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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Contributors All the authors meet all criteria for authorship in theInternational Committee of Medical Journal Editors (ICMJE) Recommendations. All authors made substantial contributions to the conception or design of the work and the acquisition and interpretation of data, contributed to the critical review and revision of the manuscript, approved the final version and agreed to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Ruscitti P, Sesti G, Cipriani P, *et al*. *Ann Rheum Dis* 2023;**82**:e119.

Received 5 February 2021
Accepted 6 February 2021
Published Online First 22 February 2021

► http://dx.doi.org/10.1136/annrheumdis-2021-220114

Ann Rheum Dis 2023;**82**:e119. doi:10.1136/annrheumdis-2021-220047

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