1 into these cells enhanced the sensitivity to such an effect of TNF-α.\(^{[27]}\)

Other mechanisms responsible for TNF-α-induced IR have been elucidated, including down-regulated expression levels of IRS-1, GLUT4, CCAAT enhancer-binding protein α, peroxisome proliferator-activated receptor (PPAR)-γ, peroxisome proliferator-activated receptor (PPAR)-γ, perilipin, and adipocyte complement-related protein of 30 kDa (Acrp30).\(^{[28]}\) In addition to directly inducing lipolysis in adipose tissues, TNF-α can reduce the expression of Acrp30, also named as adiponectin, by suppressing its promoter activity to reduce the circulating levels.\(^{[29]}\) Other mechanisms for TNF-α-mediated IR include suppression of Acrp30 expression in adipocytes.\(^{[28]}\) In particular, NF-kB-mediated suppressed synthesis of PPAR-γ, an essential gene for the induction and maintenance of adipocyte genes expression,\(^{[30]}\) is a critical determinant of insulin sensitivity in adipose tissues.\(^{[31]}\) Notably, the expression of suppressor of cytokine signaling 3 (SOCS3), an inhibitor responsible for preventing the excessive cytokine signaling, can reduce insulin-induced tyrosine phosphorylation of IRS-2.\(^{[32]}\) TNF-α has been shown to induce a sustained SOCS-3 expression in targeted tissues.\(^{[33]}\)

In human observations, elevated circulating concentrations of bioactive TNF-α have been observed in type II DM patients, as compared with the healthy individuals.\(^{[27,28]}\) A single intravenous (i.v.) infusion of recombinant TNF-α has demonstrated an alteration of glucose metabolism by lowering basal insulin levels without impairing β-cell function or hepatic insulin sensitivity in non-diabetic healthy persons.\(^{[34]}\) Moreover, a 4-d course of i.v. TNF-α infusion bought about IR, with increased homeostasis model assessment (HOMA)-IR levels, in healthy young volunteers.\(^{[35]}\) An earlier study carried out in obese non-diabetic subjects failed to demonstrate positive effects on IR by i.v. administration of a recombinant soluble TNF-α receptor/immunoglobulin G (IgG)-Fc fusion proteins (rsTNFRFPs).\(^{[36]}\) Despite increased circulating levels of adiponectin, no beneficial effects on IR were observed in the study populations with metabolic syndrome receiving the subcutaneous injection of etanercept (ETA), a rsTNFRFPs.\(^{[37,38]}\)
**Effects on IR of targeting TNF-α in RA patients**

TNF-α participates in the pathogenesis and disease progression of RA\(^\text{[49]}\), and biologics antagonizing this cytokine display significant efficacy in inhibiting arthritis activities\(^\text{[49]}\). IR in RA is driven majorly by the activity-related inflammation\(^\text{[49]}\), and elevated plasma levels of TNF-α have been demonstrated in such patients with increased IR\(^\text{[49]}\). Considerable case-control and cohort studies have shown increased risks of both type I and II DM prevalence among RA patients\(^\text{[49]}\). An association in type I DM is specific in a subgroup of RA with the presence of cyclic citrullinated peptide antibody\(^\text{[4]}\), and both diseases share susceptibility genes, including *HLA-DRB1*, *PTPN22*, *CTLA-4*, *TAGAP*, and *KIAA109-TENR-IL2-IL21*\(^\text{[4,54]}\). In a cohort with 11158 RA patients followed-up from the period of 1986 to 2010, there was an increased incidence of type II DM, substantially ascribed to factors like obesity rather than disease activity\(^\text{[61]}\). A large prospective study of 114342 women showed no differences in the type II DM occurrence between individuals with and without RA\(^\text{[57]}\); whereas, in another investigation of 48718 RA patients, there was an increased risk of type II DM compared to a healthy population with 442033 persons\(^\text{[66]}\). Despite a weaker association between RA and type II DM, such patients also have other diabetic risks, including glucocorticoid use, lifestyle factors (like alcohol and smoking), obese status, and exposure to certain traditional disease-modifying anti-rheumatic drugs that may enhance the development of diabetes\(^\text{[67]}\).

Two therapeutic modalities have been used to inactivate TNF-α in treating autoimmune-related arthritis, namely rsTNFRFP ETA and monoclonal antibodies (mAbs) comprising adalimumab (ADA), certolizumab, golimumab (GLO), and infliximab (IFX)\(^\text{[57]}\). These agents bind to TNF-α to reduce its effects on inflammatory processes; however, ETA has an additional capability to block lymphotoxin-α (LT-α)\(^\text{[57]}\). Interestingly, genetic studies have linked polymorphisms in genes encoding LT-α to patients with such IR-associated diseases as type II DM and metabolic syndrome\(^\text{[57]}\). In a cohort of 522 non-diabetic RA cases receiving the TNF-α inhibitors (TNFis) including ADA, ETA, GLO and IFX, there was a more than 50% reduction in the risk of DM development\(^\text{[61]}\). Nevertheless, another retrospective observational study with 2111 RA patients, not excluding DM, failed to demonstrate hypoglycemic effects at 6 mo following the initiation of TNFi therapy with ETA and four other mAbs\(^\text{[57]}\). Since hyperglycemia, a critical contributor to IR, can interfere with the effects of TNFi on insulin sensitivity, most published reports examined the studied population in non-diabetic RA patients. The mixed therapeutic effects with rsTNFRFP and different mAbs on IR have been demonstrated in RA patients\(^\text{[57,58,66]}\). Nevertheless, using individual blockade to examine the efficacy of TNF-α inhibition in improving insulin sensitivity would be a more appropriate approach due to distinct pharmacokinetic and pharmacodynamic actions in different TNFi under clinical administration\(^\text{[61]}\).

Table 1 summarizes 15 published studies that examined the effects of anti-TNF therapies on IR in non-diabetic RA patients\(^\text{[49-52,54-77]}\). There were four with at least two TNF (mixed therapeutic effects), eight with IFX alone, three with ADA alone, and two with ETA alone. Except for only one study with hyperinsulinemic euglycemic glucose clamp to measure IR\(^\text{[54]}\), HOMA-IR levels were calculated in other investigations. All studies with IFX or ETA alone showed improvement in IR; however, two with ADA alone failed to demonstrate such an effect\(^\text{[54,55]}\).

**ROLE OF IL-6 IN IR**

IL-6 is a multifunctional cytokine, largely produced by adipocytes and macrophages within adipose tissues as well as skeletal muscle and liver\(^\text{[78]}\). *In vitro* and *in vivo* studies have confirmed that the production of IL-6 can be regulated by insulin\(^\text{[79]}\), and hyperinsulinemia can produce an increase in IL-6 expression in adipose tissues with raised systemic levels\(^\text{[79]}\). Circulating levels of IL-6 have been observed to be elevated in type II DM patients\(^\text{[80]}\). This cytokine is a risk factor for the development of such a disease\(^\text{[80]}\). Its plasma levels have been shown to be positively correlated with the percentage of body fat\(^\text{[80]}\). Activated IKK-β, a molecular target of IR\(^\text{[81]}\), phosphorylates an inhibitor of NF-κB, IkBα, and promotes its degradation to free NF-κB and allows its entry into the nucleus\(^\text{[81]}\). This kinase can not only activate NF-κB to stimulate the production of IL-6 but it can also directly induce the serine phosphorylation of IRS-1\(^\text{[81]}\). Injection of neutralizing antibodies against IL-6 could reverse IKK-β-induced IR in mice\(^\text{[81]}\). Notably, IL-6 has a negative impact on insulin signaling by decreasing tyrosine phosphorylation of IRS-1, inhibiting activation of PKB\(^\text{[81]}\), and inducing a
Table 1 Studies on effects of anti-tumor necrosis factor therapies on insulin resistance in non-diabetic rheumatoid arthritis patients

| No. | Source            | Character | Cases, n, drug(s) | Clinical feature | Duration | Effects on IR                                  | Ref. |
|-----|-------------------|-----------|------------------|------------------|----------|-----------------------------------------------|------|
| 1   | 2004, Austria     | mAb       | 2 IFX            | Non-diabetic     | 4 or 8 mo| Improved HOMA-IR only in high-IR group        | [65] |
| 2   | 2005, Greece      | mAb       | 28 IFX           | Non-diabetic     | 6 mo     | Improved HOMA-IR only in high-IR group        | [66] |
| 3   | 2006, Spain       | mAb       | 27 IFX           | Non-diabetic     | 2 h after infusion | Improved HOMA-IR | [67] |
| 4   | 2007, Netherlands | mAb       | 5 IFX            | Non-diabetic     | 6 wk     | Improved insulin sensitivity¹                  | [68] |
| 5   | 2007, Denmark     | mAb       | 9 ADA            | Non-diabetic, high IR | 8 wk     | Ineffective HOMA-IR                          | [69] |
| 6   | 2007, China       | mAb       | 19 IFX           | Non-diabetic     | 14 wk    | Improved HOMA-IR                              | [70] |
| 7   | 2007, Turkey      | mAb       | 7 IFX            | Non-diabetic     | 5-15 mo  | Improved HOMA-IR                              | [71] |
| 8   | 2008, Spain       | mAb       | 21 IFX           | Non-diabetic     | 24 wk    | Improved HOMA-IR                              | [72] |
| 9   | 2008, Italy       | mAbs, rsTNFRFP, Mixed | 20 ETA, 18 IFX, Total 38 | Non-diabetic | 24 wk | Improved HOMA-IR | [73] |
| 10  | 2011, Spain       | mAbs, rsTNFRFP, Mixed | 8 ADA, 6 IFX, 2 ETA, Total 16 | Non-diabetic | 12 mo | Ineffective HOMA-IR | [74] |
| 11  | 2012, United Kingdom | mAbs, rsTNFRFP, Mixed | 49 IFX, 11 ADA, 1 ETA, Total 61 | Non-diabetic | 12 wk | Improved HOMA-IR in high-IR group | [75] |
| 12  | 2012, Greece      | mAbs, rsTNFRFP, Mixed | 20 IFX, 11 ETA, 1 ADA, Total 32 | Non-diabetic | 6 mo | Improved HOMA-IR in high-IR, non-obese group | [76] |
| 13  | 2019, Italy       | mAbs, rsTNFRFP, Separated | 11 IFX, 12 ETA, 10 ADA, Total 33 | Non-diabetic, non-obese | 24 wk | Improved HOMA-IR in individual group of all TNF blockers | [77] |
| 14  | 2020, Netherlands | mAb       | 28 ADA           | Non-diabetic     | 6 mo     | Ineffective HOMA-IR, improved-β-cell function| [78] |
| 15  | 2020, Taiwan      | rsTNFRFP  | 30 ETA           | Non-diabetic, non-obese | 24 wk | Improved HOMA-IR in high-IR group | [79] |

¹Measurement by hyperinsulinemic euglycemic glucose clamp only. ADA: Adalimumab; ETA: Etanercept; IFX: Infliximab; IR: Insulin resistance; mAb: monoclonal antibody; rsTNFRFP: Recombinant soluble tumor necrosis factor-α receptor fusion protein; TNF: Tumor necrosis factor; HOMA: Homeostasis model assessment.

Rapid recruitment of IRS-1 to the IL-6 receptor complex to phosphorylate the inhibitory serine residue of IRS-1 is favorable. Particularly, an inhibitory mechanism of IL-6 on insulin action is to induce the expression of SOCS-3 in target cells to reduce auto-phosphorylation of insulin receptor-β, tyrosine phosphorylation of IRS-1, association of IRS-1 with PI3K, and activation of PKB and ERK1/2[66,90]. IL-6 has also been shown to reduce the expression of adiponectin, GLUT4, IRS-1, PPAR-γ and insulin receptor-β in adipocytes[66,91]. Furthermore, IL-6 was found to be constitutively expressed by human islet cells treated with high levels of glucose, IL-6 could protect α-cells from apoptosis, whereas there was enhanced apoptosis of β-cells in the presence of IL-6[90,91].

In contrast to the above-mentioned studies which illustrate that IL-6 is a negative regulator of insulin action, results from other investigations also suggest a beneficial role of IL-6 in insulin sensitivity. Increased circulating levels of IL-6 have been detected in individuals with obesity; however, it remains undetermined whether this cytokine has favorable or detrimental effects on the obese status[92]. IL-6 receptor signaling in target cells has been shown to have protective antinflammatory effects, mediated by the skewing of macrophages towards a M2 phenotype and thus limiting the development of IR during obesity[93]. In vitro short-term treatment with IL-6 could enhance the glucose uptake in adipocytes[94]. Physical inactivity, an IR induction factor, has been demonstrated to be associated with reduced IL-6 secretion from skeletal muscle[95], while exercise can enhance the production of IL-6 by skeletal muscle, leading to an improvement in insulin sensitivity[96]. IL-6 treatment could increase the...
translocation of GLUT4 to plasma membrane via adenosine monophosphate (AMP)-activated protein kinase, to increase the insulin-mediated glucose uptake in myotube cells\cite{109}. Exposure to IL-6 induces a rapid recruitment of IRS-1 to the IL-6 receptor complex and further activation of downstream PKB signaling, resulting in the improvement of insulin action in skeletal muscle\cite{103}. \textit{In vitro} addition of IL-6 in human islet cell culture could enhance the production of glucagon-like peptide-1, a hormone which induces β-cells to secret insulin and improves hyperglycemic status\cite{111}. Interestingly, IL-6 treatment for 3 h increased glucose uptake in myocytes; on the contrary, treatment for 24 h decreased insulin-stimulated glucose uptake through impaired GLUT4 translocation and defects in IRS-1, indicating a dual role of IL-6 in regulating insulin action\cite{108}. To sum up, the effects of IL-6 on insulin-targeted tissues are dependent on distinct factors which can regulate its signaling and affect its action in different experimental settings, including therapeutic concentrations, observation kinetics, metabolic stressors (glucose or FFA) and other mediators (cytokines or chemokines)\cite{110}.

In human trials, single i.v. infusion of recombinant IL-6 in healthy volunteers could increase glucose infusion rate and glucose oxidation, as determined by measuring with a hyperinsulinemic-euglycemic clamp, suggesting that acute IL-6 treatment can enhance insulin-stimulated \textit{in vitro} glucose disposal in human\cite{114}. Conversely, a similar IL-6 infusion protocol in type II DM patients failed to alter glucose infusion rates and appearance/disappearance rates during the clamp, indicating that an acute elevation of IL-6 concentrations would not affect insulin-mediated glucose uptake in the diabetic state\cite{112}. In addition to TNFi, non-TNF-α-targeted therapy in RA includes an approved humanized IL-6R antibody tocilizumab (TCZ), which completely inhibits the IL-6 signaling through blocking the binding of this cytokine to both membrane-bound and soluble receptors\cite{110}. In particular, TCZ has been shown to reduce hemoglobin A1c (HbA1c) levels and the use of antidiabetic drugs in type II diabetic patients with active RA after a 6-mo treatment period\cite{117}. Notably, both pro- and anti-inflammatory roles have been identified for IL-6, distinguished by two specific signaling transduction cascades, \textit{i.e.} classic and trans-signaling\cite{110}. Increased evidence suggests that dual behavior of IL-6 in the development of IR and the improvement of insulin sensitivity could be related to whether it acts \textit{via} a trans-signaling or classic signaling mechanism\cite{113,115}. The trans-signaling is involved in the infiltration of macrophages into adipose tissues, resulting in a proinflammatory status with IR in obese subjects\cite{110}. On the other hand, through classic signaling in pancreatic tissues, there is increased cellular proliferation as well as insulin secretion in islet cells, resulting in an anti-inflammatory state with improvement in glycemic state\cite{115}. These findings suggest that specific inhibition of trans-signaling might produce a better outcome in improving insulin sensitivity compared with the global inhibition of IL-6. Nevertheless, intraperitoneal injection of soluble gp130Fc-an extracellular gp130 portion fused to the IgG-Fc region specifically blocking IL-6 trans- (without affecting classical) signaling\cite{116}-failed to alter the blood glucose levels in the streptozotocin-induced mouse model\cite{117}, indicating the existence of complex mechanisms of pleiotropic IL-6 signaling in glucose metabolism.

**Effects on IR of non-TNF-α targeted therapies in RA patients**

Table 2 lists the published reports examining the effects on IR in RA patients receiving non-TNF-α targeted therapies. Besides anti-IL-6 therapy, other studies include abatacept (ABA) treatment alone and mixed effects with ABA and TCZ therapy\cite{114,116,120}. In eight reports of patients receiving TCZ treatment alone, three not excluding DM cases demonstrated ineffectiveness of IR reduction in RA. ABA, a fusion protein with a CTLA-4 domain and IgG1-Fc portion interfering with T-cell co-stimulation/activation with binding to CD80/CD86 molecules, has been approved to treat RA patients\cite{123}. The proposed mechanism for improving insulin sensitivity by this biologic agent is the reduction of adipose tissue inflammation by lessening effector T-cell infiltration and polarizing macrophages to the anti-inflammatory M2 phenotype\cite{117,126}. In two studies with limited patient numbers\cite{119,127}, one failed to demonstrate the effects on IR reduction after ABA therapy for 12 wk, while another showed improved insulin sensitivity under a 6 mo treatment period. In addition, improved leptin/adiponectin ratios, an alternative marker of IR, was identified in RA patients treated with non-TNF-α targeted agents including ABA and TCZ as compared with those receiving TNFi therapy\cite{114}.
Table 2: Studies on effects of non-tumor necrosis factor-targeted therapies on insulin resistance in rheumatoid arthritis patients

| No. | Source     | Drug | Cases, n | Clinical features       | Duration | Effects on IR                        | Ref.  |
|-----|------------|------|----------|-------------------------|----------|--------------------------------------|-------|
| 1   | 2010, Germany | TCZ  | 11       | Non-diabetic            | 3 mo     | Improved HOMA-IR                     | [119] |
| 2   | 2012, United Kingdom | ABA  | 7        | Non-diabetic, active disease | 12 wk    | Ineffective HOMA-IR                 | [10]  |
| 3   | 2013, United Kingdom | TCZ  | 221      | Active disease          | 24 wk    | Improved HOMA-IR                     | [117] |
| 4   | 2013, United Kingdom | TCZ  | 62       | Active disease, JRA children | 6 wk     | Improved HOMA-IR in high-IR group   | [10]  |
| 5   | 2015, Italy  | ABA  | 15       | Non-diabetic, active disease | 6 mo     | Improved ISI, ineffective β-cell functions | [119] |
| 6   | 2015, Taiwan | TCZ  | 24       | Active disease          | 24 wk    | Improved HOMA-IR                     | [123] |
| 7   | 2015, Greece | TCZ  | 19       | Active disease          | 6 mo     | Ineffective HOMA-IR                 | [122] |
| 8   | 2017, France | TCZ  | 15       | Active disease          | 6 mo     | Ineffective HOMA-IR                 | [122] |
| 9   | 2019, Spain  | TCZ  | 50       | Non-diabetic            | 1 h after 1st infusion | Improved HOMA-IR                   | [122] |
| 10  | 2019, France | Other¹, TNFi | 107, 96 | Active disease          | 24 wk    | Improved leptin/adiponectin ratios in other group than TNFi group | [124] |
| 11  | 2020, France | TCZ  | 77       | Active disease          | 12 mo    | Ineffective HOMA-IR                 | [129] |

¹No. 10 study including other non-tumor necrosis factor-targeted agents, like abatacept and tocilizumab. ABA: Abatacept; IR: Insulin resistance; ISI: Insulin sensitivity index; JRA: Juvenile rheumatoid arthritis; TCZ: Tocilizumab; TNFi: Tumor necrosis factor inhibitor; HOMA: Homeostasis model assessment.

ROLE OF IL-1 IN IR

The IL-1 family consists of IL-1α and IL-1β (the first identified cytokines with strong proinflammatory functions), and a naturally occurring anti-inflammatory mediator, IL-1 receptor antagonist (IL-1Ra)[130]. IL-1 can regulate T-cell function by polarizing such cells towards cell-mediated immunity by inducing the development of Th1 and Th17 cells, or production of antibodies via a Th2 bias. These cytokines, IL-1β in particular, participate in regulating inflammatory diseases, as observed in diabetic patients[28]. Elevated serum con-centrations of IL-1α and production levels of IL-1β from mononuclear cells were observed in patients at the onset of type 1 DM[131,132]. IL-1β has been proposed to mediate both dysfunction and destruction of pancreatic β-cells during the autoimmune process of insulin-dependent DM (IDDM)[133]. IL-1β has also been observed in pancreatic islets of type 1 diabetic patients[134]. The IL-1 family has a role in the immune system and pancreatic β-cells[135]. Concentrations of IL-1β, together with IL-6, can predict the risk of type II DM in humans[136]. IL-1Ra-deficient mice with excessive IL-1 signaling had lower fasting insulin levels[137], and expression of IL-1Ra was diminished in pancreatic islets of type II diabetic patients[138].

It has been demonstrated that, in insulin-targeted cells, IL-1β reduces the IRS-1 expression through an ERK-dependent mechanism at the transcriptional level and an ERK-independent mechanism at the post-transcriptional level[139]. By targeting IRS-1 and activating the IKKβ/NF-kB pathway, IL-1β is capable of impairing insulin signaling and its action, thus participating in the development of IR[140,141]. In vitro exposure of human islets to high concentrations of glucose resulted in increased production of IL-1β from β-cells, followed by NF-kB activation and cellular apoptosis[142]. Although local IL-1β activity can govern inflammation of pancreatic islets and control the function of islet cells, this cytokine has been observed to exert bimodal effects on pancreatic β-cells. Short-time and lower concentration stimulation activates the β-cells to increase the release of insulin, whereas an exposure to higher concentrations can induce reduced secretion of insulin through activating NF-kB, mitogen-activated-protein-kinase and c-Jun N-terminal kinase signaling, leading to endoplasmic reticulum and mitochondrial stress and eventually activating the apoptotic machinery[143,144]. Interestingly, there is an emerging hypothetic pathogenesis for type II DM, in which an imbalance between the hyperactivity of IL-1β and the countering effect of IL-1Ra can determine the outcome of islet inflammation[145].
Collectively, these findings indicate that the IL-1 cytokine family may represent therapeutic targets to reverse the adverse metabolic consequences of DM\cite{119,154,160}.

Until now, three IL-1-targeted agents have been approved for managing inflammatory disorders, including anakinra (ANA), an IL-1Ra for treating RA and cryopyrin-associated periodic syndromes (CAPS), rilonacept (referred to as RIL), a decoy receptor consisting of extracellular IL-1R portion fused to IgG1-Fc for CAPS therapy, and canakinumab (CAN), an IL-1β mAb for autoinflammatory diseases and gouty arthritis\cite{119,154,160}. In particular, after receiving 6 mo of ANA treatment for arthritis activity, 2 RA and 3 GA patients, whose cases were combined with non-insulin-dependent DM (NIDDM), showed reduced HbA1c and fasting glucose levels, which was followed by reduction in or removal from antiidiabetic medications in 2 of the cases, implicating IL-1 as a therapeutic target in diabetic therapy\cite{119,154,160}.

**Effects on DM by applying anti-TNF-α and other targeted agents used for rheumatoid arthritis disorders**

Table 3 demonstrates the published efficacy in DM of application of anti-TNF-α and other targeted agents to treat rheumatology disorders. For two reports using TNF\(_i\) in type II diabetic patients, a short-term ETA trial for 4 wk, despite a marginally improved insulin response in i.v. glucose tolerance test, showed inefficacy in insulin sensitivity\cite{152}, while a 10-year observation with ETA and IFX therapy for RA and Crohn’s disease co-morbidities, respectively, demonstrated reduced HbA1c and fasting glucose levels\cite{148}. Interestingly, rituximab (RTX), a chimeric mAb approved for RA therapy through targeting surface CD20 molecule to deplete β-cell\cite{156}, has been applied to treat IDDM and type B insulin resistance syndrome-associated NIDDM\cite{109,129}. Although the immunopathogenic mechanism of β-cell destruction in type I DM is T-cell mediated autoimmunity, B-cells can be involved in the immune process by serving as antigen-presenting cells to present such autoantigens as cryptic peptides to which T-cells are not tolerant\cite{156}. In NOD mice, the development of insulitis has been shown to be completely abrogated upon injection of an anti-μ chain polyclonal antibody, which depletes B lymphocytes\cite{152}.

In a clinical trial, at 1 year after the first infusion of RTX in newly diagnosed type I DM patients, there were cases showing reduced HbA1c, and the required insulin doses with a higher 2 h C-peptide area under the curve (AUC)\cite{148}. After a 30 mo follow-up, the AUC, HbA1c, and insulin doses were similar between the RTX-treated and placebo groups\cite{152}, suggesting that β-cell depletion therapy does not fundamentally alter the underlying disease pathogenesis. In a subsequent observation in 3 cases with type B insulin resistance syndrome characterized by IR with refractory hyperglycemia and the presence of insulin receptor antibodies, RTX therapy reduced HbA1c levels and insulin requirement with undetectable anti-insulin receptor levels\cite{148}. Blocking T-cell costimulatory signaling with a CTLA4-Ig fusion protein could prevent DM development in NOD mice by administration before the occurrence of frank diabetic status\cite{19}. In addition to improving the insulin sensitivity in non-diabetic RA patients\cite{19}, continued administration of ABA over 2 years was shown to yield higher 2 h C-peptide AUC in recent-onset type I DM patients, implicating an ongoing T-cell activation at the time of the type I DM diagnosis\cite{19}.

Altogether there have been 16 published studies examining the effects of anti-IL-1 therapy on diabetic status, including 7 with ANA, 5 with CAN, and 1 with RIL, as well as 3 reports with the unapproved mAbs bermekimab (anti-IL-1α) and gevokizumab (anti-IL-1β)\cite{152,156,160}. Except for one ineffective study recruiting newly diagnosed type I DM\cite{156}, six other investigations have shown beneficial effects of ANA therapy on type I and II DM patients. Although CAN treatment demonstrated the efficacy in four reports with type II DM, and such therapy showed ineffectiveness in a report with type I DM\cite{119,129,131,160}. Similar to the observations from CAN therapy, there were effective results in type II but not in type I diabetic patients under gevokizumab treatment\cite{152,160}. The study examining recent-onset type I diabetic cases receiving regular RIL injection revealed a higher 2-h C-peptide AUC\cite{160}. Another investigation analyzing type II DM patients under the administration of bermekimab exhibited an increase in the secretion of insulin\cite{156}. Although there was controversial efficacy in type I diabetes sufferers, these trials have supported the beneficial effects of anti-IL-1 therapy on type II DM patients.

The Janus kinase (JAK) and signal transducers and activators of transcription (STAT) pathways include JAK 1 to 3, tyrosine kinase 2 (TYK2) and STAT 1 to 6, regulating more than 50 cytokine or hormone receptors, many of which have pathogenic roles in a variety of autoimmune and inflammation diseases\cite{128,130}. Upon activation by cytokines or hormones, JAK phosphotransferases can auto- and mutually
Table 3 Studied effects on diabetes mellitus by applying anti-tumor necrosis factor- and non-tumor necrosis factor-targeted agents for treating patients with rheumatology disorders

| No. | Source         | Drug | Mechanism | PN | Clinical feature(s) | Duration | Effect on IR or diabetic status                                                                 |
|-----|----------------|------|-----------|----|---------------------|----------|------------------------------------------------------------------------------------------------|
| 1   | 2005, United States | ETA | rSTNFRFP  | 10 | Type II DM, obese   | 4 wk     | Ineffective IS                                                                                   |
| 2   | 2007, INC       | ANA  | IL-1Ra    | 34 | Type II DM          | 13 wk    | Reduced HbA1c and increased insulin secretion at 13 wk, reduced insulin doses at 39 wk            |
| 3   | 2009, United States | RTX | CD20 mAb  | 49 | Type I DM, recent   | 1 yr     | Reduced HbA1c/insulin doses and higher 2 h C-peptide AUC at 1 yr, no differences at 30 mo       |
| 4   | 2011, United States | ABA | CTLA4-Ig  | 73 | Type I DM, recent   | 2 yr     | Higher 2 h C-peptide AUC                                                                       |
| 5   | 2011, United States | TNFi | ETA, IFX  | 8  | Type II DM          | 10 yr    | Reduced HbA1c and fasting glucose levels                                                        |
| 6   | 2011, Japan     | TCZ  | IL-6R mAb | 10 | Type II DM          | 6 mo     | Reduced HbA1c and use of antidiabetic drugs                                                    |
| 7   | 2012, INC       | CAN  | IL-1 mAb  | 151| Type II DM          | 4 wk     | Increased insulin secretion (ISR relative to glucose at 0 to 0.5 h)                             |
| 8   | 2012, INC       | CAN  | IL-1 mAb  | 372| Type II DM          | 4 mo     | Ineffective HbA1c, fasting glucose and insulin levels                                         |
| 9   | 2012, INC       | GEV  | IL-1 mAb  | 81 | Type II DM          | 13 wk    | Reduced HbA1c, increased IS and insulin secretion at single i.v. groups (0.03, 0.1 mg/kg) |
| 10  | 2013, INC       | ANA  | IL-1 Ra   | 25 | Type I DM, recent   | 9 mo     | Ineffective 2 h C-peptide AUC                                                                  |
| 11  | 2013, INC       | CAN  | IL-1 mAb  | 45 | Type I DM, recent   | 1 yr     | Ineffective 2 h C-peptide AUC                                                                  |
| 12  | 2014, INC       | CAN  | IL-1 mAb  | 14 | Type II DM          | 24 wk    | Reduced HbA1c at single i.v. 1.5 and 10 mg/kg groups                                             |
| 13  | 2015, Netherlands | ANA | IL-1Ra    | 14 | Type I DM          | 1 wk     | Reduced HbA1c, insulin doses and fasting glucose levels, increased IS                           |
| 14  | 2015, Italy     | ANA  | IL-1Ra    | 2  | Type II DM          | 6 mo     | Reduced HbA1c and fasting glucose levels, reduced or off antidiabetic therapeutics             |
| 15  | 2015, Italy     | ANA  | IL-1Ra    | 3  | Type II DM          | 6 mo     | Reduced HbA1c and fasting glucose levels                                                        |
| 16  | 2015, Germany   | BER  | IL-1 mAb  | 7  | Type II DM          | 60 d     | Increased insulin secretion                                                                    |
| 17  | 2016, Switzerland | GEV | IL-1 mAb  | 15 | Type I DM          | 1 yr     | Ineffective 2-h C-peptide AUC                                                                  |
| 18  | 2016, Switzerland | CAN | IL-1 mAb  | 6  | Type II DM          | 24 wk    | Reduced HbA1c                                                                                  |
| 19  | 2017, Japan     | RTX  | CD20 mAb  | 3  | Type II DM, insulin RS | 6-16 mo | Reduced HbA1c, and insulin doses, disappearance of IR antibody                                 |
| 20  | 2018, United States | RIL | IL-1R-Ig  | 13 | Type I DM, recent   | 26 wk    | Higher 2 h C-peptide AUC                                                                      |
| 21  | 2019, Italy     | ANA  | IL-1Ra    | 17 | Type II DM          | 6 mo     | Reduced HbA1c                                                                                  |
| 22  | 2019, Italy     | ANA  | IL-1Ra    | 15 | Type II DM          | 6 mo     | Increased IS, improved β-cell function, decreased glucagon levels                              |
Effects of anti-TNF-α and non-TNF-α-targeted therapies on IR or diabetes in PsA and AS patients

The central role of TNF-α, a critical IR inducer[79], in inflammation morbidities like AS, PsA and psoriasis (PsO) has been demonstrated by the ability of biologic agents that impede the action of TNF-α to offer substantial and comparable therapeutic effects[171,172]. In a PsA cohort, there was a 16% prevalence of IR and an association of metabolic syndrome with more severe arthritis[172]. Levels of adipokine and HOMA-IR in PsA were shown to be higher than in PsO without arthritis, and adipokine concentrations in PsA were associated with active joint counts[173]. In comparison with healthy controls, PsA patients have an increase in HOMA-IR and a higher prevalence of DM[174]. Notably, the prevalence of IDDM in PsA is higher than that in the general population[175]. and the diabetic risk appears to be increased for women and for active disease[176,177]. Elevated circulating levels of TNF-α and adipokines favor the development of IR, contributing to such an association. Since inflammation of both skin and joint combined has a greater influence on glucose metabolism than that of skin alone, there is a stronger relationship between PsA and DM than between PsO and DM[178,179]. In Table 4, three studies and three case reports are summarized that examined the effects of anti-TNF-α therapy on IR or DM status in patients with PsA/PsO[180-182]. ETA treatment could reduce fasting glucose, HbA1c and insulin levels, even with hypoglycemic episodes; however, a study with ADA therapy failed to improve fasting glucose levels[183].

Despite less evidence than has been published for RA patients, increased prevalence of IR and altered glucose metabolism have been documented in AS patients[184,185]. In four studies using TNFi treatment in AS patients, two with IFX demonstrated reduced
Table 4 Studies and case reports on effects of anti-tumor necrosis factor and non-tumor necrosis factor-targeted therapies on insulin resistance or diabetes in ankylosing spondylitis and psoriatic arthritis/psoriasis patients

| No. | Source            | Drug                | Case, n disease | Clinical feature(s) | Duration | Effect on IR or DM status                                      | Ref. |
|-----|-------------------|---------------------|-----------------|---------------------|----------|---------------------------------------------------------------|------|
| 1   | 2005, Greece      | IFX                 | 17, AS          | Non-DM              | 6 mo     | Reduced HOMA-IR in high-IR group                              | [68] |
| 2   | 2007, Italy       | ETA                 | 9, PsO          | Non-DM              | 24 wk    | Reduced HbA1c, and insulin levels                            | [188]|
| 3   | 2009, Brazil      | ETA                 | 1, PsO          | Type II DM          | 7 h      | Hypoglycemic episode                                         | [189]|
| 4   | 2009, United States | ETA                  | 1, PsO          | Type II DM          | 20 mo    | Reduced HbA1c, and fasting glucose levels, discontinuing insulin use | [189]|
| 5   | 2010, Brazil      | TNF blocker³        | 18, PsA         | Non-DM              | 6 mo     | No changes in fasting glucose levels                         | [190]|
| 6   | 2010, Brazil      | TNF blocker³        | 37, AS          | Non-DM              | 6 mo     | No changes in fasting glucose levels                         | [190]|
| 7   | 2011, United States | ADA                  | 54, PsO         | DM 13%, PsA 41%     | 16 wk    | Ineffective changes in fasting glucose levels in DM         | [191]|
| 8   | 2012, Spain       | IFX                 | 30, AS          | Non-DM              | 120 min  | Reduced HOMA-IR                                              | [192]|
| 9   | 2014, Turkey      | IFX                 | 30, AS          | Non-DM              | 12 wk    | Ineffective HOMA-IR                                         | [193]|
| 10  | 2017, United States | ETA                  | 1, PsA          | Type II DM, obesity | 12 wk    | Reduced HbA1c, and fasting glucose levels, discontinuing insulin use | [194]|
| 11  | 2018, Taiwan      | UST                 | 93, PsO         | Obesity 45%         | 24 wk    | Increased fasting glucose levels                             | [195]|
| 12  | 2018, United States | IXE                  | 2328, PsO       | DM 9%, PsA 24%      | 12 wk    | No changes in fasting glucose levels                         | [196]|
| 13  | 2019, Germany     | SEC                 | 828, PsO        | DM 10%, PsA 19%     | 52 wk    | No changes in fasting glucose levels                         | [197]|
| 14  | 2019, INC         | APR                 | 1089, PsA/O     | DM 9%               | 52 wk    | Reduced HbA1c, improvement highest in HbA1c, no less than 6.5% | [198]|
| 15  | 2019, Italy       | APR                 | 1, PsO          | Type II DM, obesity | 6 mo     | Reduced HbA1c, and fasting glucose levels, discontinuing insulin use | [199]|
| 16  | 2020, Italy       | APR                 | 113, PsA/O      | DM, 25%             | 52 wk    | Reduced fasting glucose levels                               | [200]|
| 17  | 2020, INC         | TOF                 | 474, PsA        | MetS, 42%           | 6 mo     | No increased blood glucose levels, hyperglycemic event and diabetic occurrence | [201]|
| 18  | 2021, Taiwan      | TOF                 | 5, PsA          | Non-DM, non-obese, high-IR | 12 wk    | Reduced HOMA-IR                                              | [202]|

³Tumor necrosis factor blocker in No. 5 and 6 including adalimumab, etanercept and infliximab. ADA: Adalimumab; APR: Apremilast; AS: Ankylosing spondylitis; ETA: Etanercept; IFX: Infliximab; INC: International countries; IR: Insulin resistance; IXE: Ixekizumab; MetS: Metabolic syndrome; PS: Present study; PsA: Psoriatic arthritis; PsO: Psoriasis; Ref.: Reference; SEC: Secukinumab; TNF: Tumor necrosis factor; TOF: Tofacitinib; UST: Ustekinumab; HbA1c: Hemoglobin A1c; HOMA: Homeostasis model assessment.

HOMA-IR, especially in the high-IR group[68,188,191,194,196,197]. Increased circulating Th17 numbers and elevated IL-17 Levels have been identified in type II diabetic patients[195,199]. In addition, IL-17 has been observed to be involved in the pathogenesis of a mouse model of angiotensin II type 1 receptor-induced IR by administrating IL-17 neutralizing antibody to reduce IR by lowering circulating TNF-α levels[200]. Nevertheless, a large-scale study with 2328 PsA/PsO patients receiving the infusion of ixekizumab, a humanized mAb against IL-17A[201], showed no effects in lowering fasting glucose levels[202]. An investigation of PsA/PsO patients treated with another IL-17A mAb, secukinumab[203,204], also showed no efficacy in improving glucose metabolism[205].

The inflammatory cytokine IL-23 was found to be elevated in diabetic pancreatic islets, thereby inducing β-cell oxidative and endoplasmic reticulum stress; moreover,
neutralizing IL-23 in the high-fat diet-induced obesity mouse model reduced β-cell stress and reversed the hyperglycemic state\(^{(20)}\). One study evaluating the glucose homeostasis in PsA patients receiving ustekinumab, a mAb binding the common p40 subunit of IL-12 and IL-23\(^{(20)}\), showed more elevated fasting glucose levels after a 24-wk treatment period\(^{(20)}\).

Apremilast (APR), an oral small molecule approved for PsA and PsO therapy, inhibits phosphodiesterase 4 (PDE4), an enzyme regulating intracellular levels of cyclic AMP to influence the synthesis of cytokines\(^{(20)}\). PDE4C and PDE4D, expressed in pancreatic β-cells, play a critical role in controlling the secretion of insulin\(^{(20)}\). In a large-scale study with 1089 PsA/PsO patients under APR therapy for 52 wk, there were reduced HbA1c levels found, with the highest improvement occurring in those with baseline HbA1c levels no less than 6.5%\(^{(20)}\). In addition, reduced HbA1c and fasting glucose levels with discontinuing insulin use was observed in a case with PsO and type II DM after taking APR therapy for 6 mo\(^{(20)}\). Another investigation treating PsA/PsO patients with APR for 52 wk also demonstrated reduced fasting blood glucose levels\(^{(20)}\).

Oral small molecule JAK inhibitors have emerged as a novel class of medications for PsA, and among three JAK antagonists approved for use in autoimmune disorders, only TOF has obtained approval from the FDA and EMA for PsA therapy\(^{(21)}\). This JAK inhibitor acts on the JAK-STAT pathway to mediate intracellular signaling and downregulate multiple cytokines involved in the PsA pathogenesis, including IL-2, IL-6, IL-17, IL-22, and IL-23\(^{(21)}\). Recently, emerging data from animal and human studies have showed that the JAK/STAT signaling is required for homeostasis of euglycemia, and when dysregulated, contributes to the development of IR\(^{(23)}\). Notably, in addition to the involvement in cytokine signaling activation, the JAKs/STATs pathway has been shown to regulate the function and survival of pancreatic β-cells\(^{(23)}\). Notably, animal studies have implicated targeting such a pathway in reducing IR and treating type II diabetes\(^{(21)}\). In human trials, the diabetic treatment intensification in RA combined with DM comorbidity was lowest in patients under the 9 mo TOF treatment\(^{(29)}\). There were no increased blood glucose levels, hyperglycemic events or diabetic occurrences in PsA patients receiving TOF therapy for 6 mo\(^{(21)}\).

Furthermore, we examined the effects of TOF use in 5 non-diabetic, non-obese PsA patients (1 female and 4 males; age range: 20 to 59 years, with mean age of 41.4 ± 15.5 years) with high baseline IR levels (more than 2.0)\(^{(27)}\). After a 12-wk treatment period (No. 17, Table 4), all cases have decreased articular and dermatological activities as well as reduced HOMA-IR levels (2.01-9.48 to 1.55-4.31, 4.95 ± 2.86 to 3.27 ± 1.23). Our clinical observation suggests a potential of using TOF to improve insulin sensitivity in PsA, a disease susceptible to IR and diabetes.

**CONCLUSION**

In addition to β-cell failure with inadequate insulin secretion, the crucial mechanism leading to the development of DM is the resistance of target cells to insulin, i.e. IR, indicating the ineffective strength of signaling transduction from the receptor, downstream to the final substrates of insulin action. IR is a common feature of most metabolic disorders, including atherosclerosis and hypertension, non-alcoholic fatty liver disorder, hyperlipidemia, metabolic syndrome, obesity and type II DM as well as some cases of type I DM. A variety of human inflammatory disorders with increased levels of proinflammatory cytokines, including TNF-α, IL-6 and IL-1β, have been reported to be associated with an increased risk of IR. Autoimmune-mediated arthritis conditions, including RA, PsA/PsO and AS with the involvement of proinflammatory cytokines as their central pathogenesis, have been demonstrated to be associated with IR, especially during the active disease state. There is an increasing trend towards using biologic agents and small molecule-targeted drugs to treat such disorders. Anti-TNF-α therapy, IL-1 blockade, IL-6 antagonist, JAK inhibitor or PDE4 blocker can reduce IR and improve diabetic hyperglycemia in patients with autoimmune-mediated arthritis.

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**Table 4**

| Event                        | Effect                        |
|------------------------------|-------------------------------|
| Fasting Glucose Levels       | Reduced                        |
| HbA1c Levels                 | Reduced                        |
| Articular and Dermatological Activities | Reduced |
| HOMA-IR Levels               | Reduced                        |
REFERENCES

1. Saini V. Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World J Diabetes 2010; 1: 68-75 [PMID: 21537430 DOI: 10.4239/wjd.v1.13.68]

2. Khodabandeloo H, Gorgani-Firuzjaee S, Panahi G, Meshkani R. Molecular and cellular mechanisms linking inflammation to insulin resistance and β-cell dysfunction. Transl Res 2016; 167: 228-256 [PMID: 2640801 DOI: 10.1016/j.trsl.2015.08.011]

3. Rachdaoui N. Insulin: The Friend and the Foe in the Development of Type 2 Diabetes Mellitus. Int J Mol Sci 2020; 21 [PMID: 32150819 DOI: 10.3390/ijms21051770]

4. Lavin DP, White MF, Brazil DP. IRS proteins and diabetic complications. Diabetologia 2016; 59: 2280-2291 [PMID: 27514532 DOI: 10.1007/s00125-016-4072-7]

5. Coppis KD, White MF. Regulation of insulin sensitivity by serine/threonine phosphorylation of insulin receptor substrate proteins IRS1 and IRS2. Diabetologia 2012; 55: 2565-2582 [PMID: 22869320 DOI: 10.1007/s00125-012-2644-8]

6. White MF. The IRS-signalling system: a network of docking proteins that mediate insulin action. Mol Cell Biochem 1998; 182: 3-11 [PMID: 9609109]

7. Virkamäki A, Ueki K, Kahn CR. Protein-protein interaction in insulin signaling and the molecular mechanisms of insulin resistance. J Clin Invest 1999; 103: 931-943 [PMID: 10194465 DOI: 10.1172/JCI6609]

8. Ho CK, Sriram G, Dipple KM. Insulin sensitivity predictions in individuals with obesity and type II diabetes mellitus using mathematical model of the insulin signal transduction pathway. Mol Genet Metab 2016; 119: 288-292 [PMID: 27746033 DOI: 10.1016/j.ymgme.2016.09.007]

9. Vollenweider P, Clodi M, Martin SS, Imamura T, Kavanaugh WM, Olefsky JM. An SH2 domain-containing S' inositolphosphatase inhibits insulin-induced GLUT4 translocation and growth factor-induced actin filament rearrangement. Mol Cell Biol 1999; 19: 1081-1091 [PMID: 9891043 DOI: 10.1128/mcb.19.2.1081]

10. Martin S, Millar CA, Lyttle CT, Meerlo T, Marsh BJ, Gould GW, James DE. Effects of insulin on intracellular GLUT4 vesicles in adipocytes: evidence for a secretory mode of regulation. J Cell Sci 2000; 113 Pt 19: 3427-3438 [PMID: 10984434]

11. Cho H, Mu J, Kim JK, Thorvaldsen JL, Chu Q, Crenshaw EB 3rd, Kaestner KH, Bartolomei MS, Shulman GI, Birnbaum MJ. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKB beta). Science 2001; 292: 1728-1731 [PMID: 11387480 DOI: 10.1126/science.292.5522.1728]

12. Nemoto T, YanagitA T, Kanai T, Wada A. Drug development targeting the glycogen synthase kinase-3beta (GSK-3beta)-mediated signal transduction pathway: the role of GSK-3beta in the maintenance of steady-state levels of insulin receptor signaling molecules and N(47)S hypertension channel in adrenal chromaffin cells. J Pharmacol Sci 2009; 109: 157-161 [PMID: 19179806 DOI: 10.1254/jphs.082069]

13. Hujlund K. Metabolism and insulin signaling in common metabolic disorders and inherited insulin resistance. Dan Med J 2014; 61: B4890 [PMID: 25123125]

14. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest 2016; 126: 12-22 [PMID: 26727229 DOI: 10.1172/JCI77812]

15. Sesti G. Pathophysiology of insulin resistance. Best Pract Res Clin Endocrinol Metab 2006; 20: 665-679 [PMID: 17161338 DOI: 10.1016/j.bpan.2006.09.007]

16. Yip SC, Saha S, Chernoff J. PTP1B: a double agent in metabolism and oncogenesis. Trends Biochem Sci 2010; 35: 442-449 [PMID: 20381358 DOI: 10.1016/j.tibs.2010.03.004]

17. Zabolotny JM, Haj FG, Kim YB, Kim HJ, Shulman GI, Kim JK, Neel BG, Kahn BB. Transgenic overexpression of protein-tyrosine phosphatase 1B in muscle causes insulin resistance, but overexpression with leukocyte antigen-related phosphatase does not additively impair insulin action. J Biol Chem 2004; 279: 24844-24851 [PMID: 15031294 DOI: 10.1074/jbc.M310688200]

18. Elchelby M, PAYETTE P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Martin S, Saha S, Chernoff J. PTP1B: a double agent in metabolism and oncogenesis. Trends Biochem Sci 2010; 35: 442-449 [PMID: 20381358 DOI: 10.1016/j.tibs.2010.03.004]

19. Zabolotny JM, Haj FG, Kim YB, Kim HJ, Shulman GI, Kim JK, Neel BG, Kahn BB. Transgenic overexpression of protein-tyrosine phosphatase 1B in muscle causes insulin resistance, but overexpression with leukocyte antigen-related phosphatase does not additively impair insulin action. J Biol Chem 2004; 279: 24844-24851 [PMID: 15031294 DOI: 10.1074/jbc.M310688200]

20. Elchelby M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Martin S, Saha S, Chernoff J. PTP1B: a double agent in metabolism and oncogenesis. Trends Biochem Sci 2010; 35: 442-449 [PMID: 20381358 DOI: 10.1016/j.tibs.2010.03.004]

21. Pirola L, Ferraz JC. Role of pro- and anti-inflammatory phenomena in the physiopathology of type 2 diabetes and obesity. World J Biol Chem 2017; 8: 120-128 [PMID: 28588755 DOI: 10.4331/wjbc.v8.i12.120]

22. Lucchetti MM, Benfarenco D, Gabrielli A. Biologics in Inflammatory and Immunomediated Arthritis. Curr Pharm Biotechnol 2017; 18: 989-1007 [PMID: 29278210 DOI: 10.4239/wjd.v12i3.68]
23 Straub RH. Insulin resistance, selfish brain, and selfish immune system: an evolutionarily positively selected program used in chronic inflammatory diseases. Arthritis Res Ther 2014; 16 Suppl 2: S4 [PMID: 25608958 DOI: 10.1186/ar4688]

24 Nicolau J, Lequerre T, Bacquet H, Vittecoq O. Rheumatoid arthritis, insulin resistance, and diabetes. Joint Bone Spine 2017; 84: 411-416 [PMID: 27777170 DOI: 10.1016/j.jbspin.2016.09.001]

25 Perez-Chada LM, Merola JF. Comorbidities associated with psoriatic arthritis: Review and update. Clin Immunol 2020; 214: 108397 [PMID: 32229290 DOI: 10.1016/j.clim.2020.108397]

26 Kanety H, Feinstein R, Papa MZ, Hemi R, Karasik A. Tumor necrosis factor alpha-induced phosphorylation of insulin receptor substrate-1 (IRS-1). Possible mechanism for suppression of insulin-stimulated tyrosine phosphorylation of IRS-1. J Biol Chem 1995; 270: 23780-23784 [PMID: 7559552 DOI: 10.1074/jbc.270.40.23780]

27 Ruan H, Lodish HF. Insulin resistance in adipose tissue: Direct and indirect effects of tumor necrosis factor-alpha. Cytokine Growth Factor Rev 2003; 14: 447-455 [PMID: 12948526 DOI: 10.1016/s1359-6101(03)00052-2]

28 Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE. Reversal of obesity and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. Science 2001; 293: 1673-1677 [PMID: 11533494 DOI: 10.1126/science.1061620]

29 Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996; 271: 665-668 [PMID: 8571133 DOI: 10.1126/science.271.5249.665]

30 Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komnaro R, Ouchi N, Kuriyama H, Nakamura T, Shimomura I, Matsuzawa Y. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 2001; 50: 2094-2099 [PMID: 11522676 DOI: 10.2337/diabetes.50.9.2094]

31 Ruan H, Miles PD, Ladd CM, Ross K, Golub TR, Olefsky JM, Lodish HF. Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor-alpha: Implications for insulin resistance. Diabetes 2002; 51: 3176-3188 [PMID: 12401708 DOI: 10.2337/diabetes.51.11.3176]

32 Ruan H, Hacohen N, Golub TR, Van Parisis L, Lodish HF. Tumor necrosis factor-alpha suppresses adipocyte-specific genes and activates expression of preadipocyte genes in 3T3-L1 adipocytes: nuclear factor-kappaB activation by TNF-alpha is obligatory. Diabetes 2002; 51: 1313-1336 [PMID: 11978627 DOI: 10.2337/diabetes.51.5.1319]

33 Tamori Y, Masugi J, Nishino N, Kasuga M. Role of peroxisome proliferator-activated receptor-gamma in maintenance of the characteristics of mature 3T3-L1 adipocytes. Diabetes 2002; 51: 2045-2055 [PMID: 12086932 DOI: 10.2337/diabetes.51.7.2045]

34 Ruan H, Pownall HJ, Lodish HF. Trogilitazone antagonizes tumor necrosis factor-alpha-induced reprogramming of adipocyte gene expression by inhibiting the transcriptional regulatory functions of NF-kappaB. J Biol Chem 2003; 278: 28181-28192 [PMID: 12732648 DOI: 10.1074/jbc.M303141200]

35 Pedrosa JAB, Ramos-Lobo AM, Donato J Jr. SOCS3 as a future target to treat metabolic disorders. Hormones (Athens) 2019; 18: 127-136 [PMID: 30414080 DOI: 10.1007/s42000-018-0078-5]

36 Emanuelli B, Peraldi P, Filloux C, Chavey C, Freidinger K, Hilton DJ, Hotamisligil GS, Van Obberghen E. SOCS-3 inhibits insulin signaling and is up-regulated in response to tumor necrosis factor-alpha in the adipose tissue of obese mice. J Biol Chem 2001; 276: 47944-47949 [PMID: 11604392 DOI: 10.1074/jbc.M104602200]

37 Winkler G, Salomon F, Harmos G, Salomon D, Speer G, Salamon D, Speer G, Simon K, Cseh K. Elevated serum tumor necrosis factor-alpha concentrations and bioactivity in Type 2 diabetics and patients with android type obesity. Diabetes Res Clin Pract 1998; 42: 169-174 [PMID: 9925347 DOI: 10.1016/s0168-8227(98)00109-0]

38 Winkler G, Salomon F, Salomon D, Speer G, Simon K, Cseh K. Elevated serum tumour necrosis factor-alpha levels can contribute to the insulin resistance in Type II (non-insulin-dependent) diabetes and in obesity. Diabetologia 1998; 41: 860-861 [PMID: 9696931 DOI: 10.1007/s001250051000]

39 Ihle CT, Fischer CP, Plomgaard P, van Hall G, Pedersen BK. The acute effects of low-dose TNF-α on glucose metabolism and β-cell function in humans. Mediators Inflamm 2014; 2014: 295478 [PMID: 24692847 DOI: 10.1155/2014/295478]

40 Nielsen ST, Lehrskov-Schmidt L, Krogh-Madsen L, Solomon TP, Lehrskov-Schmidt L, Holst JJ, Ruan H. Tumour necrosis factor-alpha infusion produced insulin resistance but no change in the in vivo effect in healthy volunteers. Diabetes Metab Res Rev 2013; 29: 655-663 [PMID: 23904405 DOI: 10.1002/dmr.2441]

41 Paquot N, Castillo MJ, Lefèbvre PJ, Scheen AJ. No increased insulin sensitivity after a single intravenous administration of a recombinant human tumor necrosis factor receptor:Fc fusion protein in obese insulin-resistant patients. J Clin Endocrinol Metab 2000; 85: 1316-1319 [PMID: 10720082 DOI: 10.1210/jcem.85.3.6417]

42 Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med 2006; 166: 902-908 [PMID: 16636217 DOI: 10.1001/archinte.166.8.902]

43 Stanley TL, Zammi MV, Johnsen S, Rasheed S, Makimura H, Lee H, Khor VK, Ahima RS,
Wang CR et al. Targeted-therapies on IR in autoimmune-mediated arthritis

Grinspoon SK. TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. J Clin Endocrinol Metab 2011; 96: E146-E150 [PMID: 21047923 DOI: 10.1210/jc.2010-1170]

Taylor PC, Feldmann M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. Nat Rev Rheumatol 2009; 5: 578-582 [PMID: 19798034 DOI: 10.1038/nrrheum.2009.181]

Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. Int Immunol 2015; 27: 55-62 [PMID: 25411043 DOI: 10.1093/immunufx102]

Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum 2006; 54: 2765-2775 [PMID: 16947779 DOI: 10.1002/art.22053]

Costa NT, Veiga Iriyoda TM, Kallaur AP, Delongui F, Alfieri DF, Lozovsky MA, Amín RB, Delfino VD, Dichi I, Simão AN. Influence of Insulin Resistance and TNF-α on the Inflammatory Process, Oxidative Stress, and Disease Activity in Patients with Rheumatoid Arthritis. Oxid Med Cell Longev 2016; 2016: 8962763 [DOI: 10.1155/2016/8962763]

Jiang P, Li H, Li X. Diabetes mellitus risk factors in rheumatoid arthritis: a systematic review and meta-analysis. Clin Exp Rheumatol 2015; 33: 115-121 [PMID: 25535750]

Liao KP, Gunnarsson M, Källberg H, Ding B, Plenge RM, Padyukov L, Karlsson EW, Klæreskog L, Askling J, Alfredsson L. Specific association of type 1 diabetes mellitus with anti-cytokine triggered peptide-positive rheumatoid arthritis. Arthritis Rheum 2009; 60: 653-660 [PMID: 19248096 DOI: 10.1002/art.24362]

Chatzikiyrakiou A, Voulgaris PV, Lambropoulos A, Georgiou I, Drosos AA. Validation of the TAGAP rs212389 polymorphism in rheumatoid arthritis susceptibility. Joint Bone Spine 2013; 80: 543-544 [PMID: 23453471 DOI: 10.1016/j.jbspin.2013.01.008]

Hollis-Moffatt JE, Chen-Xu M, Topless R, Dalbeth N, Gow PJ, Harrison AA, Highton J, Jones PB, Nissen M, Smith MD, van Rij A, Jones GT, Stamp LK, Merriman TR. Only one independent genetic variants between three autoimmune disorders: rheumatoid arthritis, type 1 diabetes and coeliac disease. Arthritis Res Ther 2010; 12: R175 [PMID: 20854658 DOI: 10.1186/ar3139]

Chatzikiyrakiou A, Voulgaris PV, Lambropoulos A, Georgiou I, Drosos AA. Validation of the TAGAP rs212389 polymorphism in rheumatoid arthritis susceptibility. Joint Bone Spine 2013; 80: 543-544 [PMID: 23453471 DOI: 10.1016/j.jbspin.2013.01.008]

Hollis-Moffatt JE, Chen-Xu M, Topless R, Dalbeth N, Gow PJ, Harrison AA, Highton J, Jones PB, Nissen M, Smith MD, van Rij A, Jones GT, Stamp LK, Merriman TR. Only one independent genetic association with rheumatoid arthritis within the KIAA1109-TENR-IL2-IL21 Locus in Caucasian sample sets: confirmation of association of rs6822844 with rheumatoid arthritis at a genome-wide level of significance. Arthritis Res Ther 2010; 12: R116 [PMID: 20553587 DOI: 10.1186/ar3053]

Dubreuil M, Rho YH, Man A, Zhu Y, Zhang Y, Love TJ, Ogdie A, Gelfand JM, Choi HK. Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid arthritis: a UK population-based cohort study. Rheumatology (Oxford) 2014; 53: 346-352 [PMID: 24185762 DOI: 10.1093/rheumatology/kez343]

Solomon DH, Karlsson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, Stampfer MJ, Curhan GC. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003; 107: 1303-1307 [PMID: 12628952 DOI: 10.1161/01.cir.0000045612.26458.b2]

Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis 2010; 69: 2114-2117 [PMID: 20584807 DOI: 10.1136/ard.2009.125476]

Jinesh S. Pharmaceutical aspects of anti-inflammatory TNF-blocking drugs. Inflammopharmacology 2015; 23: 71-77 [PMID: 25687751 DOI: 10.1007/10787-015-0229-0]

Zhai S, Mysler E, Moots RJ. Etanercept for the treatment of rheumatoid arthritis. Immunotherapy 2018; 10: 433-445 [PMID: 29482402 DOI: 10.2217/imt-2017-0155]

Hamid YH, Urhammer SA, Glümer C, Borch-Johnsen K, Jørgensen T, Hansen T, Pedersen O. The common T60N polymorphism of the lymphotoxin-alpha gene is associated with type 2 diabetes and other phenotypes of the metabolic syndrome. Diabetologia 2005; 48: 445-451 [PMID: 15729581 DOI: 10.1007/s00125-004-1659-1]

Upadhyay V, Fu YX. Lymphotxin alpha promotes host defense and metabolic illness from innate lymphoid cells. Cytokine Growth Factor Rev 2014; 25: 227-233 [PMID: 24411493 DOI: 10.1016/j.cytovr.2013.12.007]

Atoheh JL, Bili A, Sartorius JA, Kirchner HL, Morris SJ, Dancea S, Wasko MC. Diabetes mellitus risk in rheumatoid arthritis: reduced incidence with anti-tumor necrosis factor α therapy. Arthritis Care Res (Hoboken) 2012; 64: 215-221 [PMID: 21972198 DOI: 10.1002/acr.20657]

Wood PR, Manning E, Baker JF, England B, Davis L, Cannon GW, Mikuls TR, Caplan L. Blood glucose changes surrounding initiation of tumor-necrosis factor inhibitors and conventional disease-modifying anti-rheumatic drugs in veterans with rheumatoid arthritis. World J Diabetes 2018; 9: 53-58 [PMID: 29531640 DOI: 10.4239/wjd.v9.i2.53]

Seribol B, Ferrone C, Cutolo M. Longterm anti-tumor necrosis factor-alpha treatment in patients with refractory rheumatoid arthritis: relationship between insulin resistance and disease activity. J Rheumatol 2008; 35: 355-357 [PMID: 18260166]

Ferraz-Amaro I, Arce-Franco M, Muñiz J, López-Fernández J, Hernández-Hernández V, Franco A,
Quevedo J, Martínez-Martin J, Díaz-González F. Systemic blockade of TNF-α does not improve insulin resistance in humans. *Horm Metab Res* 2011; 43: 801-808 [PMID: 22009376 DOI: 10.1055/s-0031-1287783]

Stagakis L, Bertsaïs G, Karvounaris S, Kavousanaki M, Virla D, Raptopoulou A, Kardassias D, Bosampas DT, Sidiro poulos PI. Anti-tumor necrosis factor therapy improves insulin resistance, beta cell function and insulin signaling in active rheumatoid arthritis patients with high insulin resistance. *Arthritis Res Ther* 2012; 14: R141 [PMID: 22691241 DOI: 10.1186/ar3874]

Stavropoulos-Kalinoglou A, Metso sis GS, Panoulas VF, Nightingale P, Koutedakis Y, Kitas GD. Anti-tumour necrosis factor alpha therapy improves insulin sensitivity in normal-weight but not in obese patients with rheumatoid arthritis. *Arthritis Res Ther* 2012; 14: R116 [PMID: 22765047 DOI: 10.1186/ar3906]

Yazdani-Biuki B, Stelzl H, Brezinschek HP, Herrmann J, Mueller T, Kripp P, Graninger W, Wascher TC. Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF-alpha antibody infliximab. *Eur J Clin Invest* 2004; 34: 641-642 [PMID: 15379764 DOI: 10.1111/j.1365-2362.2004.01390.x]

Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* 2005; 64: 765-766 [PMID: 1548960 DOI: 10.1136/ard.2004.026534]

Gonzalez-Gay MA, De Matías JM, Gonzalez-Juanatey C, García-Porrúa C, Sanchez-Andrade A, Martín J, Llorca J. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 83-86 [PMID: 16539824]

Huvers FC, Popa C, Netea MG, van den Hoogen FH, Tack CJ. Improved insulin sensitivity by anti-TNFalpha antibody treatment in patients with rheumatic diseases. *Ann Rheum Dis* 2007; 66: 558-559 [PMID: 17760784 DOI: 10.1136/ard.2006.062323]

Rosevinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha therapy. *Scand J Rheumatol* 2007; 36: 91-96 [PMID: 17476613 DOI: 10.1080/03009740601179605]

Tam LS, Tomlinson B, Chu TT, Li TK, Li EK. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. *Clin Rheumatol* 2007; 26: 1495-1498 [PMID: 17237906 DOI: 10.1007/s10067-007-0539-8]

Oguz FM, Oguz A, Uzunulu M. The effect of infliximab treatment on insulin resistance in patients with rheumatoid arthritis. *Acta Clin Belg* 2007; 62: 218-222 [PMID: 17849692 DOI: 10.1179/ach.2007.035]

Seriolo B, Paolino S, Ferrone C, Cutolo M. Impact of long-term anti-TNF-alpha treatment on insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 159-60; author reply 160 [PMID: 18328169]

Corrado A, Colia R, Rotondo C, Sanpao lo E, Cantatore FP. Changes in serum adipokines profile and insulin resistance in patients with rheumatoid arthritis treated with anti-TNF-alpha. *Curr Med Res Opin* 2019; 35: 2197-2205 [PMID: 31197188 DOI: 10.1007/s00298-019-165988]

van den Oever IAM, Baniaamam M, Simsek S, Raterman HG, van Denderen JC, van Eijk IC, Peters MJL, van der Horst-Bruinsma IE, Smulders YM, Nurmohamed MT. The effect of anti-TNF treatment on body composition and insulin resistance in patients with rheumatoid arthritis. *Rheumatol Int* 2020 [PMID: 32776224 DOI: 10.1007/s00296-020-04666-4]

Wang CR, Liu MF. Recombinant Soluble TNFα Receptor Fusion Protein Therapy Reduces Insulin Resistance in Non-Diabetic Active Rheumatoid Arthritis Patients. *ACR Open Rheumatol* 2020; 2: 401-406 [PMID: 32503139 DOI: 10.1002/acr2.11157]

Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab* 1997; 82: 4196-4200 [PMID: 9398739 DOI: 10.1210/jcem.82.12.4450]

Fasshauer M, Klein J, Lossner U, Paschke R. Interleukin (IL)-6 mRNA expression is stimulated by insulin, isoproterenol, tumour necrosis factor alpha, growth hormone, and IL-6 in 3T3-L1 adipocytes. *Horm Metab Res* 2003; 35: 147-152 [PMID: 12734774 DOI: 10.1055/s-2003-39075]

Krogh-Madsen R, Plomgaard P, Keller P, Keller C, Pedersen BK. Insulin stimulates interleukin-6 and tumor necrosis factor-alpha gene expression in human subcutaneous adipose tissue. *Am J Physiol Endocrinol Metab* 2004; 286: E234-E238 [PMID: 14552168 DOI: 10.1152/ajpendo.00274.2003]

Kado S, Nagase T, Nagata N. Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus. *Acta Diabetol* 1999; 36: 67-72 [PMID: 10436255 DOI: 10.1007/s005920050147]

Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; 286: 327-334 [PMID: 11466099 DOI: 10.1001/jama.286.3.327]

Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res* 2001; 9: 414-417 [PMID: 11445664 DOI: 10.1038/oby.2001.54]

Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/l kappa B/NF-kappa B axis in obesity-and diet-induced insulin resistance. *Int J Obes Relat Metab Disord* 2003; 27 Suppl 3: S49-S52 [PMID: 14704745 DOI: 10.1038/sj.ijo.0802501]

Tanaka H, Fujita N, Tsuruo T. 3-Phosphoinositide-dependent protein kinase-1-mediated IkappaB
Interleukin-6 enhances insulin signaling and glucose uptake in l6 myotubes.

10.2337/db05-1404

In vitro increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6.

Interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6.

Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in hepatocytes.

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Serine phosphorylation of insulin receptor substrate 1 by inhibitor kappa B kinase complex.

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AMP-activated protein kinase.

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Insulin receptor substrate 1 by inhibitor kappa B kinase complex.

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Insulin receptor substrate 1 by inhibitor kappa B kinase complex.

DOI:
Castañeda S, Fernandez-Veleido S, de Alvaro C, Lorenzo M. Dual role of interleukin-6 in regulating insulin sensitivity in murine skeletal muscle. *Diabetes* 2008; 57: 3211-3221 [PMID: 18796617 DOI: 10.2337/db07-1062]

Akbari M, Hassan-Zadeh V. IL-6 signalling pathways and the development of type 2 diabetes. *Inflammopharmacology* 2018; 26: 685-698 [PMID: 29508109 DOI: 10.1007/s10787-018-0458-0]

Yamaguchi S, Katahira H, Ozawa S, Nakamichi Y, Tanaka T, Shimoyama T, Takahashi K, Yoshimoto K, Imazumim US, Nagamatsu S, Ishida H. Activators of AMP-activated protein kinase enhance GLUT4 translocation and its glucose transport activity in 3T3-L1 adipocytes. *Am J Physiol Endocrinol Metabol* 2005; 289: E643-9 [PMID: 15928020 DOI: 10.1152/ajpendo.00456.2004]

Harder-Lauridsen NM, Krogh-Madsen R, Holst JJ, Plomgaard P, Leick L, Pedersen BK, Fischer CP. Effect of IL-6 on the insulin sensitivity in patients with type 2 diabetes. *Am J Physiol Endocrinol Metabol* 2014; 306: E769-E778 [PMID: 24473436 DOI: 10.1152/ajpendo.00571.2013]

Tanaka T, Narazaki M, Yoshimoto K. Therapeutic targeting of the interleukin-6 receptor. *Ann Rev Pharmacol Toxicol* 2012; 52: 199-219 [PMID: 21910626 DOI: 10.1146/annurev-pharmtox-010611-134715]

Ogata A, Morishima A, Hirano T, Hishitani Y, Hagihara K, Shima Y, Narazaki M, Tanaka T. Improvement of HbA1c during treatment with humanised anti-interleukin-6 receptor antibody, tocilizumab. *Ann Rheum Dis* 2011; 70: 1164-1165 [PMID: 20980285 DOI: 10.1136/ard.2010.132845]

Qu D, Liu J, Lau CW, Huang Y. IL-6 in diabetes and cardiovascular complications. *Br J Pharmacol* 2014; 171: 3595-3603 [PMID: 24697653 DOI: 10.1111/bjp.12713]

Kraakman MJ, Kammoun HL, Allen TL, Deswaerte V, Henstridge DC, Estevez E, Matthews VB, Neil B, White DA, Murphy AJ, Pejs J, Yang C, Risica S, Bruce CR, Du XJ, Bobik A, Lee-Young S, Grembiale RD. Abatacept improves whole-body insulin sensitivity in rheumatoid arthritis: an observational study. *Br J Pharmacol* 2014; 172: 18796617 DOI: 10.1371/journal.pone.0014328

Mirjafari HR, Mirjafari HW, Wang J, Klearman M, Harari O, Bruce I. FR10132: Insulin resistance is improved by tocilizumab therapy in rheumatoid arthritis: results from the tosoward study. *Ann Rheum Dis* 2013; 72: A12-A15 [DOI: 10.1136/annrheumdis-2013-eular.1259]

Mirjafari HR, Ruperto N, Brunner HI, Zuber Z, Zulian F, Mantzourani I, Hassan-Zadeh V, Narazaki M, Kishimoto T. Therapeutic targeting of the interleukin-6 receptor. *Annu Rev Pharmacol Toxicol* 2014; 54: 32422539 DOI: 10.1107/br.2020.101574

Schultz O, Oberhauser F, Saech J, Rubbert-Roth A, Hahn M, Krone W, Laudes M. Effects of interleukin-6 trans-signaling inhibition on oxidative stress and inflammatory cytokine levels in juvenile idiopathic arthritis: results from the TENDER study. *PLoS One* 2010; 5: e14328 [PMID: 21779199 DOI: 10.1371/journal.pone.0014328]

Wong CR et al. Targeted-therapies on IR in autoimmune-mediated arthritis 2011; 17: 1481-1489 [PMID: 22037645 DOI: 10.1038/nm.2513]

Nieco-Vazquez I, Fernández-Veleido S, de Alvaro C, Lorenzo M. Dual role of interleukin-6 in regulating insulin sensitivity in murine skeletal muscle. *Diabetes* 2008; 57: 3211-3221 [PMID: 18796617 DOI: 10.2337/db07-1062]
effect of the IL-6 receptor blockade on insulin resistance and insulin sensitivity in non-diabetic patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 465-473 [PMID: 30418124]

124 **Vironne A**, Bastard JP, Fellihi S, Capeau J, Rouanet S, Sibilia J, Ravaud P, Berenbaum F, Gottenberg JE, Sellam J. Comparative effect of tumour necrosis factor inhibitors vs other biological agents on cardiovascular risk-associated biomarkers in patients with rheumatoid arthritis. *RMD Open* 2019; 5: e000897 [PMID: 31431365 DOI: 10.1136/rmdopen-2019-000897]

125 **Toussriot E**, Marotte H, Mullenan D, Cormier G, Coury F, Gaudin P, Denis E, Bonnet C, Damade R, Graaer JL, Abdesslem TA, Guillibert-Karras C, Liòt F, Hilliquin P, Sacchi A, Wendling D, Le Geoff B, Pyraveau M, Damoulou G. Increased high molecular weight adiponectin and lean mass during tocilizumab treatment in patients with rheumatoid arthritis: a 12-month multicentre study. *Arthritis Res Ther* 2020; 22: 224 [PMID: 32993784 DOI: 10.1186/s13075-020-02297-9]

126 **Blair HA**, Deeks ED. Abatacept: A Review in Rheumatoid Arthritis. *Drugs* 2017; 77: 1221-1233 [PMID: 28680166 DOI: 10.1007/s40265-017-0775-4]

127 **Fujii M**, Inoguchi T, Batcheluun B, Sugiyma N, Kobayashi K, Sonoda N, Takayanagi R. CTLA-4lg immunotherapy of obesity-induced insulin resistance by manipulation of macrophage polarization in adipose tissues. *Biochem Biophys Res Commun* 2013; 438: 103-109 [PMID: 23872146 DOI: 10.1016/j.bbrc.2013.07.034]

128 **Dinarello CA**. Immunological and inflammatory functions of the interleukin-1 family. *Ann Rev Immunol* 2009; 27: 519-550 [PMID: 19302047 DOI: 10.1146/annurev.immunol.021908.132612]

129 **Besedovsky HO**, Del Rey A. Physiologic vs diabetogenic effects of interleukin-1: a question of weight. *Curr Pharm Des* 2014; 20: 4733-4740 [PMID: 24588826 DOI: 10.2174/1381612820666140130204401]

130 **Ciampolillo A**, Guastamacchia E, Caragiuolo L, Lollino G, De Robertis O, Lattanzio V, Giorgino R. In vitro secretion of interleukin-1 beta and interferon-gamma by peripheral blood lymphomononuclear cells in diabetic patients. *Diabetes Res Clin Pract* 1993; 21: 87-93 [PMID: 8269823 DOI: 10.1016/0168-8227(93)90054-9]

131 **Hussain MJ**, Peakman M, Gallati H, Lo SS, Hawa M, Viberti GC, Watkins PJ, Leslie RD, Vergani D. Elevated serum levels of macrophage-derived cytokines precede and accompany the onset of IDDM. *Diabetologia* 1996; 39: 60-69 [PMID: 8726064 DOI: 10.1007/BF00400441]

132 **Mandrup-Poulsen T**. The role of interleukin-1 in the pathogenesis of IDDM. *Diabetologia* 1996; 39: 1005-1029 [PMID: 8772824 DOI: 10.1007/BF00400649]

133 **Nicoletti F**, Di Marco R, Barcellini W, Magro G, Schorlemmer HU, Kurrie R, Lunetta M, Grasso S, Zaccone P, Meroni P. Protection from experimental autoimmune diabetes in the non-obese diabetic mouse with soluble interleukin-1 receptor. *Eur J Immunol* 1994; 24: 1843-1847 [PMID: 8056041 DOI: 10.1002/eji.1830240818]

134 The role of interleukin-1 in the pathogenesis of insulin-dependent diabetes mellitus. *Diabetologia* 1994; 37: 42-43 [PMID: 7851688]

135 **Mandrup-Poulsen T**, Pickersgill L, Donath MY. Blockade of interleukin 1 in type 1 diabetes mellitus. *Nat Rev Endocrinol* 2010; 6: 158-166 [PMID: 20173777 DOI: 10.1038/nrendo.2009.271]

136 **Spranger J**, Kroke A, Mühlig M, Hoffmann K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 2003; 52: 812-817 [PMID: 12606524 DOI: 10.2337/diabetes.52.3.812]

137 **Matsuki T**, Horai R, Sudo K, Iwakura Y. IL-1 plays an important role in lipid metabolism by regulating insulin levels under physiological conditions. *J Exp Med* 2003; 198: 877-888 [PMID: 12975454 DOI: 10.1084/jem.20030299]

138 **Maedler K**, Sergeev P, Ehses JA, Mathe Z, Bosco D, Berney T, Dayer JM, Reinecke M, Halban PA, Donath MY. Leptin modulates beta cell expression of IL-1 receptor antagonist and release of IL-1beta in human islets. *Proc Natl Acad Sci USA* 2004; 101: 8138-8143 [PMID: 15141093 DOI: 10.1073/pnas.030563101]

139 **Jager J**, Grémeaux T, Cormont M, Le Marchand-Brustel Y, Tanti JF. Interleukin-1beta-induced insulin resistance in adipocytes through down-regulation of insulin receptor substrate-1 expression. *Endocrinology* 2007; 148: 241-251 [PMID: 17038556 DOI: 10.1210/en.2006-0692]

140 **Tilg H**, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. *Mol Med* 2008; 14: 222-231 [PMID: 18235842 DOI: 10.2119/2007-00119.Tilg]

141 **Reimers JJ**. Interleukin-1 beta induced transient diabetes mellitus in rats. A model of the initial events in the pathogenesis of insulin-dependent diabetes mellitus? *Dan Med Bull* 1998; 45: 157-180 [PMID: 9587701]

142 **Maedler K**, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, Kaiser N, Halban PA, Donath MY. Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002; 110: 851-860 [PMID: 12235117 DOI: 10.1121/1235117]

143 **Mandrup-Poulsen T**, Donath MY, Mandrup-Poulsen T. Role of IL-1beta in type 2 diabetes. *Curr Opin Endocrinol Diabetes Obes* 2010; 17: 314-321 [PMID: 20888114 DOI: 10.1097/MED.0b013e32833f6dc6]

144 **Mistry A**, Savic S, van der Hilst JCH. Interleukin-1 Blockade: An Update on Emerging Indications. *BioDrugs* 2017; 31: 207-221 [PMID: 28497222 DOI: 10.1007/s40265-017-0224-7]

145 **Ruscitti P**, Cipriani P, Cantarini L, Liakoulis V, Vitale A, Carubbi F, Barardiucy O, Galeazzi M, Valentie M, Giacomelli R. Efficacy of inhibition of IL-1 in patients with rheumatoid arthritis and type 2 diabetes mellitus: two case reports and review of the literature. *J Med Case Rep* 2015; 9: 123
sensitivity in insulin resistant patients with type 1 diabetes mellitus.

van Asseldonk EJ, Noe A. 2013; Diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lervang HH, Perrild H, Mandrup-Poulsen T; AIDA Study Group. Interleukin-1 antagonism in type 1 diabetes. Diabetes TrialNet Canakinumab Study Group, Pickersgill L, de Koning E, Ziegler AG, Böehm B, Marks JB, Raskin P, Sanda S, Schatz D, Wherrett DK, Wilson DM, Krischer JP, Skyler JS; Type 1 Diabetes TrialNet Abatacept Study Group. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 378: 412-419 [DOI: 10.1016/S0140-6736(11)60886-6].

Isiri K, Iyoda M, Shikida Y, Inokuchi T, Morikawa T, Hara N, Hirano T, Shibata T. Rituximab for the treatment of type B insulin resistance syndrome: a case report and review of the literature. Diabet Med 2017; 34: 1788-1791 [PMID: 29044634 DOI: 10.1111/dme.13524].

Noorchashm H, Noorchashn N, Kern J, Rostami SY, Barker CP, Naji A. B-cells are required for the initiation of insulitis and sialitis in nonobese diabetic mice. Diabetes 1997; 46: 941-946 [PMID: 9166620 DOI: 10.2337/dbah.46.6.941].

Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, Gottlieb PA, Marks JB, Mcgee PF, Morgan AM, Raskin P, Rodriguez H, Schatz DA, Wherrett DK, Wilson DM, Lachin JM, Skyler JS; Type 1 Diabetes TrialNet Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function: two-year results. Diabetes Care 2014; 37: 453-459 [PMID: 24026563 DOI: 10.2337/dc13-0626].

Lenschow DJ, Ho SC, Sattar H, Rhee L, Gray G, Nabavi N, Herold KC, Bluestone JA. Differential effects of anti-B7-1 and anti-B7-2 monoclonal antibody treatment on the development of diabetes in the nonobese diabetic mouse. J Exp Med 1995; 181: 1145-1155 [PMID: 7552678 DOI: 10.1084/jem.181.3.1145].

Orban T, Bundy B, Becker DJ, Dimiglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Marks JB, Monzavi R, Moran A, Raskin P, Rodriguez H, Russell WE, Schatz D, Wherrett D, Wilson DM, Krischer JP, Skyler JS; Type 1 Diabetes TrialNet Abatacept Study Group. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 378: 412-419 [PMID: 21719096 DOI: 10.1016/S0140-6736(11)60886-5].

Larsen CM, Faulenburch M, Vaag A, Volund A, Ehes JA, Sießberg B, Mandrup-Poulsen T, Donath MY. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 2007; 356: 1517-1526 [PMID: 17429083 DOI: 10.1056/NEJMoa065213].

Rissinan A, Howard CP, Botha J, Thuren T; Global Investigators. Effect of anti-IL-1β antibody (canakinumab) on insulin secretion rates in impaired glucose tolerance or type 2 diabetes: results of a randomized, placebo-controlled trial. Diabetes Obes Metab 2012; 14: 1088-1096 [PMID: 22726220 DOI: 10.1111/j.1463-1326.2012.01637.x].

Ridker PM, Howard CP, Walter V, Everett B, Libby P, Hensens J, Thuren T; CANTOS Pilot Investigative Group. Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 2012; 126: 2739-2748 [PMID: 23129601 DOI: 10.1161/CIRCULATIONAHA.112.122556].

Cavelti-Weder C, Briasanos-Brunner A, Keller C, Stahl MA, Kurz-Levin M, Zayed H, Solinger AM, Mandrup-Poulsen T, Dinarello CA, Donath MY. Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. Diabetes Care 2012; 35: 1654-1662 [PMID: 22699287 DOI: 10.2337/dc11-2219].

Moran A, Bundy B, Becker DJ, Dimiglio LA, Gitelman SE, Goland R, Greenbaum CJ, Herold KC, Marks JB, Raskin P, Sanda S, Schatz D, Wherrett DK, Wilson DM, Krischer JP, Skyler JS; Type 1 Diabetes TrialNet Canakinumab Study Group, Pickersgill L, de Koning E, Ziegler AG, Böehm B, Badenhoop K, Schloot N, Bak JF, Pozzilli P, Mauricio D, Donath MY, Castaño L, Wängner A, Lervang HH, Perrild H, Mandrup-Poulsen T; AIDA Study Group. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet 2013; 381: 1905-1915 [PMID: 23562090 DOI: 10.1016/S0140-6736(13)00239-9].

Noe A, Howard C, Thuren T, Taylor A, Skerjancie A. Pharmacokinetic and pharmacodynamic characteristics of single-dose Canakinumab in patients with type 2 diabetes mellitus. Clin Ther 2014; 36: 1625-1637 [PMID: 25240532 DOI: 10.1016/j.clinthera.2014.08.004].

van Asseldonk EJ, van Poppel PC, Ballak DB, Stienstra R, Netea MG, Tack CJ. One week treatment with the IL-1 receptor antagonist anakinra leads to a sustained improvement in insulin sensitivity in insulin resistant patients with type 1 diabetes mellitus. Clin Immunol 2015; 160: 155-162 [PMID: 26073226 DOI: 10.1016/j.clim.2015.06.003].
Wang CR et al. Targeted-therapies on IR in autoimmune-mediated arthritis

163 Timper K, Seelig E, Tsalikis DA, Donath MY. Safety, pharmacokinetics, and preliminary efficacy of a specific anti-IL-1alpha therapeutic antibody (MABp1) in patients with type 2 diabetes mellitus. *J Diabetes Complications* 2015; 29: 955-960 [PMID: 26139558 DOI: 10.1016/j.jdiacomp.2015.05.019]

164 Seelig E, Timper K, Falconer C, Stoeckli R, Bilz S, Oram R, McDonald TJ, Donath MY. Interleukin-1 antagonism in type 1 diabetes: effects of long duration. *Diabetes Metab* 2016; 42: 453-456 [PMID: 27720360 DOI: 10.1016/j.diabet.2016.08.005]

165 Stahl M, Becker M, Grün N, Michels S. SYSTEMIC INTERLEUKIN 1ß INHIBITION IN PROLIFERATIVE DIABETIC RETINOPATHY: A Prospective Open-Label Study Using Canakuminub. *Retina* 2016; 36: 385-391 [PMID: 26218500 DOI: 10.1002/ar.22000]

166 White PC, Adhikari S, Grishman EM, Sumpter KM. A phase I study of anti-inflammatory therapy with rilonacept in adolescents and adults with type 1 diabetes mellitus. *Pediatr Diabetes* 2018; 19: 788-793 [PMID: 29504185 DOI: 10.1111/pedi.12634]

167 Ruscitti P, Maseda F, Alvaro S, Airó P, Battafarano N, Cantarini L, Cantatore FP, Carlino G, D’Abrasca V, Frassi M, Frediani B, Iacono D, Liakoulis V, Maggio R, Mulé R, Pantano I, Previte I, Sinigaglia L, Valenti M, Viapiana O, Cipriani P, Giacomelli R. Anti-interleukin-1 treatment in patients with rheumatoid arthritis and type 2 diabetes (TRACK): A multicentre, open-label, randomised controlled trial. *PLoS Med* 2019; 16: e1002901 [PMID: 31513665 DOI: 10.1371/journal.pmed.1002901]

168 Ruscitti P, Ursini F, Cipriani P, Greco M, Alvaro S, Vasiliki L, Di Benedetto P, Carubbi F, Berardi Curiti O, Gulletta E, De Sarro G, Giacomelli R. IL-1 inhibition improves insulin resistance and adipokines in rheumatoid arthritis patients with comorbid type 2 diabetes: An observational study. *Medicine (Baltimore)* 2019; 98: e14587 [PMID: 30762811 DOI: 10.1097/MD.0000000000014587]

169 Schwartz DM, Bonelli M, Gadina M, O’Shea JJ. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol* 2016; 12: 25-36 [PMID: 26633291 DOI: 10.1038/nrrheum.2015.167]

170 Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects. *Drugs* 2017; 77: 521-546 [PMID: 28255960 DOI: 10.1007/s40265-017-0701-9]

171 Hosseini A, Gharibi T, Marofi F, Javadian M, Babaloo Z, Baradaran B. Janus kinase inhibitors: A therapeutic strategy for cancer and autoimmune diseases. *J Cell Physiol* 2020; 235: 5903-5924 [PMID: 32072644 DOI: 10.1002/jcp.29593]

172 Sarzì-Puttini P, Ceribelli A, Marotto D, Batticciotto A, Atzeni F. Systemic rheumatic diseases: From biological agents to small molecules. *Autoimmun Rev* 2019; 18: 583-592 [PMID: 30959214 DOI: 10.1016/j.autrev.2018.12.009]

173 Caporali R, Zavaglia D. Real-world experience with tofacitinib for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 485-495 [PMID: 30183607]

174 Tao JH, Zou YF, Feng XL, Li J, Wang F, Pan FM, Ye DQ. Meta-analysis of TYK2 gene polymorphisms association with susceptibility to autoimmunity and inflammatory diseases. *Med Biol Res* 2011; 38: 4663-4672 [PMID: 23114022 DOI: 10.1007/s11033-010-0601-5]

175 Corbit KC, Camporez JPG, Tran JL, Wilson CG, Lowe DA, Nordstrom SM, Ganesan K, Perry RJ, Ibrahim MA, Isah MS, Ibrahim S. Inhibition of JAK-STAT and NF-κB signalling systems could be a novel therapeutic target against insulin resistance and type 2 diabetes. *Life Sci* 2019; 239: 117045 [PMID: 31730866 DOI: 10.1016/j.lfs.2019.117045]

176 Colloca D, Hull W, Mastrocola R, Chiavza F, Cento AS, Murphy C, Verta R, Alves GF, Gaudioso G, Fava F, Yaqoob M, Aragno M, Tuohy K, Thiemermann C, Collino M. Baricitinib counteracts metaflammation, thus protecting against diet-induced metabolic abnormalities in mice. *Mol Metab* 2020; 39: 101009 [PMID: 32413585 DOI: 10.1016/j.molmet.2020.101009]

177 Chen SK, Lee H, Jin Y, Liu J, Kim SC. Use of biologic or targeted-synthetic disease-modifying anti-rheumatic drugs and risk of diabetes treatment intensification in patients with rheumatoid arthritis and diabetes mellitus. *Rheumatol Adv Pract* 2020; 4: rkaa027 [PMID: 32914050 DOI: 10.1093/rap/rkaa027]

178 Bradley JR. TNF-mediated inflammatory disease. *J Pathol* 2008; 214: 149-160 [PMID: 18161752 DOI: 10.1002/path.2287]

179 Bravo A, Kavanagh A. Bedside to bench: defining the immunopathogenesis of psoriatic arthritis. *Nat Rev Rheumatol* 2019; 15: 645-656 [PMID: 31485004 DOI: 10.1038/s41584-019-0285-8]

180 Haroon M, Gallacher P, Heffernan E, FitzGerald O. High prevalence of metabolic syndrome and of insulin resistance in psoriatic arthritis is associated with the severity of underlying disease. *J Rheumatol* 2014; 41: 1357-1365 [PMID: 24931949 DOI: 10.3899/jrheum.140021]

181 Eder L, Jayakar J, Pollock R, Pellet F, Thavaneswaran A, Chandran V, Rosen CF, Gladman DD. Serum adipokines in patients with psoriatic arthritis and psoriasis alone and their correlation with disease activity. *Ann Rheum Dis* 2013; 72: 1956-1961 [PMID: 23243196 DOI: 10.1136/annrheumdis-2012-20325]

182 Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, Li TK, Yu T, Zhu YE, Wong KC, Kun EW, Li EK. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls-the role of inflammation. *Rheumatology (Oxford)* 2008; 47: 718-723 [PMID: 18400833 DOI: 10.1093/rheumatology/keg215]
Wang CR et al. Targeted-therapies on IR in autoimmune-mediated arthritis

10.1093/rheumatology/ken096

184 Dreher J, Freund T, Cohen AD. Psoriatic arthritis and diabetes: a population-based cross-sectional study. Dermatol Res Pract 2013; 2013: 580404 [PMID: 23843781 DOI: 10.1155/2013/580404]

185 Eder L, Chandran V, Cook R, Gladman DD. The Risk of Developing Diabetes Mellitus in Patients with Psoriatic Arthritis: A Cohort Study. J Rheumatol 2017; 44: 286-291 [PMID: 28148695 DOI: 10.3899/jrheum.160861]

186 Nas K, Karkucak M, Durmus B, Karataş S, Capkun E, Kaya A, Ucmak D, Akar ZA, Cevik R, Kilic E, Kilic G, Ozgocmen S. Comorbidities in patients with psoriatic arthritis: a comparison with rheumatoid arthritis and psoriasis. Int J Rheum Dis 2015; 18: 873-879 [PMID: 26173043 DOI: 10.1111/1756-185X.12580]

187 Radner H, Lesperance T, Accort NA, Solomon DH. Incidence and Prevalence of Cardiovascular Risk Factors Among Patients With Rheumatoid Arthritis, Psoriasis, or Psoriatic Arthritis. Arthritis Care Res (Hoboken) 2017; 69: 1510-1518 [PMID: 27998029 DOI: 10.1002/acr.23171]

188 Marra M, Campanati A, Testa R, Sirolla C, Bonfigli AR, Franceschi C, Marchegiani F, Offidani A. Effect of etanercept on insulin sensitivity in nine patients with psoriasis. J Int Immunopharmacol Pharmacol 2007; 20: 731-736 [PMID: 18179745 DOI: 10.1016/j.jip.2006.12.012]

189 Wambier CG, Foss-Freitas MC, Paschoal RS, Tomazini MV, Simão JC, Foss MC, Foss NT. Severe hypoglycemia after initiation of anti-tumor necrosis factor therapy with etanercept in a patient with generalized pustular psoriasis and type 2 diabetes mellitus. J Am Acad Dermatol 2009; 60: 883-885 [PMID: 19389539 DOI: 10.1016/j.jaad.2008.10.009]

190 Cheung D, Breyer-Ash M. Persistent hypoglycemia in a patient with diabetes taking etanercept for the treatment of psoriasis. J Am Acad Dermatol 2009; 60: 1032-1036 [PMID: 19217693 DOI: 10.1016/j.jaad.2008.12.012]

191 da Silva RS, Bonfá E, de Moraes JC, Saad CG, Ribeiro AC, Gonçalves CR, de Carvalho JF. Effects of anti-TNF therapy on glucose metabolism in patients with ankylosing spondylitis, psoriatic arthritis or juvenile idiopathic arthritis. Biologicals 2010; 38: 567-569 [PMID: 20638299 DOI: 10.1016/j.biologicals.2010.05.003]

192 Kimball AB, Bensimon AG, Guerin A, Yu AP, Wu EQ, Okun MM, Bao Y, Gupta SR, Mulani PM. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with comorbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. Am J Clin Dermatol 2011; 12: 51-62 [PMID: 21110526 DOI: 10.2165/1130640-000000000-000000]

193 Pfeifer EC, Saxson DR, Janson RW. Etanercept-Induced Hypoglycemia in a Patient With Psoriatic Arthritis and Diabetes. J Investig Med High Impact Case Rep 2017; 5: 3234709617727760 [PMID: 29721512 DOI: 10.1177/2324709617727760]

194 Mathieu S, Motreff P, Soubrier M. Spondyloarthropathies: an independent cardiovascular risk factor?. Joint Bone Spine 2010; 77: 542-545 [PMID: 20646947 DOI: 10.1016/j.jbspin.2010.05.001]

195 Genre F, López-Mejías R, Miranda-Filloy JA, Ubiña B, Carnero-López B, Blanco R, Pina T, González-Juanatey C, Llorca J, González-Gay MA. Adipokines, biomarkers of endothelial activation, and metabolic syndrome in patients with ankylosing spondylitis. Biomed Res Int 2014; 2014: 860651 [PMID: 24757680 DOI: 10.1155/2014/860651]

196 Miranda-Filloy JA, Llorca J, Carnero-López B, González-Juanatey C, Blanco R, González-Gay MA. TNF-alpha antagonist therapy improves insulin sensitivity in non-diabetic ankylosing spondylitis patients. Clin Exp Rheumatol 2012; 30: 850-855 [PMID: 22765845]

197 Ersozlu Bozkirli ED, Bozkirli E, Yucel AE. Effects of infliximab treatment in terms of cardiovascular risk and insulin resistance in ankylosing spondylitis patients. Mod Rheumatol 2014; 24: 335-339 [PMID: 24225046 DOI: 10.3109/14397595.2013.843752]

198 Jagannathan-Bogdan M, McDonnell ME, Shin H, Rehman Q, Hasturk H, Apovian CM, Nikolajczyk BS. Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes. J Immunol 2011; 186: 1162-1172 [PMID: 21169542 DOI: 10.4049/jimmunol.1002615]

199 Zhang C, Xiao C, Wang P, Xu W, Zhang A, Li Q, Xu X. The alteration of Th1/Th2/Th17/Treg paradigm in patients with type 2 diabetes mellitus: Relationship with diabetic nephropathy. Hum Immunol 2014; 75: 289-296 [PMID: 24530745 DOI: 10.1016/j.humimm.2014.02.007]

200 Obshima K, Mogi M, Jing F, Iwanami J, Tsukuda K, Min LJ, Higaki J, Horiuichi M. Roles of interleukin 17 in angiotensin II type 1 receptor-mediated insulin resistance. Hypertension 2012; 59: 493-499 [PMID: 22184328 DOI: 10.1161/HYPERTENSIONAHA.111.183178]

201 O'Reilly DD, Rahman P. A review of ixekizumab in the treatment of psoriatic arthritis. Expert Rev Clin Immunol 2018; 14: 993-1002 [PMID: 30366063 DOI: 10.1080/1744666X.2018.1540931]

202 Egeberg A, Wu JJ, Kornan N, Solomon JA, Goldblum O, Zhao F, Mallbris L. Ixekizumab treatment shows a neutral impact on cardiovascular parameters in patients with moderate-to-severe plaque psoriasis: Results from UNCOVER-1, UNCOVER-2, and UNCOVER-3. J Am Acad Dermatol 2018; 79: 104-109.e8 [PMID: 29548945 DOI: 10.1016/j.jaad.2018.02.074]

203 Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. Ther Adv Chronic Dis 2018; 9: 5-21 [PMID: 29344327 DOI: 10.1177/2040622317738910]

204 Gerdes S, Pointer A, Papavassilis C, Reinhardt M. Effects of secukinumab on metabolic and liver parameters in plaque psoriasis patients. J Eur Acad Dermatol Venereol 2020; 34: 533-541 [PMID: 31599476 DOI: 10.1111/jdv.16064]
Hasnain SZ, Borg DJ, Harcourt BE, Tong H, Sheng YH, Ng CP, Das I, Wang R, Chen AC, Loudovaris T, Kay TW, Thomas HE, Whitehead JP, Forbes JM, Prins JB, McGuckin MA. Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress. *Nat Med* 2014; 20: 1417-1426 [PMID: 25362253 DOI: 10.1038/nm.3705]

Yiu ZZ, Warren RB. Ustekinumab for the treatment of psoriasis: an evidence update. *Semin Cutan Med Surg* 2018; 37: 143-147 [PMID: 30215630 DOI: 10.12788/j.sder.2018.040]

Ng CY, Tzeng IS, Liu SH, Chang YC, Huang YH. Metabolic parameters in psoriatic patients treated with interleukin-12/23 blockade (ustekinumab). *J Dermatol* 2018; 45: 309-313 [PMID: 28980716 DOI: 10.1111/1346-8138.14079]

Haber SL, Hamilton S, Bank M, Leong SY, Pierce E. Apremilast: A Novel Drug for Treatment of Psoriasis and Psoriatic Arthritis. *Ann Pharmaco"
