Correspondence on 'Disease activity, cytokines, chemokines and the risk of incident diabetes in rheumatoid arthritis'

We read with interest the article by Baker *et al* evaluating possible associations between the rheumatoid inflammatory process and the incidence of diabetes.[1] In this work, many cytokines were significantly associated with the risk of diabetes, but only interleukin (IL)-1α and IL-6 were independent predictors.[1] Due to the specific study design, the authors did not differentiate between type 1 diabetes (T1D) and type 2 diabetes (T2D), although the prevalence of T1D is expected to be very low, considering the mean age of involved patients.[1] However, despite this limitation, these findings are of considerable interest since they furtherly reinforce the idea of a possible pathogenic loop between the rheumatoid inflammatory process and the glucose derangement, making more difficult the management of both diseases.[2]

In the study by Baker *et al*, IL-1α strongly predicted the occurrence of diabetes.[1] A growing body of evidence suggests the role of IL-1 family in pathogenesis of T2D, inducing to β-cell apoptosis.[2–4] Thus, IL-1 inhibition may be considered a new therapeutic strategy in improving glucose abnormalities, although conflicting results are available in the literature.[5–9] A recent large randomised trial with canakinumab, a human monoclonal antibody targeting IL-1β, did not show a significant reduction on incidence of T2D.[5] Conversely, a strong improvement of glucose derangement was shown following IL-1 inhibition with anakinra, a human IL-1 receptor antagonist blocking both IL-1α and IL-1β, in patients with T2D and in those with both rheumatoid arthritis (RA) and T2D.[6 7] In fact, a persistent reduction of glycated haemoglobin (HbA1c) was reported with anakinra in patients with T2D as well as in those with both RA and T2D.[6–9] Furthermore, patients with both diseases may 'bidirectionally' benefit from anakinra, simultaneously improving both metabolic and articular inflammatory parameters.[2] In a multicentre, open-label, randomised, controlled trial, anakinra induced a significant reduction of HbA1c associated with the achievement of clinical remission or minimal disease activity after 6 months of therapy in patients with RA and T2D.[7] In addition, long-term findings from this study showed that the maintenance of RA remission over time was associated with glucocorticoids discontinuation, thus reducing their metabolic side effects.[9] In fact, the maintenance of remission would reduce the occurrence of T2D, as it is the pivotal goal in managing the cardiometabolic risk in RA.[10] Taking together these observations and the data by Baker *et al*,[1] a possible explanation of the different efficacy of these IL-1 inhibiting agents on T2D could be related to their specific mechanisms of action. Both IL-1α and IL-1β may activate IL-1 type I receptor, thus inducing the inflammatory response. Anakinra, competitively inhibiting both IL-1α and IL-1β with the binding to the cognate receptor, would fully control the IL-1 pathway. Conversely, canakinumab selectively binds IL-1β, but it does not affect either IL-1α or IL-1 receptor antagonist.

In addition, Baker *et al* showed that IL-6, another proinflammatory cytokine, resulted to be a significant predictor of diabetes similarly to IL-1α.[1] This finding confirmed previous data, showing an increased peripheral insulin resistance associated with high levels of IL-6 and furtherly supporting the role of inflammation in glucose derangement.[11] Differently, from IL-1 pathway, mainly involved at β-cell level, the action of IL-6 seems to be more effective in peripheral tissues. IL-6 effects were studied in liver and adipose cells, relevant actors in peripheral insulin activity and resistance.[12 13] IL-6 impaired insulin signalling in cultured hepatocytes, leading to inhibition of insulin-stimulated tyrosine phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 and glycogen synthesis.[12] Furthermore, IL-6 inhibition enhanced the hepatic insulin sensitivity in experimental models (reviewed in Fève and Bastard).[11] Similarly, chronic IL-6 stimulation induced insulin resistance in adipocytes by decreasing the transcription of IRS-1, glucose transporter type 4 and peroxisome proliferator-activated receptor γ, decreasing insulin-stimulated phosphorylation of insulin receptor IRS-1, extracellular signal-regulated kinase (ERK) 1 and ERK2 and reducing insulin-stimulated glucose transport and lipogenesis.[13 14] These metabolic effects may result in increased glucose levels associated with a peripheral insulin resistance. Based on these observations and the data by Baker *et al*,[1] a possible therapeutic strategy to improve peripheral insulin resistance by using IL-6 inhibiting agents has been proposed in patients with RA.[15]

In conclusion, data deriving from the study of Baker *et al* may furtherly reinforce the idea of a pathogenic mutual enhancement between the rheumatoid inflammatory process and the occurrence of diabetes.[1] In addition, these data may highlight the possible therapeutic role of inhibiting proinflammatory cytokines in targeting RA and associated metabolic comorbidity, counteracting a pathogenic vicious loop including glucose derangement and inflammation. Finally, in the era of precision medicine, the presence of T2D could identify a subset of patients with RA likely benefitting of specific cytokines inhibition, possibly reducing the potential failure of therapies and tailoring the medical treatment to the individual characteristics.

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REFERENCES

1 Baker JF, England BR, George M. Disease activity, cytokines, chemokines and the risk of incident diabetes in rheumatoid arthritis. *Ann Rheum Dis* 2021;80:566–72.
2 Giacomelli R, Ruscitti P, Alvaro S, *et al*. IL-1β at the crossroad between rheumatoid arthritis and type 2 diabetes: may we kill two birds with one stone? *Expert Rev Clin Immunol* 2016;12:849–55.
3 Dinarello MY, Mandrup-Poulsen TCA. Targeting innate immune mediators in type 1 and type 2 diabetes. *Nat Rev Immunol* 2019;19:734–46.
4 Berchtold LA, Prause M, Størling J. Mandrup-Poulsen T. cytokines and pancreatic β-cell apoptosis. *Adv Clin Chem* 2016;75:99–158.
5 Everett BM, Donath MY, Pradhan AD, *et al*. Anti-Inflammatory therapy with canakinumab for the prevention and management of diabetes. *J Am Coll Cardiol* 2018;71:2392–401.
6 Larsen CM, Faulenbach M, Vaag A, *et al*. Interleukin-1–Receptor antagonist in type 2 diabetes mellitus. *N Engl J Med* 2007;356:1517–26.
7 Ruscitti P, Masedu F, Alvaro S, *et al*. 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.
8 Larsen CM, Faulenbach M, Vaag A, *et al*. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. *Diabetes Care* 2009;32:1663–8.
9 Ruscitti P, Berardicurti O, Cipriani P. On behalf of track Study Group. benefits of anakinra versus TNF inhibitors in rheumatoid arthritis and type 2 diabetes: long-term findings from participants furtherly followed-up in track study, a multicentre, open-label, randomised, controlled trial. *Clin Exp Rheumatol* 2021.
10 Ruscitti P, Cipriani P, Liakouli V. Occurrence and predictive factors of high blood pressure, type 2 diabetes, and metabolic syndrome in rheumatoid arthritis: findings from a 3-year, multicentre, prospective, observational study. *Clin Exp Rheumatol* 2020.
11 Fève B, Bastard J-P. The role of interleukins in insulin resistance and type 2 diabetes mellitus. *Nat Rev Endocrinol* 2009;5:305–11.
12 Senn JJ, Klover PJ, Nowak IA, *et al*. Interleukin-6 induces cellular insulin resistance in hepatocytes. *Diabetes* 2002;51:3391–9.
13 Lagathu C, Bastard J-P, Auclair M, *et al*. Chronic interleukin-6 (IL-6) treatment increased IL-6 secretion and induced insulin resistance in adipocyte: prevention by rosiglitazone. *Biochem Biophys Res Commun* 2003;311:372–9.
14 Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-α, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* 2003;278:45777–84.
15 Ursini F, Russo E, Ruscitti P, *et al*. The effect of non–TNF-targeted biologics and small molecules on insulin resistance in inflammatory arthritis. *Autoimmun Rev* 2018;17:399–404.