**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 74740

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Immediate-release** **tofacitinib reduces insulin resistance in non-diabetic active rheumatoid arthritis patients: A single-center retrospective study**

Wang CR *et al*. Tofacitinib reduces insulin resistance in RA

Chrong-Reen Wang, Hung-Wen Tsai

**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

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

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

**Received:** January 14, 2022

**Revised:** April 18, 2022

**Accepted: May 28, 2022**

**Published online:**

**Abstract**

BACKGROUND

An increased risk of insulin resistance (IR) has been identified in rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of pathogenic cytokines. Biologics targeting proinflammatory cytokines can control the disease and improve insulin sensitivity in RA. Although Janus kinase (JAK) signaling can regulate cytokine receptors and participate in RA pathogenesis, it remains to be elucidated whether there is a reduction of IR in such patients under JAK inhibitor (JAKi) therapy.

AIM

To study the effect of JAKi treatment on the reduction of IR in RA patients with active disease.

METHODS

A retrospective study was carried out from April 1, 2017 to March 31, 2021 in a population of non-diabetic patients with active RA who were undergoing tofacitinib (TOF) therapy with 5 mg twice-daily immediate-release formulation.

RESULTS

Fifty-six RA patients, aged 30 years to 75 years (mean ± SD: 52.3 ± 11.1) with disease activity score 28 values ranging from 4.54 to 7.37 (5.82 ± 0.74), were classified into high-IR (> 2.0) and low-IR (≤ 2.0) groups based on their baseline homeostatic model assessment (HOMA)-IR levels. They had no previous exposure to JAKi, and received TOF therapy for no less than 6 mo. In 30 patients who were naïve to biologics, after a 24-week therapeutic period, the high-IR group showed reduced HOMA-IR levels (3.331 ± 1.036 *vs* 2.292 ± 0.707, *P* < 0.001). In another 26 patients who were exposed to tumor necrosis factor-αor interleukin-6 blockers, the high-IR group, despite having achieved a decrease but with lower magnitude than in naïve patients, showed reduced HOMA-IR levels (2.924 ± 0.790 *vs* 2.545 ± 1.080, *P* = 0.018).

CONCLUSION

In this retrospective study, reduced IR was achieved in non-diabetic active RA patients following 24 wk of TOF therapy.

**Key Words:** Insulin resistance; Rheumatoid arthritis; Diabetes mellitus; Tofacitinib; Janus kinase inhibitor

Wang CR, Tsai HW. Immediate-release tofacitinib reduces insulin resistance in non-diabetic active rheumatoid arthritis patients: A single-center retrospective study. *World J Diabetes* 2022; In press

**Core Tip:** An increased risk of insulin resistance (IR) has been identified in rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of pathogenic cytokines. In addition to controlling RA activity, biologics targeting proinflammatory cytokines have been shown to reduce IR, while it remains to be elucidated whether Janus kinase inhibitor therapy can cause IR reduction in such patients. This retrospective study carried out in non-diabetic active RA patients classified into high-IR and low-IR groups before tofacitinib (TOF) therapy demonstrated reduced IR by 24 wk of TOF treatment in the active RA patients with high baseline IR status.

**INTRODUCTION**

A critical mechanism causing diabetes development is the resistance of target cells to the action of insulin, with ineffective strength of signaling from the receptor to the final action substrates and requiring beyond-normal insulin concentrations to maintain euglycemic status[1,2]. Insulin resistance (IR) manifests from a blockade of tissues to the insulin action upon the uptake, metabolism or storage of glucose, a common feature of human disorders such as diabetes, hyperlipidemia, metabolic syndrome, fatty liver, and obesity[1]. Furthermore, an increased risk of IR has been identified in various inflammatory disorders with increased levels of proinflammatory cytokines like interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α[3].

Rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of proinflammatory cytokines, has been demonstrated to be associated with IR during its activity[4]. TNF-α is involved in IR pathogenesis through the phosphorylation of inhibitory serine residue of insulin receptor substrate-1 (IRS-1) and reduction of tyrosine phosphorylation of IRS-1 and the β-subunit of the insulin receptor[5,6]. Inactivation of TNF-α by use of recombinant soluble receptor fusion proteins or monoclonal antibodies for IR reduction has been successfully demonstrated in active RA[7]. IL-6 can exert a negative influence on insulin signaling by decreasing tyrosine phosphorylation of IRS-1, inducing recruitment of IRS-1 to its receptor complex for serine phosphorylation, and reducing autophosphorylation of tyrosine residues in the insulin receptor[8,9]. Under treatment with tocilizumab (TCZ; an IL-6 receptor antibody) to inhibit IL-6 signaling in RA, decreased IR was identified in an investigation of 221 active patients as well as in other studies with smaller sample sizes[10-13]. IL-1β is able to impair insulin signaling through activation of the IKKβ/NF-κB pathway to target IRS-1 through serine phosphorylation[14,15]. Anakinra, an IL-1 receptor antagonist, has been shown to reduce IR in active RA with comorbid type 2 diabetes[16,17]. Altogether, these observations indicate that, biologic therapy targeting pathogenic cytokines can not only control disease activity but also improve insulin sensitivity in active RA patients.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, including JAKs 1 to 3, STATs 1 to 6, and tyrosine kinase 2, regulates many cytokine and hormone receptors with pathogenic roles in a variety of inflammatory disorders[18]. Notably, different cytokine receptors can recruit their own combinations of JAKs and STATs to activate distinct processes in individual targeted cells, while antagonizing a JAK can suppress more than one cytokine pathway, expanding the efficacy in using such an antagonist in cytokine-targeted therapy[19]. Notably, tofacitinib (TOF) is the first small-molecule pan-JAK inhibitor (JAKi) targeting JAKs 1 to 3[20]. It has been approved by the United States’ Federal Food and Drug Administration in 2012 and by European Medicines Agency in 2017 for the treatment of RA patients with moderate to high activity and an inadequate response to methotrexate[21]. This JAKi can act on the JAK/STAT pathway to block the intracellular signaling of multiple cytokines and hormones involved in the pathogeneses of RA and IR[20,22]. In RA patients, significantly reduced circulating levels of pro-inflammatory cytokines IL-6 and TNF-α, two crucial mediators of IR, were observed since week 4 after initiation of TOF therapy[23,24]. Furthermore, in a recent large-scale survey of 10019 RA patients with type 1 or 2 diabetic co-morbidity, the diabetic treatment intensification, *i.e*. addition of a new anti-diabetic medication, was found to be lower for those using TOF than for those using other TNF-α inhibitors or non-TNF-α-targeted biologics[25]. Based on the above findings, there is a therapeutic potential to reduce the IR in active RA patients by TOF therapy.

In this retrospective investigation, the effect of TOF treatment (specifically, 5 mg twice-daily immediate-release formulation) on IR reduction was investigated in 56 non-diabetic patients with active RA, naïve or exposed to biologic therapy and classified into high- and low-IR groups according to the baseline levels of the homeostatic model assessment (HOMA)-IR score.

**MATERIALS AND METHODS**

***Study* *design and patients***

This study was carried out to analyze the effect of TOF on IR in active RA patients who met the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria[26]. Each patient received regular monthly follow-up at an outpatient rheumatology clinic of National Cheng Kung University Hospital from April 1, 2017 to March 31, 2021. This study was approved by the Institutional Review Board and conducted according to the guidelines of Declaration of Helsinki. Before receiving the 5 mg twice-daily immediate-release TOF formulation, all patients had manifested inadequate therapeutic responses to methotrexate for at least 6 mo, having received a weekly dosage of up to 15 mg and at least one conventional synthetic disease-modifying anti-rheumatic drug (DMARD) at an adequate daily dosage. In addition, low-dose prednisolone was selectively prescribed (daily dosage of no more than 10 mg). Furthermore, patients were excluded from this study if they had previous exposure to targeted synthetic DMARDs treatment or were known to have diabetes, endocrine abnormalities, or critical medical disorders involving heart, lung, liver, and kidney.

***Data collection and measurements***

A detailed review was performed to collect data on the patients’ demographic, clinical, laboratory and medication profiles. In addition to body mass index (BMI), clinical data included the 28-joint Disease Activity Score (DAS28) for RA activity[27], classifying as high (> 5.1), moderate (3.2-5.1) or low activity (2.6-3.2) and remission (< 2.6)[28]. Laboratory parameters included rheumatoid factor (RF)/anti-citrullinated peptide antibody (ACPA), C-reactive protein/erythrocyte sedimentation rate, and fasting blood levels of glucose and insulin. Seropositive RA was defined by the presence of either ACPA or RF. In addition to TOF, medication profiles were reviewed for use of prednisolone, conventional synthetic DMARDs with cyclosporin, hydroxychloroquine, leflunomide and sulfasalazine, and biologic synthetic DMARDs with abatacept, adalimumab (ADA), etanercept (ETA), golimumab (GOL), rituximab, and TCZ. For the calculation of IR, HOMA-IR, insulin (μU/mL) × glucose (mg/dL)/405, and Quantitative Insulin Sensitivity Check Index (QUICKI), 1/(log insulin (μU/mL) + glucose (mg/dL) were used in this study. The baseline HOMA-IR levels before TOF therapy were used to classify patients into high-IR (> 2.0) and low-IR (≤ 2.0) groups[7,29]. HOMA-IR and QUICKI measurements were obtained from all participants before and after a 24-wk therapeutic period. Furthermore, in the high-IR group, serial calculation data were available in selected patients before and after the TOF treatment.

***Statistical analyses***

Results were expressed as the mean ± SD. Serial HOMA-IR levels before and after starting TOF therapy were compared with the two-way analysis of variance with a post-hoc test. DAS28, HOMA-IR and QUICKI levels before and after a 24-wk therapeutic period were compared by using the Wilcoxon signed rank test. Different values and frequencies between high-IR and low-IR groups were compared using the Mann-Whitney and the chi-square/Fisher’s exact tests, respectively. Spearman correlation coefficient test was used to correlate DAS28 values and HOMA-IR levels. A *P* value less than 0.05 was considered as significant in this study.

**RESULTS**

***Baseline characteristics of active RA patients before TOF therapy***

Fifty-six patients with 84% females and 88% seropositivity, aged 30 years to 75 years (52.3 ± 11.1 years), received TOF therapy for no less than 6 mo. They had BMI ranging from 19.2 kg/m2 to 26.3 kg/m2 (22.6 ± 2.0 kg/m2), following the obesity definition of at least 27 kg/m2 by the Ministry of Health and Welfare, Taiwan. Their DAS28 values varied from 4.54 to 7.37 (5.82 ± 0.74), all with moderate to high activity. None had exposure to JAKi or succumbed to diabetes, endocrine or critical medical disorders involving major organs, fulfilling the selection criteria in this study.

Before the TOF treatment, 30 patients were naïve to biologic synthetic DMARDs therapy, and their DAS28 values varied from 5.16 to 7.37 (6.291 ± 0.530), all with high disease activity. Table 1 shows the demographic, clinical, laboratory and medication data for 30 naïve patients, classified into high- (*n* = 18) and low-IR (*n* = 12) groups according to their baseline HOMA-IR levels. There were no differences between high- and low-IR groups regarding age, sex, BMI, seropositivity and medication profile with prescription frequencies of various conventional synthetic DMARDs and low-dose prednisolone, as well as weekly methotrexate or daily/total prednisolone dosages. Before TOF therapy, there was a positive correlation between DAS28 values and HOMA-IR levels (*r* = 0.379, *P* = 0.039; Figure 1A), whereas a negative correlation was found between DAS28 values and QUICKI levels (*r* = -0.423, *P* = 0.020). Furthermore, higher DAS28 values were found in the high-IR group compared to the low-IR group (6.499 ± 0.472 *vs* 5.980 ± 0.470, *P* = 0.008), indicating that IR is driven by disease activity in RA patients[7,30]. Notably, there were no changes in the patients’ medication profiles during the 24-wk therapeutic period, with the exception of additional use of TOF.

In addition, 2 patients had an episode of single-dermatome herpes zoster (HZ) infection, both of which responded to valacyclovir therapy, with an incidence rate of 3.03 *per* 100 person-years. There is a general increased risk of HZ infection in RA patients[31], but especially in those receiving specific immunosuppressive therapy, including prednisolone (no less than 10 mg/d), methotrexate and anti-TNF-α biologics[32]. Interestingly, by analyzing health plan data from the United States, TOF-treated RA patients show an incidence rate of 3.87 *per* 100 person-years in HZ infection[33].

***Effects of TOF therapy on IR in 30 active RA patients naïve to biologics***

For 3 patients in the high-IR group, there were serial HOMA-IR calculations available for baseline at week 0 and after starting TOF therapy at weeks 4, 8, 12 and 24 (Figure 1B). In comparison with baseline levels, these patients who were naïve to biologics showed significantly lower levels only at week 24 but not at weeks 4, 8 or 12 (Figure 1B, week 0 *vs* weeks 24, 5.243 ± 0.571 *vs* 3.433 ± 0.664, *P* < 0.01). Further comparison with baseline HOMA-IR levels was carried out at week 24.

The levels of HOMA-IR and QUICKI before and after TOF therapy in the high-IR and the low-IR groups are shown in Table 2 and Figure 2. There were significantly reduced DAS28 values in both the high-IR and low-IR groups after the 24-wk TOF treatment (high-IR: 6.499 ± 0.472 *vs* 3.006 ± 0.445, *P* < 0.001; low-IR: 5.980 ± 0.470 *vs* 3.244 ± 0.614, *P* < 0.001). Significantly decreased HOMA-IR levels were found in the high-IR group (3.331 ± 1.036 *vs* 2.292 ± 0.707, *P* < 0.001; Figure 2B) but not in the low-IR group (1.602 ± 0.294 *vs* 1.430 ± 0.293, *P* = 0.139; Figure 2C), while significantly increased QUICKI levels were observed in the high-IR group (0.3207 ± 0.0135 *vs* 0.3397 ± 0.0154, *P* < 0.001; Figure 2E) but not in the low-IR group (0.3573 ± 0.0117 *vs* 0.3634 ± 0.0122, *P* = 0.156; Figure 2F). Furthermore, reduced HOMA-IR levels were observed in 17 patients in the high-IR group, while 7 patients in the low-IR group had a reduction in IR (high-IR *vs* low-IR: 94.4% *vs* 58.3%, *P* = 0.026). Despite observing no reduced IR after the TOF treatment in the low-IR group, a greater decrease in the values of DAS28 was found in 7 patients with decreased HOMA-IR levels, compared to 5 patients who showed no decrease (2.977 ± 0.237 *vs* 2.529 ± 0.362, *P* = 0.018), implicating reduced IR involvement in the responses to TOF therapy in active RA patients.

***Effects of TOF therapy on IR in 26 active RA patients exposed to biologics***

Before TOF therapy, 26 patients had been exposed to biologic synthetic DMARDs for at least 6 mo; the DMARDs included ADA, ETA, GOL and TCZ. This group of patients was consisted of 85% females, 89% with seropositivity, ages 40 years to 75 years (54.7 ± 10.6) and BMI 19.2 to 26.2 (22.96 ± 2.02). Their DAS28 values varied from 4.54 to 6.74 (5.265 ± 0.547), lower than that in those naïve to biologics (5.16 to 7.37, 6.291 ± 0.530, *P* < 0.001). The patients were divided into high- (*n* =19) and low-IR (*n* = 7) groups according to the baseline levels of HOMA-IR. All patients received methotrexate, while 5 patients in the high-IR group and 1 patient in the low-IR group received low-dose prednisolone therapy. No differences were found in the prescription frequencies of conventional synthetic DMARDs and low-dose prednisolone between two groups of patients.

The levels of HOMA-IR and QUICKI before and after TOF therapy in the high-IR and low-IR groups are shown in Table 3 and Figure 3. There were significantly reduced DAS28 values in both the high-IR and low-IR groups after the 24-wk TOF treatment (high-IR; 5.316 ± 0.807 *vs* 3.070 ± 0.466, *P* < 0.001; low-IR: 5.124 ± 0.470 *vs* 3.000 ± 0.672, *P* = 0.016). Significantly decreased HOMA-IR levels were found in the high-IR group (2.924 ± 0.790 *vs* 2.545 ± 1.080, *P* = 0.018; Figure 3B) but not in the low-IR group (1.527 ± 0.159 *vs* 1.453 ± 0.478, *P* = 0.781; Figure 3C), while significantly increased QUICKI levels were observed in the high-IR group (0.3273 ± 0.0117 *vs* 0.3372 ± 0.0214, *P* = 0.008; Figure 3E) but not the in low-IR group (0.3589 ± 0.0059 *vs* 0.3648 ± 0.0204, *P* = 0.813; Figure 2F).

**DISCUSSION**

In this retrospective study, active RA patients receiving a 24-wk TOF treatment had significantly reduced IR among those with high baseline HOMA-IR levels. Furthermore, the clinical use of biologic synthetic DMARDs, including IL-6 and TNF-α blockers, has been demonstrated to reduce IR in non-diabetic active RA patients[22]. For patients with high IR before TOF therapy, baseline HOMA-IR levels were greater in those naïve to biologic agents than in those with an exposure history to anti-IL-6/TNF-α blocker (3.331 ± 1.036 *vs* 2.924 ± 0.790), while after therapy, there was a decrease in HOMA-IR levels with higher magnitude in naïve than exposed patients (31% *vs* 13% reduction, respectively). These results demonstrated, in this study, the effect of prescribed biologics on IR in active RA patients before TOF therapy. In addition to type 2 diabetes, IR is a crucial pathophysiological feature of obesity, with both conditions being characterized by persistent low-grade inflammation with increased levels of proinflammatory cytokines[34]. A reduction in IR has been identified in RA patients with a normal weight but not in those with obese status under anti-TNF-α therapy[35]. Despite no identified obesity in the present investigation (all patients had BMI < 27 kg/m2), there were higher BMI levels for patients without IR reduction (*n* = 7) when compared to those with reduced IR (*n* = 30) in the high-IR group of patients naïve or exposed to biologic therapy (without *vs* with IR reduction: 24.53 ± 2.07 *vs* 22.49 ± 1.91 kg/m2,*P*= 0.019), reflecting an influence of increased BMI on IR.

Recent investigations have indicated that when prescribed chronically, glucocorticoid (GC) can impair glucose tolerance and induce IR through stimulation of hepatic gluconeogenesis, alteration of insulin release from pancreatic β cells, and decrease in the sensitivity of the liver and muscle to insulin[36]. Since GC therapy is associated with a risk of developing type 2 diabetes, the EULAR recommends to wean RA patients off prednisolone use as early as possible[37]. Although methotrexate may enhance the actions of insulin on glucose transport and metabolism by increasing the extracellular concentration of adenosine, a retrospective study with 21340 RA patients under a 12-year follow-up demonstrated that the risk of type 2 diabetes was not lower with the use of methotrexate[38]. Hydroxychloroquine has beneficial effects on the release and sensitivity of insulin, and a multicenter prospective study with 4950 RA patients showed a lower risk of developing type 2 diabetes in those receiving hydroxychloroquine treatment[39]. In this study, only 14 patients (25%) received low-dose prednisolone prescription before TOF therapy, and most of them (86%) had reduced HOMA-IR levels after therapy. Furthermore, there were no differences in the prescription frequencies and the dosages of various conventional synthetic DMARDs between the two patient groups with different baseline IRs, and their medication profiles were stable throughout the therapeutic period. In the present investigation, the effects of 24-wk TOF therapy on IR reduction could be identified in RA patients with high baseline DAS28 values and HOMA-IR levels. Notably, reduced IR in active RA only with high baseline IR has been demonstrated by studies with IR classification occurring before anti-IL-6 or anti-TNF-α therapy[7,11,35,40-42].

Accumulated evidence has indicated that the JAK-STAT pathway is required for normal homeostasis of metabolic processes, and when it is dysregulated it contributes to the development of obesity and diabetes type 2 associated with chronic low-grade inflammatory response[43]. Numerous investigations have found the involvement of JAK-STAT signaling in peripheral metabolic organs with adipose, liver, muscle and pancreas, and in diabetes types 1 and 2[44]. A crucial role of JAK signaling, involving JAK2 in particular, has been recognized in regulating metabolic processes with glucose tolerance, insulin sensitivity and adiposity through studies using conditional genetic ablation mouse models. Mice with hepatocyte-specific deletion of JAK2 had reduced adiposity, increased pancreatic β-cell mass and complete protection against high-fat diet (HFD)-induced IR and glucose intolerance[45]. Mice with adipocyte-specific loss of JAK2 showed increased insulin sensitivity and resistance to HFD-induced metabolic inflammation[46]. Furthermore, besides an involvement in the activation of cytokine signaling pathways, the JAK-STAT pathway has been shown to regulate the function and survival of the β cells[43,44]. In the non-obese diabetic mouse model, disruption of STAT1 could inhibit interferon-γ-induced β cell apoptosis[47], while treating mice with a JAK1/JAK2 inhibitor reversed diabetes through blockade of the MHC class I upregulation on β cells[48]. Notably, experiments with diabetic animal models have demonstrated that systemic administration of TOF, a pan-JAKi, could normalize impaired glucose tolerance and insulin response in Lnk deficient mice, and reduce IR and improve β-cell function in fructose/streptozotocin-induced rats[49,50]. In this clinical study, oral TOF therapy showed a beneficent effect on IR reduction in active RA patients. In sum, these findings implicate JAK-STAT signaling as a pharmacological target in diabetes and the potential for JAKi use in treating diabetic patients.

**CONCLUSION**

In this retrospective study, we observed a reduction of IR following 24-wk TOF therapy with 5 mg twice-daily immediate-release formulation in non-diabetic RA patients with active disease. Further prospective studies can be performed in both non-diabetic patients and those with comorbid diabetes to clearly elucidate the effect of TOF on IR in active RA.

**ARTICLE HIGHLIGHTS**

***Research background***

An increased risk of insulin resistance (IR) has been identified in rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of pathogenic cytokines. Biologics targeting proinflammatory cytokines can control the disease and improve insulin sensitivity in RA.

***Research motivation***

Although Janus kinase (JAK) signaling can regulate cytokine receptors and participate in RA pathogenesis, it remains to be elucidated whether there is a reduction of IR in such patients under JAK inhibitor (JAKi) therapy.

***Research objectives***

This study examined the effect of JAKi treatment on the reduction of IR in RA with active disease.

***Research methods***

A retrospective study was carried out in non-diabetic active RA patients under tofacitinib (TOF) therapy with 5 mg twice-daily immediate-release formulation from 2017 to 2021.

***Research results***

Fifty-six RA patients aged 30 years to 75 years (52.3 ± 11.1) with DAS 28 values 4.54 to 7.37 (5.82 ± 0.74), were classified into high- and low-IR groups based on the baseline homeostatic model assessment (HOMA)-IR levels. For the 30 patients naive to biologics, after a 24-wk therapeutic period, reduced levels of HOMA-IR were observed in the high-IR group (3.331 ± 1.036 *vs* 2.292 ± 0.707, *P* < 0.001). In another 26 patients exposed to tumor necrosis factor-α or interleukin-6 blockers, despite showing a decrease with lower magnitude than that observed in the naïve patients, reduced HOMA-IR levels were also identified in the high-IR group (2.924 ± 0.790 *vs* 2.545 ± 1.080, *P* = 0.018).

***Research conclusions***

In this retrospective study, our results demonstrated reduced IR following 24-wk TOF therapy in non-diabetic active RA patients.

***Research perspectives***

Further prospective studies can be performed in both non-diabetic patients and those with comorbid diabetes to clearly elucidate the effect of TOF on IR in active RA.

**ACKNOWLEDGEMENTS**

The authors are indebted to all of the doctors/nurses involved in the management of RA patients at the National Cheng Kung University Hospital (NCKUH). The statistical analyses of this study were performed with help from the Biostatistics Consulting Center at the NCKUH.

**REFERENCES**

1 **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]

2 **Saltiel AR**. Insulin signaling in health and disease. *J Clin Invest* 2021; **131** [PMID: 33393497 DOI: 10.1172/JCI142241]

3 **Khodabandehloo 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: 26408801 DOI: 10.1016/j.trsl.2015.08.011]

4 **Nicolau J**, Lequerré 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]

5 **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]

6 **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]

7 **Wang CR**, Liu MF. Recombinant Soluble TNF-α Receptor Fusion Protein Therapy Reduces Insulin Resistance in Non-Diabetic Active Rheumatoid Arthritis Patients. *ACR Open Rheumatol* 2020; **2**: 401-406 [PMID: 32530139 DOI: 10.1002/acr2.11157]

8 **Fasshauer M**, Kralisch S, Klier M, Lossner U, Bluher M, Klein J, Paschke R. Insulin resistance-inducing cytokines differentially regulate SOCS mRNA expression via growth factor- and Jak/Stat-signaling pathways in 3T3-L1 adipocytes. *J Endocrinol* 2004; **181**: 129-138 [PMID: 15072573 DOI: 10.1677/joe.0.1810129]

9 **Rehman K**, Akash MSH, Liaqat A, Kamal S, Qadir MI, Rasul A. Role of Interleukin-6 in Development of Insulin Resistance and Type 2 Diabetes Mellitus. *Crit Rev Eukaryot Gene Expr* 2017; **27**: 229-236 [PMID: 29199608 DOI: 10.1615/CritRevEukaryotGeneExpr.2017019712]

10 **Schultz O**, Oberhauser F, Saech J, Rubbert-Roth A, Hahn M, Krone W, Laudes M. Effects of inhibition of interleukin-6 signalling on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. *PLoS One* 2010; **5**: e14328 [PMID: 21179199 DOI: 10.1371/journal.pone.0014328]

11 **Mirjafari HW,** Wang J, Klearman M, Harari O, Bruce I. FRI0132: Insulin resistance is improved by tocilizumab therapy in rheumatoid arthritis: results from the toward study. *Ann Rheum Dis* 2013; **72:** A12-A15 [DOI: 10.1136/annrheumdis-2013-eular.1259]

12 **Chen DY**, Chen YM, Hsieh TY, Hsieh CW, Lin CC, Lan JL. Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. *Arthritis Res Ther* 2015; **17**: 52 [PMID: 25889426 DOI: 10.1186/s13075-015-0559-8]

13 **Castañeda S**, Remuzgo-Martínez S, López-Mejías R, Genre F, Calvo-Alén J, Llorente I, Aurrecoechea E, Ortiz AM, Triguero A, Blanco R, Llorca J, González-Gay MA. Rapid beneficial 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]

14 **Gao Z**, Hwang D, Bataille F, Lefevre M, York D, Quon MJ, Ye J. Serine phosphorylation of insulin receptor substrate 1 by inhibitor kappa B kinase complex. *J Biol Chem* 2002; **277**: 48115-48121 [PMID: 12351658 DOI: 10.1074/jbc.M209459200]

15 **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]

16 **Ruscitti P**, Masedu F, Alvaro S, Airò P, Battafarano N, Cantarini L, Cantatore FP, Carlino G, D'Abrosca V, Frassi M, Frediani B, Iacono D, Liakouli V, Maggio R, Mulè R, Pantano I, Prevete 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]

17 **Ruscitti P**, Ursini F, Cipriani P, Greco M, Alvaro S, Vasiliki L, Di Benedetto P, Carubbi F, Berardicurti 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]

18 **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]

19 **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]

20 **Schwartz DM**, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017; **17**: 78 [PMID: 29282366 DOI: 10.1038/nrd.2017.267]

21 **T Virtanen A**, Haikarainen T, Raivola J, Silvennoinen O. Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. *BioDrugs* 2019; **33**: 15-32 [PMID: 30701418 DOI: 10.1007/s40259-019-00333-w]

22 **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**: 238-260 [PMID: 33758645 DOI: 10.4239/wjd.v12.i3.238]

23 **Migita K**, Izumi Y, Jiuchi Y, Kozuru H, Kawahara C, Izumi M, Sakai T, Nakamura M, Motokawa S, Nakamura T, Kawakami A. Effects of Janus kinase inhibitor tofacitinib on circulating serum amyloid A and interleukin-6 during treatment for rheumatoid arthritis. *Clin Exp Immunol* 2014; **175**: 208-214 [PMID: 24665995 DOI: 10.1111/cei.12234]

24 **Li Y**, Yuan L, Yang J, Lei Y, Zhang H, Xia L, Shen H, Lu J. Changes in Serum Cytokines May Predict Therapeutic Efficacy of Tofacitinib in Rheumatoid Arthritis. *Mediators Inflamm* 2019; **2019**: 5617431 [PMID: 31780862 DOI: 10.1155/2019/5617431]

25 **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]

26 **Aletaha D**, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62**: 2569-2581 [PMID: 20872595 DOI: 10.1002/art.27584]

27 **Smolen JS**, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum* 1995; **38**: 38-43 [PMID: 7818569 DOI: 10.1002/art.1780380106]

28 **Singh JA**, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T; American College of Rheumatology. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2016; **68**: 1-25 [PMID: 26545825 DOI: 10.1002/acr.22783]

29 **Pfützner A**, Kunt T, Hohberg C, Mondok A, Pahler S, Konrad T, Lübben G, Forst T. Fasting intact proinsulin is a highly specific predictor of insulin resistance in type 2 diabetes. *Diabetes Care* 2004; **27**: 682-687 [PMID: 14988285 DOI: 10.2337/diacare.27.3.682]

30 **Gallagher L**, Cregan S, Biniecka M, Cunningham C, Veale DJ, Kane DJ, Fearon U, Mullan RH. Insulin-Resistant Pathways Are Associated With Disease Activity in Rheumatoid Arthritis and Are Subject to Disease Modification Through Metabolic Reprogramming: A Potential Novel Therapeutic Approach. *Arthritis Rheumatol* 2020; **72**: 896-902 [PMID: 31840936 DOI: 10.1002/art.41190]

31 **Yun H**, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, Saag KG, Singh J, Curtis JR. Risk of Herpes Zoster in Autoimmune and Inflammatory Diseases: Implications for Vaccination. *Arthritis Rheumatol* 2016; **68**: 2328-2337 [PMID: 26990731 DOI: 10.1002/art.39670]

32 **Liao TL**, Chen YM, Liu HJ, Chen DY. Risk and severity of herpes zoster in patients with rheumatoid arthritis receiving different immunosuppressive medications: a case-control study in Asia. *BMJ Open* 2017; **7**: e014032 [PMID: 28057661 DOI: 10.1136/bmjopen-2016-014032]

33 **Curtis JR**, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016; **75**: 1843-1847 [PMID: 27113415 DOI: 10.1136/annrheumdis-2016-209131]

34 **Johnson AM**, Olefsky JM. The origins and drivers of insulin resistance. *Cell* 2013; **152**: 673-684 [PMID: 23415219 DOI: 10.1016/j.cell.2013.01.041]

35 **Stavropoulos-Kalinoglou A**, Metsios 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**: R160 [PMID: 22765047 DOI: 10.1186/ar3900]

36 **van Raalte DH**, Brands M, van der Zijl NJ, Muskiet MH, Pouwels PJ, Ackermans MT, Sauerwein HP, Serlie MJ, Diamant M. Low-dose glucocorticoid treatment affects multiple aspects of intermediary metabolism in healthy humans: a randomised controlled trial. *Diabetologia* 2011; **54**: 2103-2112 [PMID: 21562755 DOI: 10.1007/s00125-011-2174-9]

37 **Peters MJ**, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, McInnes IB, Haentzschel H, Gonzalez-Gay MA, Provan S, Semb A, Sidiropoulos P, Kitas G, Smulders YM, Soubrier M, Szekanecz Z, Sattar N, Nurmohamed MT. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010; **69**: 325-331 [PMID: 19773290 DOI: 10.1136/ard.2009.113696]

38 **Solomon DH**, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* 2011; **305**: 2525-2531 [PMID: 21693740 DOI: 10.1001/jama.2011.878]

39 **Wasko MC**, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, Ward MM. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 2007; **298**: 187-193 [PMID: 17622600 DOI: 10.1001/jama.298.2.187]

40 **Yazdani-Biuki B**, Stelzl H, Brezinschek HP, Hermann J, Mueller T, Krippl 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]

41 **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: 15458960 DOI: 10.1136/ard.2004.026534]

42 **Stagakis I**, Bertsias G, Karvounaris S, Kavousanaki M, Virla D, Raptopoulou A, Kardassis D, Boumpas DT, Sidiropoulos 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]

43 **Gurzov EN**, Stanley WJ, Pappas EG, Thomas HE, Gough DJ. The JAK/STAT pathway in obesity and diabetes. *FEBS J* 2016; **283**: 3002-3015 [PMID: 26972840 DOI: 10.1111/febs.13709]

44 **Dodington DW**, Desai HR, Woo M. JAK/STAT - Emerging Players in Metabolism. *Trends Endocrinol Metab* 2018; **29**: 55-65 [PMID: 29191719 DOI: 10.1016/j.tem.2017.11.001]

45 **Shi SY**, Martin RG, Duncan RE, Choi D, Lu SY, Schroer SA, Cai EP, Luk CT, Hopperton KE, Domenichiello AF, Tang C, Naples M, Dekker MJ, Giacca A, Adeli K, Wagner KU, Bazinet RP, Woo M. Hepatocyte-specific deletion of Janus kinase 2 (JAK2) protects against diet-induced steatohepatitis and glucose intolerance. *J Biol Chem* 2012; **287**: 10277-10288 [PMID: 22275361 DOI: 10.1074/jbc.M111.317453]

46 **Corbit KC**, Camporez JPG, Tran JL, Wilson CG, Lowe DA, Nordstrom SM, Ganeshan K, Perry RJ, Shulman GI, Jurczak MJ, Weiss EJ. Adipocyte JAK2 mediates growth hormone-induced hepatic insulin resistance. *JCI Insight* 2017; **2**: e91001 [PMID: 28194444 DOI: 10.1172/jci.insight.91001]

47 **Bako HY**, 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]

48 **Mori T**, Suzuki-Yamazaki N, Takaki S. Lnk/Sh2b3 Regulates Adipose Inflammation and Glucose Tolerance through Group 1 ILCs. *Cell Rep* 2018; **24**: 1830-1841 [PMID: 30110639 DOI: 10.1016/j.celrep.2018.07.036]

49 **Gysemans CA**, Ladrière L, Callewaert H, Rasschaert J, Flamez D, Levy DE, Matthys P, Eizirik DL, Mathieu C. Disruption of the gamma-interferon signaling pathway at the level of signal transducer and activator of transcription-1 prevents immune destruction of beta-cells. *Diabetes* 2005; **54**: 2396-2403 [PMID: 16046307 DOI: 10.2337/diabetes.54.8.2396]

50 **Trivedi PM**, Graham KL, Scott NA, Jenkins MR, Majaw S, Sutherland RM, Fynch S, Lew AM, Burns CJ, Krishnamurthy B, Brodnicki TC, Mannering SI, Kay TW, Thomas HE. Repurposed JAK1/JAK2 Inhibitor Reverses Established Autoimmune Insulitis in NOD Mice. *Diabetes* 2017; **66**: 1650-1660 [PMID: 28292965 DOI: 10.2337/db16-1250]

**Footnotes**

**Institutional review board statement:** This study was approved by the Ethics Committee of National Cheng Kung University Hospital, No. B-ER-105-108.

**Informed consent statement:** The Institutional Review Board waived the requirement of informed consent from each patient due to the study being classified as a retrospective review of medical records.

**Conflict-of-interest statement:** All theauthors report no relevant conflicts of interest for this article.

**Data sharing statement:** The data of this study can be provided to researchers by the corresponding author upon reasonable request.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** January 14, 2022

**First decision:** April 18, 2022

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** Taiwan

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

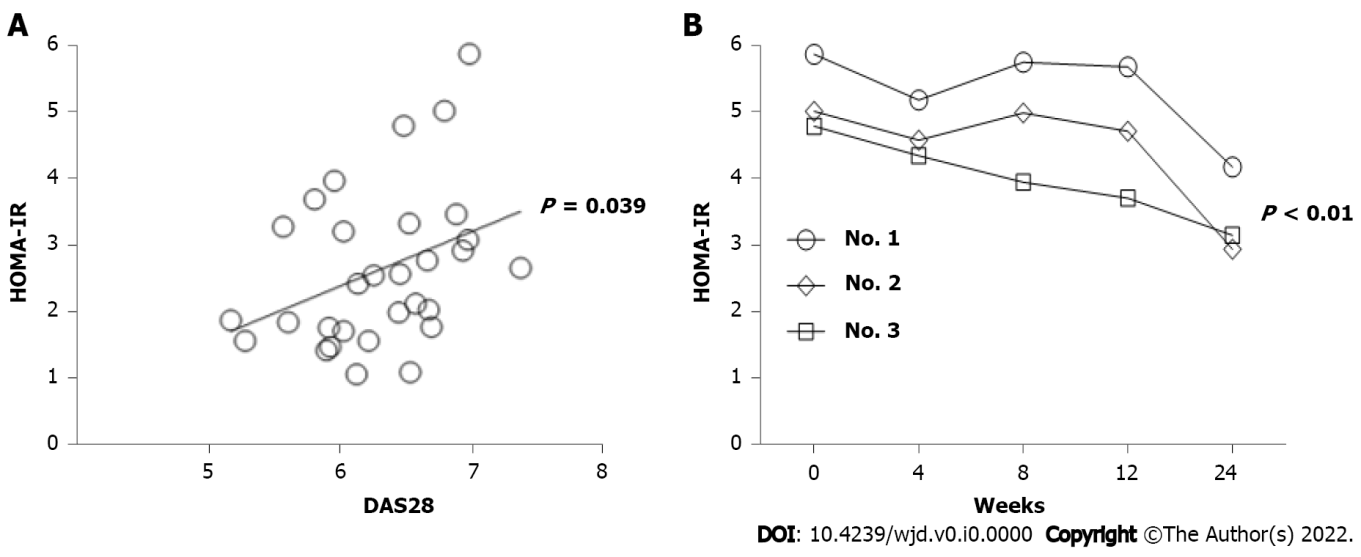
Grade C (Good): 0

Grade D (Fair): 0

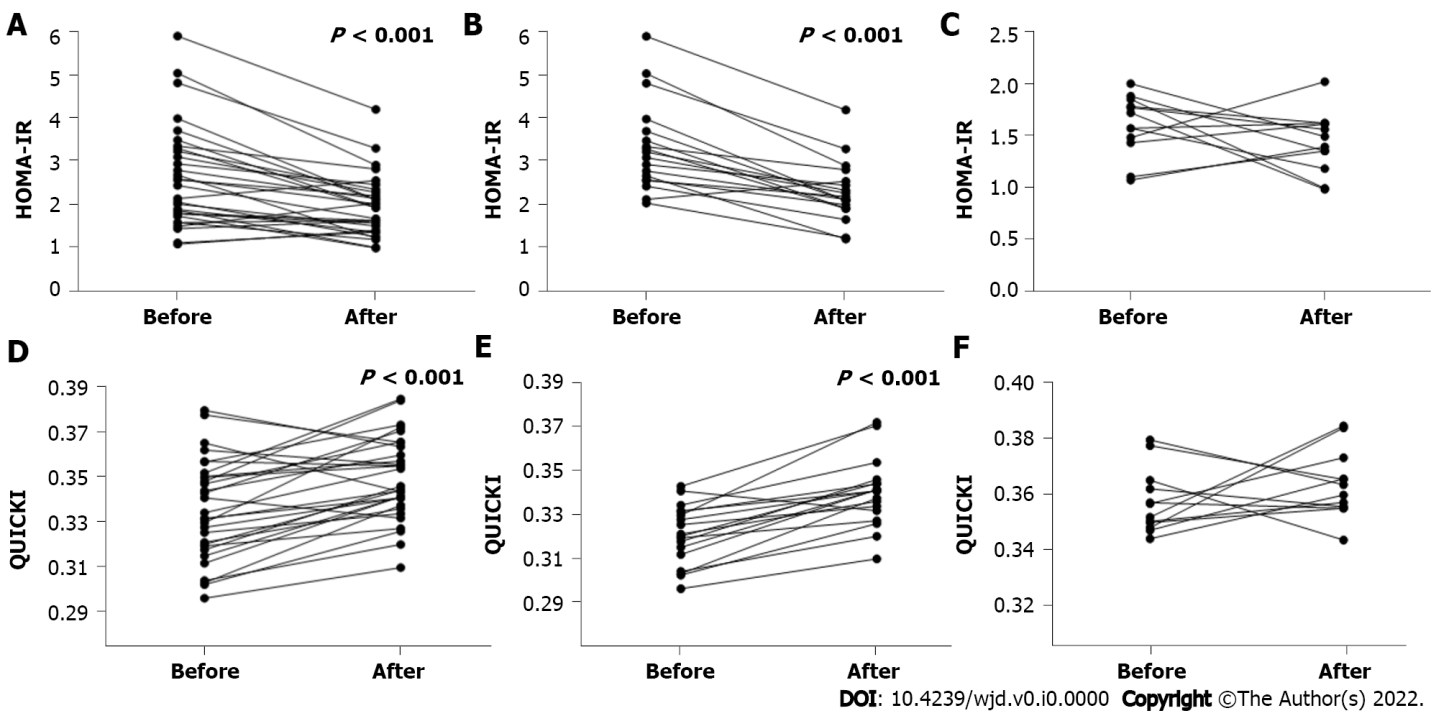
Grade E (Poor): 0

**P-Reviewer:** El-Shishtawy MM, Egypt; Shao JQ, China **A-Editor:** Yao (Online Science Editor) QG, China **S-Editor:** Fan JR **L-Editor:** A **P-Editor:** Fan JR

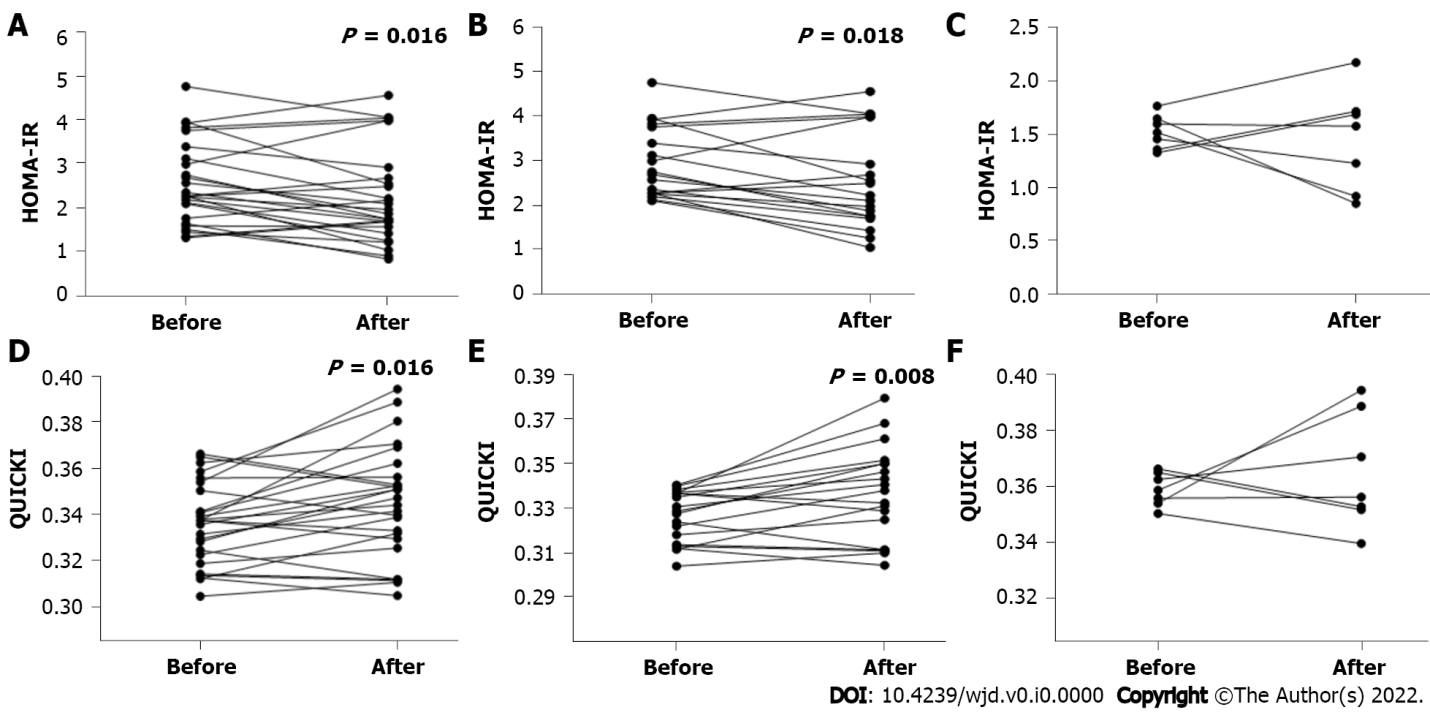
**Figure Legends**



**Figure 1 Characteristics of homeostatic model assessment-insulin resistance** **levels in active rheumatoid arthritis patients naïve to biologic synthetic disease-modifying anti-rheumatic drugs.** A: Positive correlation between 28-joint disease activity score 28 values and homeostatic model assessment (HOMA)-insulin resistance (IR) levels (*P* = 0.039) before tofacitinib (TOF) therapy; B:Serial calculations of HOMA-IR levels in 3 patients with high baseline IR at weeks 0, 4, 8, 12 and 24 after TOF therapy. There were significantly lower levels at week 24 as compared with those at week 0 (*P* < 0.01). HOMA-TR: Homeostatic model assessment-insulin resistance.



**Figure 2 Homeostatic model assessment-insulin resistance** **and Quantitative Insulin Sensitivity Check Index levels in 30 active rheumatoid arthritis patients naïve to biologic agents before and 24 wk after tofacitinib therapy.** A: Homeostatic model assessment (HOMA)-insulin resistance (IR) levels in all 30 patients at weeks 0 and 24 after tofacitinib (TOF) therapy (*P* < 0.001); B: HOMA-IR levels in the high-IR group with 18 patients at weeks 0 and 24 after TOF therapy (*P* < 0.001); C: HOMA-IR levels in the low-IR group with 12 patients at weeks 0 and 24 after TOF therapy; D: Quantitative Insulin Sensitivity Check Index (QUICKI) levels in all 30 patients at weeks 0 and 24 after TOF therapy (*P* < 0.001); E: QUICKI levels in the high-IR group with 18 patients at weeks 0 and 24 after TOF therapy (*P* < 0.001); F: QUICKI levels in the low-IR group with 12 patients at weeks 0 and 24 after TOF therapy. QUICKI: Quantitative Insulin Sensitivity Check Index; HOMA-TR: Homeostatic model assessment-insulin resistance.



**Figure 3 Homeostatic model assessment-insulin resistance** **and Quantitative Insulin Sensitivity Check Index levels in 26 active rheumatoid arthritis patients exposed to biologic agents before and 24 wk after tofacitinib therapy.** A: Homeostatic model assessment (HOMA)-insulin resistance (IR) levels in all 26 patients at weeks 0 and 24 after tofacitinib (TOF) therapy (*P* = 0.016); B: HOMA-IR levels in the high-IR group with 19 patients at weeks 0 and 24 after TOF therapy (*P* = 0.018); C: HOMA-IR levels in the low-IR group with 7 patients at weeks 0 and 24 after TOF therapy; D: Quantitative Insulin Sensitivity Check Index(QUICKI) levels in all 26 patients at weeks 0 and 24 after TOF therapy (*P* = 0.016); E: QUICKI levels in the high-IR group with 19 patients at weeks 0 and 24 after TOF therapy (*P* = 0.008); F: QUICKI levels in the low-IR group with 7 patients at weeks 0 and 24 after TOF therapy. QUICKI: Quantitative Insulin Sensitivity Check Index; HOMA-TR: Homeostatic model assessment-insulin resistance.

**Table 1 Baseline data of 30 active rheumatoid arthritis patients** **naïve to biologics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **All (*n* = 30)** | **High-IR (*n* = 18)** | **Low-IR (*n* = 12)** | ***P* value1** |
| Sex (female %) | 83.3 | 77.8 | 91.7 | 0.622 |
| Age (yr) | 50.3 ± 11.4 (30-74) | 49.2 ± 10.5 (30-65) | 51.8 ± 12.9 (31-74) | 0.445 |
| BMI (kg/m2) | 22.32 ± 1.93 (19.3-26.3) | 22.56 ± 2.15 (19.7-26.3) | 21.97 ± 1.57 (19.3-24.8) | 0.624 |
| Seropositivity (%) | 86.7 | 83.3 | 91.7 | 0.632 |
| DAS28 | 6.291 ± 0.530 (5.16-7.37) | 6.499 ± 0.472 (5.56-7.37) | 5.980 ± 0.470 (5.16-6.69) | 0.008 |
| ESR (mm/h) | 51.7 ± 17.2 (26-88) | 54.4 ± 18.5 (28-88) | 47.6 ± 14.8 (28-70) | 0.279 |
| CRP (mg/L) | 21.20 ± 6.90 (10.4-36.5) | 22.27 ± 7.31 (10.4-36.5) | 19.71 ± 6.21 (10.7-29.5) | 0.341 |
| Glucose (mg/dL) | 88.7 ± 8.5 (66-104) | 90.8 ± 9.3 (66-104) | 85.6 ± 6.1 (77-98) | 0.035 |
| Insulin (μU/mL) | 11.870 ± 5.029 (4.64-24.84) | 14.710 ± 4.527 (9.07-24.84) | 7.605 ± 1.410 (4.64-9.14) | < 0.001 |
| HOMA-IR | 2.639 ± 1.185 (1.07-5.89) | 3.331 ± 1.036 (2.04-5.89) | 1.602 ± 0.294 (1.07-2.00) | < 0.001 |
| QUICKI | 0.3353 ± 0.0222 (0.296-0.380) | 0.3207 ± 0.0135 (0.296-0.343) | 0.3573 ± 0.0117 (0.344-0.380) | < 0.001 |
| Methotrexate (%) | 100 | 100 | 100 | 1.0 |
| Dosage (mg/wk) | 15 | 15 | 15 | 1.0 |
| Prednisolone (%) | 26.7 | 22.2 | 33.3 | 0.678 |
| Daily dosage2 (mg/d) | 5.6 ± 1.8 | 6.3 ± 2.5 | 5.0 ± 0.0 | 1.0 |
| Total dosage3 (mg) | 865.6 ± 258.4 | 887.5 ± 386.5 | 843.8 ± 71.8 | 0.914 |
| Hydroxychloroquine (%) | 100 | 100 | 100 | 1.0 |
| Sulfasalazine (%) | 20.0 | 16.7 | 25.0 | 0.660 |
| Leflunomide (%) | 10.0 | 11.1 | 8.3 | 1.0 |

1High-IR *vs* Low-IR.

2Average daily prednisolone dosage in 1-mo period before enrolment into this study.

3Total exposure of prednisone dosages in 6-mo period before enrolment into this study.

HOMA-IR: Homeostatic model assessment-insulin resistance; QUICKI: Quantitative Insulin Sensitivity Check Index; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: Disease Activity Score 28.

**Table 2** **Insulin resistance change in 30 active rheumatoid arthritis patients naïve to biologics by tofacitinib therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group** | **Before** | **After** | ***P* value1** |
| All (*n* = 30) |  |  |  |
| DAS28 | 6.291 ± 0.530 (5.16-7.37) | 3.101 ± 0.522 (2.08-4.21) | < 0.001 |
| Decrease in DAS28 |  | 3.194 ± 0.609 (1.94-4.36) |  |
| HOMA-IR | 2.639 ± 1.185 (1.07-5.89) | 1.947 ± 0.714 (0.98-4.19) | < 0.001 |
| QUICKI | 0.3353 ± 0.0222 (0.296-0.380) | 0.3492 ± 0.0183 (0.310-0.385) | < 0.001 |
| High IR (*n* = 18) |  |  |  |
| DAS28 | 6.499 ± 0.472 (5.56-7.37) | 3.006 ± 0.444 (2.52-4.21) | < 0.001 |
| Decrease in DAS28 |  | 3.499 ± 0.536 (2.36-4.36) |  |
| HOMA-IR | 3.331 ± 1.036 (2.04-5.89) | 2.292 ± 0.707 (1.21-4.19) | < 0.001 |
| QUICKI | 0.3207 ± 0.0135 (0.296-0.343) | 0.3397 ± 0.0154 (0.310-0.372) | < 0.001 |
| Low IR (*n* = 12) |  |  |  |
| DAS28 | 5.980 ± 0.470 (5.16-6.69) | 3.244 ± 0.614 (2.08-3.99) | < 0.001 |
| Decrease in DAS28 |  | 2.736 ± 0.389 (1.94-3.23) |  |
| HOMA-IR | 1.602 ± 0.294 (1.07-2.00) | 1.430 ± 0.293 (0.98-2.02) | 0.139 |
| QUICKI | 0.3573 ± 0.0117 (0.344-0.380) | 0.3634 ± 0.0122 (0.343-0.385) | 0.156 |

1Before *vs* after TOF therapy.

HOMA-IR: Homeostatic model assessment-insulin resistance; QUICKI: Quantitative Insulin Sensitivity Check Index; DAS28: Disease Activity Score 28.

**Table 3** **Insulin resistance change in 26 active rheumatoid arthritis patients exposed to biologics by tofacitinib therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Group** | **Before** | **After** | ***P* value1** |
| All (*n* = 26) |  |  |  |
| DAS28 | 5.265 ± 0.547 (4.54-6.74) | 3.051 ± 0.516 (2.11-3.99) | < 0.001 |
| Decrease in DAS28 |  | 2.214 ± 0.688 (1.08-3.49) |  |
| HOMA-IR | 2.548 ± 0.925 (1.33-4.75) | 2.251 ± 1.067 (0.85-4.55) | 0.016 |
| QUICKI | 0.3358 ± 0.0177 (0.305-0.366) | 0.3446 ± 0.0242 (0.305-0.394) | 0.016 |
| High IR (*n* = 19) |  |  |  |
| DAS28 | 5.316 ± 0.807 (4.63-6.74) | 3.070 ± 0.466 (2.42-3.90) | < 0.001 |
| Decrease in DAS28 |  | 2.246 ± 0.672 (1.08-3.49) |  |
| HOMA-IR | 2.924 ± 0.790 (2.10-4.75) | 2.545 ± 1.080 (1.05-4.55) | 0.018 |
| QUICKI | 0.3273 ± 0.0117 (0.305-0.341) | 0.3372 ± 0.0214 (0.305-0.380) | 0.008 |
| Low IR (*n* = 7) |  |  |  |
| DAS28 | 5.124 ± 0.332 (4.54-5.48) | 3.000 ± 0.672 (2.11-3.99) | 0.016 |
| Decrease in DAS28 |  | 2.124 ± 0.778 (1.25-3.33) |  |
| HOMA-IR | 1.527 ± 0.159 (1.33-1.77) | 1.453± 0.478 (0.85-2.18) | 0.781 |
| QUICKI | 0.3589 ± 0.0059 (0.350-0.366) | 0.3648 ± 0.0204 (0.340-0.394) | 0.813 |

1Before *vs* after TOF therapy.

HOMA-IR: Homeostatic model assessment-insulin resistance; QUICKI: Quantitative Insulin Sensitivity Check Index; TOF: Tofacitinib; DAS28: Disease Activity Score 28.