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Mustafa Altay, MD, Professor, Chief, Department of Endocrinology and Metabolism, Health Sciences University Turkey, Keçiören Training and Research Hospital, Kuşcağız, Ankara 54600, Turkey. mustafa.altay@sbu.edu.tr

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The WJD is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJD as 3.247; IF without journal self cites: 3.222; Ranking: 70 among 143 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yan-Jie Ma*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

March 15, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



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.

Author contributions: Wang CR designed the review and wrote the paper; Wang CR and Tsai HW collected and analyzed the clinical data.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

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Manuscript source: Invited manuscript

Specialty type: Endocrinology and metabolism

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-1 β , 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

Country/Territory of origin: Taiwan**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
 Grade B (Very good): 0
 Grade C (Good): 0
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: December 21, 2020**Peer-review started:** December 21, 2020**First decision:** January 7, 2021**Revised:** January 7, 2021**Accepted:** January 21, 2021**Article in press:** January 21, 2021**Published online:** March 15, 2021**P-Reviewer:** Qiong L**S-Editor:** Fan JR**L-Editor:** A**P-Editor:** Ma YJ

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Core Tip: The crucial mechanism leading to development of diabetes mellitus is the resistance of target cells to insulin, *i.e.* insulin resistance (IR), indicating the ineffective strength of signaling transduction from the receptor, downstream to the final substrates of insulin action. Autoimmune-mediated arthritis including rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, with the involvement of proinflammatory cytokines like tumor necrosis factor (TNF)- α , interleukin (IL)-6 and IL-1 β as their central pathogenesis, has been demonstrated to be associated with IR. Anti-TNF- α therapy, IL-1 blockade, IL-6 antagonist, Janus kinase inhibitor and phosphodiesterase type 4 blocker can reduce IR and improve diabetic hyperglycemia in autoimmune-mediated arthritis.

Citation: Wang CR, Tsai HW. Anti- and non-tumor necrosis factor- α -targeted therapies effects on insulin resistance in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. *World J Diabetes* 2021; 12(3): 238-260

URL: <https://www.wjgnet.com/1948-9358/full/v12/i3/238.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v12.i3.238>

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)^[1,2]. 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 transmembrane insulin receptor consists of two extracellular α and two intracellular β subunits linked by disulphide bonds^[3]. 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)^[4]. 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^[5].

The phosphorylated IRS can act as a docking protein for various effector molecules possessing the src homology 2 (SH2) domain^[2]. 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 comprised of Fyn, C-terminal Src kinase, SH2 domain-containing inositol polyphosphate 5'-phosphatase and SH2-containing protein tyrosine phosphatase 2^[6,7]. 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)^[8]. 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-3 β ^[9-12]. Most of the physiological effects of insulin are mediated by the signaling pathway involving the activated IRS and SH2 domain proteins^[1-3], 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^[2], 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^[13,14]. 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^[2,14]. 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^[17], whereas mice lacking the PTP1B gene had a reduced risk of IR with higher insulin sensitivity in peripheral tissues^[18]. In human, overexpression of the PTP1B protein has been observed in an obesity-related IR status^[19], implicating reduction of PTP1B levels as a therapeutic strategy for IR^[20].

Miscellaneous inflammatory disorders in human with increased levels of proinflammatory cytokines, as measured by tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6 depending on the study designs, have been reported to be associated with increased risk of developing IR^[2,21]. There are commonly encountered autoimmune-mediated arthritis conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS)^[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^[26,27]. *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 κ B kinase (IKK)- β has been identified as the cellular kinase responsible for the serine phosphorylation of IRS-1 in response to TNF- α stimulation^[28]. 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 ^[29].

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 , perilipin, and adipocyte complement-related protein of 30 kDa (Acrp30)^[27]. 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 concentrations, leading to a decrease in fatty acid oxidation in skeletal muscle and consequently a rise in free fatty acid (FFA) levels and induction of IR^[27,30,31]. Notably, activation of nuclear factor- κ B (NF- κ B), a key mediator in most of the TNF- α responses, is associated with the repression of adipocyte-related genes involved in the uptake and storage of FFA and glucose essential for the function of adipocytes^[32]. In particular, NF- κ B-mediated suppressed synthesis of PPAR- γ , an essential gene for the induction and maintenance of adipocyte genes expression^[33], is a critical determinant of insulin sensitivity in adipose tissues^[34]. 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-1^[35]. TNF- α has been shown to induce a sustained SOCS-3 expression in targeted tissues^[36].

In human observations, elevated circulating concentrations of bioactive TNF- α have been observed in type II DM patients, as compared with the healthy individuals^[37,38]. 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^[39]. Moreover, a 4-d course of i.v. TNF- α infusion brought about IR, with increased homeostasis model assessment (HOMA)-IR levels, in healthy young volunteers^[40]. 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)^[41]. 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 rsTNFRFP^[42,43].

Effects on IR of targeting TNF- α in RA patients

TNF- α participates in the pathogenesis and disease progression of RA^[44], and biologics antagonizing this cytokine display significant efficacy in inhibiting arthritis activities^[45]. IR in RA is driven majorly by the activity-related inflammation^[46], and elevated plasma levels of TNF- α have been demonstrated in such patients with increased IR^[47]. Considerable case-control and cohort studies have shown increased risks of both type I and II DM prevalence among RA patients^[48]. An association in type I DM is specific in a subgroup of RA with the presence of cyclic citrullinated peptide antibody^[49], and both diseases share susceptibility genes, including *HLA-DRB1*, *PTPN22*, *CTLA-4*, *TAGAP*, and *KIAA109-TENR-IL2-IL21*^[49-53]. 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^[54]. A large prospective study of 114342 women showed no differences in the type II DM occurrence between individuals with and without RA^[55]; 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^[56]. 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^[24].

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)^[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)^[58]. 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^[59,60]. In a cohort of 522 non-diabetic RA cases receiving the TNF- α inhibitors (TNFi) including ADA, ETA, GLO and IFX, there was a more than 50% reduction in the risk of DM development^[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^[62]. 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^[63-66]. 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^[57].

Table 1 summarizes 15 published studies that examined the effects of anti-TNF therapies on IR in non-diabetic RA patients^[63-77]. There were four with at least two TNFi (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^[70], 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^[71,76].

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^[78]. *In vitro* and *in vivo* studies have confirmed that the production of IL-6 can be regulated by insulin^[79], and hyperinsulinemia can produce an increase in IL-6 expression in adipose tissues with raised systemic levels^[80]. Circulating levels of IL-6 have been observed to be elevated in type II DM patients^[81]. This cytokine is a risk factor for the development of such a disease^[82]. Its plasma levels have been shown to be positively correlated with the percentage of body fat^[83]. Activated IKK- β , a molecular target of IR^[84], phosphorylates an inhibitor of NF- κ B, I κ B α , and promotes its degradation to free NF- κ B and allows its entry into the nucleus^[85]. This kinase can not only activate NF- κ B to stimulate the production of IL-6 but it can also directly induce the serine phosphorylation of IRS-1^[86]. Injection of neutralizing antibodies against IL-6 could reverse IKK- β -induced IR in mice^[87]. Notably, IL-6 has a negative impact on insulin signaling by decreasing tyrosine phosphorylation of IRS-1, inhibiting activation of PKB^[88], 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 (s)	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	[67]
2	2005, Greece	mAb	28 IFX	Non-diabetic	6 mo	Improved HOMA-IR only in high-IR group	[68]
3	2006, Spain	mAb	27 IFX	Non-diabetic	2 h after infusion	Improved HOMA-IR	[69]
4	2007, Netherlands	mAb	5 IFX	Non-diabetic	6 wk	Improved insulin sensitivity ¹	[70]
5	2007, Denmark	mAb	9 ADA	Non-diabetic, high IR	8 wk	Ineffective HOMA-IR	[71]
6	2007, China	mAb	19 IFX	Non-diabetic	14 wk	Improved HOMA-IR	[72]
7	2007, Turkey	mAb	7 IFX	Non-diabetic	5-15 mo	Improved HOMA-IR	[73]
8	2008, Spain	mAb	21 IFX	Non-diabetic	24 wk	Improved HOMA-IR	[74]
9	2008, Italy	mAbs, sTNFRFP, Mixed	20 ETA, 18 IFX, Total 38	Non-diabetic	24 wk	Improved HOMA-IR	[63]
10	2011, Spain	mAbs, rsTNFRFP, Mixed	8 ADA, 6 IFX, 2 ETA, Total 16	Non-diabetic	12 mo	Ineffective HOMA-IR	[64]
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	[65]
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	[66]
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	[75]
14	2020, Netherlands	mAb	28 ADA	Non-diabetic	6 mo	Ineffective HOMA-IR, improved- β -cell function	[76]
15	2020, Taiwan	rsTNFRFP	30 ETA	Non-diabetic, non-obese	24 wk	Improved HOMA-IR in high-IR group	[77]

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^[89]. 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^[90,91]. IL-6 has also been shown to reduce the expression of adiponectin, GLUT4, IRS-1, PPAR- γ and insulin receptor- β in adipocytes^[91-93]. Furthermore, IL-6 was found to be constitutively expressed by human pancreatic α and β cells, with local islet IL-6 levels reduced in type I but elevated in type II DM patients^[94,95]. In 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^[96].

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^[97]. IL-6 receptor signaling in target cells has been shown to have protective antiinflammatory effects, mediated by the skewing of macrophages towards a M2 phenotype and thus limiting the development of IR during obesity^[98]. *In vitro* short-term treatment with IL-6 could enhance the glucose uptake in adipocytes^[99]. Physical inactivity, an IR induction factor, has been demonstrated to be associated with reduced IL-6 secretion from skeletal muscle^[100], while exercise can enhance the production of IL-6 by skeletal muscle, leading to an improvement in insulin sensitivity^[101]. 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^[102]. 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^[103]. *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 secrete insulin and improves hyperglycemic status^[104]. 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^[105]. 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)^[106].

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 *in vivo* glucose disposal in human^[107]. 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^[108]. 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^[109]. 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^[110]. Notably, both pro- and anti-inflammatory roles have been identified for IL-6, distinguished by two specific signaling transduction cascades, *i.e.* classic and trans-signaling^[111]. 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 *via* a trans-signaling or classic signaling mechanism^[106,111]. The trans-signaling is involved in the infiltration of macrophages into adipose tissues, resulting in a proinflammatory status with IR in obese subjects^[112]. 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^[113]. 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^[114]—failed to alter the blood glucose levels in the streptozotocin-induced mouse model^[115], 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^[65,116-125]. 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 by binding to CD80/CD86 molecules, has been approved to treat RA patients^[126]. 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^[119,127]. In two studies with limited patient numbers^[65,118], 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^[124].

Table 2 Studies on effects of non-tumor necrosis factor-targeted therapies on insulin resistance in rheumatoid arthritis patients

No.	Source	Drug	Cases, <i>n</i>	Clinical features	Duration	Effects on IR	Ref.
1	2010, Germany	TCZ	11	Non-diabetic	3 mo	Improved HOMA-IR	[116]
2	2012, United Kingdom	ABA	7	Non-diabetic, active disease	12 wk	Ineffective HOMA-IR	[65]
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	[118]
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	[120]
7	2015, Greece	TCZ	19	Active disease	6 mo	Ineffective HOMA-IR	[121]
8	2017, France	TCZ	15	Active disease	6 mo	Ineffective HOMA-IR	[122]
9	2019, Spain	TCZ	50	Non-diabetic	1 h after 1 st infusion	Improved HOMA-IR	[123]
10	2019, France	Other ¹ , 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	[125]

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-1 α and IL-1 β (the first identified cytokines with strong proinflammatory functions), and a naturally occurring anti-inflammatory mediator, IL-1 receptor antagonist (IL-1Ra)^[128]. 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-1 β in particular, participate in regulating inflammatory diseases, as observed in diabetic patients^[129]. Elevated serum concentrations of IL-1 α and production levels of IL-1 β from mononuclear cells were observed in patients at the onset of type I DM^[130,131]. IL-1 β has been proposed to mediate both dysfunction and destruction of pancreatic β -cells during the autoimmune process of insulin-dependent DM (IDDM)^[132]. Antagonizing IL-1 with soluble receptor or IL-1Ra has been shown to reduce the incidences of type I DM in non-obese diabetic (NOD) mice and diabetic BB rats^[133,134], indicating a modulatory role of IL-1 on the immune system and pancreatic β -cells^[135]. Concentrations of IL-1 β , 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-1 β 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 IKK β /NF- κ B pathway, IL-1 β is capable of impairing insulin signaling and its action, thus participating in the development of IR^[139,140]. *In vitro* exposure of human islets to high concentrations of glucose resulted in increased production of IL-1 β from β -cells, followed by NF- κ B activation and cellular apoptosis^[141]. Although local IL-1 β 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- κ B, mitogen-activated-protein-kinase and c-Jun N-terminal kinase signaling, leading to endoplasmic reticulum and mitochondrial stress and eventually activating the apoptotic machinery^[142]. Interestingly, there is an emerging hypothetical pathogenesis for type II DM, in which an imbalance between the hyperactivity of IL-1 β and the countering effect of IL-1Ra can determine the outcome of islet inflammation^[143].

Collectively, these findings indicate that the IL-1 cytokine family may represent therapeutic targets to reverse the adverse metabolic consequences of DM^[134,141,143].

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-1 β mAb for autoinflammatory diseases and gouty arthritis^[144]. 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 HbA_{1c} and fasting glucose levels, which was followed by reduction in or removal from antidiabetic medications in 2 of the cases, implicating IL-1 as a therapeutic target in diabetic therapy^[145,146].

Effects on DM by applying anti-TNF- α and other targeted agents used for rheumatology 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 TNFi 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^[147], while a 10-year observation with ETA and IFX therapy for RA and Crohn's disease co-morbidities, respectively, demonstrated reduced HbA_{1c} and fasting glucose levels^[148]. Interestingly, rituximab (RTX), a chimeric mAb approved for RA therapy through targeting surface CD20 molecule to deplete β -cell^[149], has been applied to treat IDDM and type B insulin resistance syndrome-associated NIDDM^[150,151]. 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^[150]. In NOD mice, the development of insulinitis has been shown to be completely abrogated upon injection of an anti- μ chain polyclonal antibody, which depletes B lymphocytes^[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 HbA_{1c} and the required insulin doses with a higher 2 h C-peptide area under the curve (AUC)^[150]. After a 30 mo follow-up, the AUC, HbA_{1c} and insulin doses were similar between the RTX-treated and placebo groups^[153], 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 HbA_{1c} levels and insulin requirement with undetectable anti-insulin receptor levels^[151]. 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^[154]. In addition to improving the insulin sensitivity in non-diabetic RA patients^[119], 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^[155].

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-1 α) and gevokizumab (anti-IL-1 β)^[145,146,156-168]. Except for one ineffective study recruiting newly diagnosed type I DM^[160], six other investigations have shown beneficent 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^[157,158,160,161,165]. Similar to the observations from CAN therapy, there were effective results in type II but not in type I diabetic patients under gevokizumab treatment^[159,164]. The study examining recent-onset type I diabetic cases receiving regular RIL injection revealed a higher 2-h C-peptide AUC^[166]. Another investigation analyzing type II DM patients under the administration of bermekimab exhibited an increase in the secretion of insulin^[163]. 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^[169,170]. 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	Ref.
1	2005, United States	ETA	rSTNFRFP	10	Type II DM, obese	4 wk	Ineffective IS	[147]
2	2007, INC	ANA	IL-1Ra	34	Type II DM	13 wk	Reduced HbA _{1c} and increased insulin secretion at 13 wk, reduced insulin doses at 39 wk	[156]
3	2009, United States	RTX	CD20 mAb	49	Type I DM, recent	1 yr	Reduced HbA _{1c} /insulin doses and higher 2 h C-peptide AUC at 1 yr, no differences at 30 mo	[150]
4	2011, United States	ABA	CTLA4-Ig	73	Type I DM, recent	2 yr	Higher 2 h C-peptide AUC	[155]
5	2011, United States	TNFi	ETA, IFX	8	Type II DM	10 yr	Reduced HbA _{1c} and fasting glucose levels	[148]
6	2011, Japan	TCZ	IL-6R mAb	10	Type II DM	6 mo	Reduced HbA _{1c} and use of antidiabetic drugs	[110]
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)	[157]
8	2012, INC	CAN	IL-1 mAb	372	Type II DM	4 mo	Ineffective HbA _{1c} , fasting glucose and insulin levels	[158]
9	2012, INC	GEV	IL-1 mAb	81	Type II DM	13 wk	Reduced HbA _{1c} , increased IS and insulin secretion at single i.v. groups (0.03, 0.1 mg/kg)	[159]
10	2013, INC	ANA	IL-1 Ra	25	Type I DM, recent	9 mo	Ineffective 2 h C-peptide AUC	[160]
11	2013, INC	CAN	IL-1 mAb	45	Type I DM, recent	1 yr	Ineffective 2 h C-peptide AUC	[160]
12	2014, INC	CAN	IL-1 mAb	14	Type II DM	24 wk	Reduced HbA _{1c} at single i.v. 1.5 and 10 mg/kg groups	[161]
13	2015, Netherlands	ANA	IL-1Ra	14	Type I DM	1 wk	Reduced HbA _{1c} , insulin doses and fasting glucose levels, increased IS	[162]
14	2015, Italy	ANA	IL-1Ra	2	Type II DM	6 mo	Reduced HbA _{1c} and fasting glucose levels, reduced or off antidiabetic therapeutics	[145]
15	2015, Italy	ANA	IL-1Ra	3	Type II DM	6 mo	Reduced HbA _{1c} and fasting glucose levels	[146]
16	2015, Germany	BER	IL-1 mAb	7	Type II DM	60 d	Increased insulin secretion	[163]
17	2016, Switzerland	GEV	IL-1 mAb	15	Type I DM	1 yr	Ineffective 2-h C-peptide AUC	[164]
18	2016, Switzerland	CAN	IL-1 mAb	6	Type II DM	24 wk	Reduced HbA _{1c}	[165]
19	2017, Japan	RTX	CD20 mAb	3	Type II DM, insulin RS	6-16 mo	Reduced HbA _{1c} and insulin doses, disappearance of IR antibody	[151]
20	2018, United States	RIL	IL-1R-Ig	13	Type I DM, recent	26 wk	Higher 2 h C-peptide AUC	[166]
21	2019, Italy	ANA	IL-1Ra	17	Type II DM	6 mo	Reduced HbA _{1c}	[167]
22	2019, Italy	ANA	IL-1Ra	15	Type II DM	6 mo	Increased IS, improved β -cell function, decreased glucagon levels	[168]

23	2020, United States	TOF	JAKi	634	Type I, II DM	9 mo	DM treatment (insulin/non-insulin) intensification lowest in using TOF	[178]
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ABA: Abatacept; ADA: Adalimumab; ANA: Anakinra; AUC: Area under the curve; BER: Beremkimab; CAN: Canakinumab; DM: Diabetes mellitus; ETA: Etanercept; GEV: Gevokizumab; IFX: Infliximab (a TNF mAb); Ig: Immunoglobulin; INC: International countries; Insulin RS: Insulin resistance syndrome; IR: Insulin receptor; IS: Insulin sensitivity; ISR: Insulin secretion rate; i.v.: Intravenous; JAKi: Janus kinase inhibitor; mAb: Monoclonal antibody; PN: Patient numbers; Ra: Receptor antagonist; RIL: Riloncept; rTNFRFP: Recombinant soluble tumor necrosis factor- α receptor fusion protein; TCZ: Tocilizumab; TNFi: Tumor necrosis factor inhibitor; TOF: Tofacitinib; RTX: Rituximab; HbA1c: Hemoglobin A1c; IL: Interleukin.

phosphorylate tyrosine residues as well as the intracellular tail of receptor subunits, recruiting and docking of the downstream signaling molecules, STATs. These transcription factors can be phosphorylated by JAKs, leading to homo- or hetero-dimerization and further translocation into the nucleus to bind their associated promoters and regulate the transcription of target genes. Individual cytokine receptors can recruit their own combinations of JAKs/STATs to activate different processes in targeted cells, and antagonizing a specific JAK can impede more than one cytokine pathway, expanding the efficacy in using such antagonists^[171]. Notably, rheumatology disorders are often characterized by activation of cytokine signaling pathways with distinct expression profiles, generating the rationale for using JAK inhibitors as cytokine-targeted therapy^[172]. In particular, tofacitinib (TOF) is the first small molecule oral selective JAK1 and JAK3 inhibitor approved in 2017 by the Federal Food and Drug Administration (FDA) and in 2018 by the European Medicines Agency (EMA) for treating RA patients^[173]. In addition, the identification of a link between JAKs/TYK2 gene polymorphisms and IDDM has brought about a therapeutic potential in targeting the JAK-STAT pathways in such patients^[174].

Accumulated evidence from animal studies has suggested a substantial pathogenic role of the JAK/STAT pathways in the development of low-grade chronic inflammatory response contributing to obesity and type II DM^[175-177]. Notably, in a type II diabetic rat model induced by fructose/streptozotocin administration, treating with TOF alone, despite more potent efficacy in combination with aspirin to inhibit the NF- κ B signaling, could lower serum proinflammatory cytokine expressions and skeletal muscle SOCS-3 Levels, resulting in reduced IR with decreased blood glucose and HOMA-IR levels and improved β -cell function with increased serum insulin and HOMA- β levels^[176]. Moreover, in a recent survey of more than 10000 RA patients with type I or II DM co-morbidity under a 9 mo follow-up, the diabetic treatment intensification was found to be lowest in those using TOF than others receiving TNFi and non-TNF- α -targeted therapies^[178].

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^[27], 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^[179,180]. In a PsA cohort, there was a 16% prevalence of IR and an association of metabolic syndrome with more severe arthritis^[181]. 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^[182]. In comparison with healthy controls, PsA patients have an increase in HOMA-IR and a higher prevalence of DM^[183]. Notably, the prevalence of IDDM in PsA is higher than that in the general population^[25], and the diabetic risk appears to be increased for women and for active disease^[184,185]. 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^[186,187]. 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^[188-193]. 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^[192].

Despite less evidence than has been published for RA patients, increased prevalence of IR and altered glucose metabolism have been documented in AS patients^[194,195]. 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, <i>n</i> 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 HbA _{1c} 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 HbA _{1c} and fasting glucose levels, discontinuing insulin use	[190]
5	2010, Brazil	TNF blocker ¹	18, PsA	Non-DM	6 mo	No changes in fasting glucose levels	[191]
6	2010, Brazil	TNF blocker ¹	37, AS	Non-DM	6 mo	No changes in fasting glucose levels	[191]
6	2011, United States	ADA	54, PsO	DM 13%, PsA 41%	16 wk	Ineffective changes in fasting glucose levels in DM	[192]
7	2012, Spain	IFX	30, AS	Non-DM	120 min	Reduced HOMA-IR	[196]
8	2014, Turkey	IFX	30, AS	Non-DM	12 wk	Ineffective HOMA-IR	[197]
9	2017, United States	ETA	1, PsA	Type II DM, obesity	12 wk	Reduced HbA _{1c} and fasting glucose levels, discontinuing insulin use	[193]
10	2018, Taiwan	UST	93, PsO	Obesity 45%	24 wk	Increased fasting glucose levels	[207]
11	2018, United States	IXE	2328, PsO	DM 9%, PsA 24%	12 wk	No changes in fasting glucose levels	[202]
12	2019, Germany	SEC	828, PsO	DM 10%, PsA 19%	52 wk	No changes in fasting glucose levels	[204]
13	2019, INC	APR	1089, PsA/O	DM 9%	52 wk	Reduced HbA _{1c} , improvement highest in HbA _{1c} no less than 6.5%	[210]
14	2019, Italy	APR	1, PsO	Type II DM, obesity	6 mo	Reduced HbA _{1c} and fasting glucose levels, discontinuing insulin use	[211]
15	2020, Italy	APR	113, PsA/O	DM, 25%	52 wk	Reduced fasting glucose levels	[212]
16	2020, INC	TOF	474, PsA	MetS, 42%	6 mo	No increased blood glucose levels, hyperglycemic event and diabetic occurrence	[217]
17	2021, Taiwan	TOF	5, PsA	Non-DM, non-obese, high-IR	12 wk	Reduced HOMA-IR	PS

¹Tumor 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; HbA_{1c}: Hemoglobin A_{1c}; HOMA: Homeostasis model assessment.

HOMA-IR, especially in the high-IR group^[68,191,196,197].

Increased circulating Th17 numbers and elevated IL-17 Levels have been identified in type II diabetic patients^[198,199]. 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 administering 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], also showed no efficacy in improving glucose metabolism^[204].

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^[205]. One study evaluating the glucose homeostasis in PsA patients receiving ustekinumab, a mAb binding the common p40 subunit of IL-12 and IL-23^[206], showed more elevated fasting glucose levels after a 24-wk treatment period^[207].

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^[208]. PDE4C and PDE4D, expressed in pancreatic β -cells, play a critical role in controlling the secretion of insulin^[209]. In a large-scale study with 1089 PsA/PsO patients under APR therapy for 52 wk, there were reduced HbA_{1c} levels found, with the highest improvement occurring in those with baseline HbA_{1c} levels no less than 6.5%^[210]. In addition, reduced HbA_{1c} 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^[211]. Another investigation treating PsA/PsO patients with APR for 52 wk also demonstrated reduced fasting blood glucose levels^[212].

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^[213]. 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^[213,214]. 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^[215]. 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^[215,216]. Notably, animal studies have implicated targeting such a pathway in reducing IR and treating type II diabetes^[175-177]. In human trials, the diabetic treatment intensification in RA combined with DM comorbidity was lowest in patients under the 9 mo TOF treatment^[178]. There were no increased blood glucose levels, hyperglycemic events or diabetic occurrences in PsA patients receiving TOF therapy for 6 mo^[217]. 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)^[77]. 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-1 β , 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.

ACKNOWLEDGEMENTS

The authors are indebted to the physicians and nurses involved in the diagnosis and management of patients reported from the National Cheng Kung University Hospital (NCKUH). The Institutional Review Board of NCKUH approved this study (No. B-ER-

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