

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)-1 α 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-1 α 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-1 β , 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-1 α and IL-1 β , 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-1 α and IL-1 β may activate IL-1 type I receptor, thus inducing the inflammatory response. Anakinra, competitively inhibiting both IL-1 α and IL-1 β with the binding to the cognate receptor, would fully control the IL-1 pathway. Conversely, canakinumab selectively binds IL-1 β , but it does not affect either IL-1 α 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-1 α .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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