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Review

Rheumatoid arthritis, insulin resistance, and diabetes

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ABSTRACT

Recent progress in the management of rheumatoid arthritis (RA) is turning attention toward comorbidities, such as diabetes. The objectives of this review are to clarify the links between RA and diabetes and to assess potential effects of disease-modifying antirheumatic drugs (DMARDs) on diabetes. The increased insulin resistance seen in RA is closely linked to the systemic inflammation induced by certain proinflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin-6. The prevalence of type 2 diabetes is increased in patients with RA. Furthermore, certain DMARDs including hydroxychloroquine, methotrexate, TNFα antagonist, and interleukin-1β antagonists seem to improve the markers of glucose metabolism. In contrast, glucocorticoids tend to adversely affect glycemic control, particularly when taken chronically. Consequently, a crucial yet insufficiently applied rule is that cardiovascular risk factors must be sought and treated routinely, particularly as the choice of the DMARD may affect glucose metabolism.

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1. Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with rheumatoid arthritis (RA) [1,2]. Cardiovascular events (e.g., stroke, myocardial infarction, and peripheral arterial disease) are as common in RA as in type II diabetes [3]. The classical cardiovascular risk factors (type II diabetes, hypertension, dyslipidemia, and smoking) do fully account for this excess cardiovascular risk [4], which is largely ascribable to induction by the systemic inflammation of insulin resistance (IR), a known risk factor for cardiovascular disease and type II diabetes [5]. Numerous studies have established that the inflammation mediators involved in RA (e.g., interleukin-6 [IL-6] and tumor necrosis factor alpha [TNFα]) are associated with IR and type II diabetes [6].

The objectives of this review are to clarify the links between RA, IR, and type II diabetes, to discuss genetic associations of RA with type I diabetes, and to evaluate potential effects of disease-modifying antirheumatic drugs (DMARDs) on markers of glucose metabolism.

2. Insulin resistance and rheumatoid arthritis

2.1. Definition of insulin resistance

IR is the need for an increase in insulin release to obtain a quantitatively normal response to the hormone, i.e., as a decrease in the effectiveness of insulin on its target organs. IR plays a central role in the pathophysiology of metabolic syndrome, which is associated with a 2-fold increase in the risk of cardiovascular disease [7]. The reference standard for quantifying IR is the hyperinsulinemic-euglycemic clamp, which is too complicated, however, to be suitable for everyday practice. Among the available alternative methods is the homeostatic model assessment for IR (HOMA-IR) based on mathematical equations that describe the relation between fasting blood glucose and insulin (Box 1).

2.2. Prevalence of insulin resistance in rheumatoid arthritis (RA)

The prevalence of IR is higher in patients with RA than in the general population (51% in recent-onset RA and 58% in longstanding RA vs. 19% in controls) [8–10]. IR in RA is partly ascribable to obesity with an increase in fat mass, the presence of rheumatoid factors (RFs), and the activity of the disease. IR correlates significantly with certain markers for inflammation (TNFα and C-reactive protein [CRP]) [8,11]. In a study of 66 patients with untreated RA

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Box 1: Methods used to measure insulin resistance and insulin sensitivity.

Insulin resistance:

- HOMA-IR: [insulinemia (μU/mL) × glycemia (mmol/L)]/22.5;
- HOMA-IR values > 2.4 indicate insulin resistance.

Insulin sensitivity:

- QUICKI (quantitative insulin sensitivity check index): 1/(log [insulinemia (μU/mL)] + log [glycemia (mmol/L)]).

diagnosed within the past year, IR as assessed by the HOMA-IR was more common and more severe than in the age- and sex-matched controls [12]. In addition, IR was more severe in the patients with high disease activity (DAS 28 > 5.5) compared to those with moderate disease activity (3.6 ≤ DAS 28 ≤ 5.5) [12]. However, IR does not correlate with all proinflammatory cytokines or all rheumatic diseases [10,13]. For instance, IR did not correlate with the severity of inflammation in patients with systemic lupus erythematosus (SLE), despite serum TNFα concentrations similar to those seen in patients with RA [13]. The main contributors to IR were obesity (high body mass index [BMI]) in SLE and serum IL-6 in RA [13]. In another study, however, IR in patients with RA was associated with CRP level, RF positivity, and prednisone therapy but not with serum IL-6 measured at a single point in time [10]. Patients with low IL-6 levels had greater IR compared to age- and sex-matched controls with similar IL-6 levels, and patients with high levels of IL-6 had similar IR compared to controls [10]. The discrepancy between low IL-6 and high IR suggests the presence of non-inflammatory factors responsible for IR [10]. Furthermore, the discrepancy between high IL-6 and IR similar to that in controls may indicate a ceiling to the effect of IL-6 on IR, as suggested for TNFα [10]. However, the single IL-6 assay performed in this study may have only partly captured the effect of IL-6 on IR [10]. Other studies also showed that prolonged exposure to elevated IL-6 levels induced IR, suggesting different mechanisms to IR in SLE and RA [14]. Thus, inflammation may promote IR in addition to other factors such as RF positivity and glucocorticoid therapy.

2.3. *Inflammation and insulin resistance*

Systemic inflammation as measured by TNFα, IL-1β, or IL-6 levels depending on the study increases the risk of developing IR. These cytokines, particularly TNFα, promote the development of atheroma and IR [15–19] (Fig. 1 and Box 2). The mechanism by which TNFα contributes to IR has been clarified. Normally, insulin stimulates the tyrosine kinase activity of its receptor, which phosphorylates various substrates including insulin receptor substrate 1 (IRS-1). Phosphorylated IRS-1 interacts with other proteins, triggering the insulin signaling pathway via phosphorylation of protein kinase B (Akt), thereby stimulating cell growth, glucose transport, glycogen synthesis, gluconeogenesis, and protein synthesis. Binding of TNFα to its receptor activates the sphingomyelinases, triggering interactions between TNFα and insulin signaling pathways. Via the sphingomyelinases, TNFα decreases tyrosine phosphorylation of the insulin receptor and IRS-1 kinase and induces serine phosphorylation of IRS-1, which becomes an insulin receptor inhibitor in adipocytes and skeletal muscle cells. Thus, instead of behaving only as a substrate for the insulin receptor, IRS-1 induces a negative feedback loop that decreases the enzymatic activity of the receptor, thereby inhibiting its signaling pathway (Fig. 1). IR is therefore now viewed as a true cardiovascular risk factor. IR is associated with a 1.7-fold increase in the risk

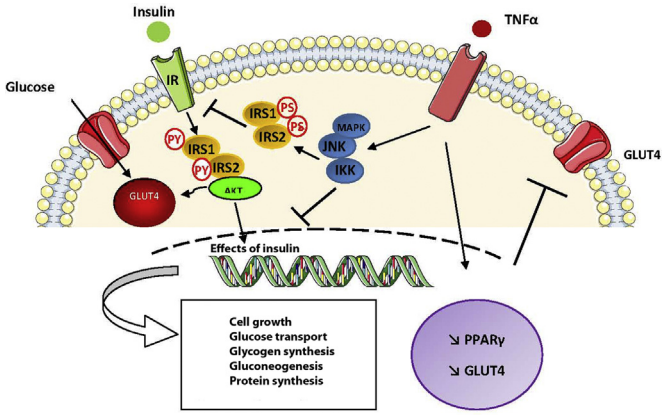

Fig. 1. Changes in the insulin receptor signaling pathway induced by TNFα. Binding of TNFα to its receptor activates the sphingomyelinases, MAP kinases, the NFκB pathway, and protease cascade involved in apoptotic cell death. Via the sphingomyelinases, TNFα modifies the insulin receptor signaling pathway by diverting IRS-1 away from it, thereby inducing insulin resistance. Ir, insulin receptor; Y, tyrosine; S, serine; IRS-1, substrate 1 of the insulin receptor; PI3K, phosphoinositide kinase 3; TNFα, tumor necrosis factor α; IKK, serine kinase IKK; PPARγ, peroxisome proliferator activator-receptor γ; GLUT4, glucose transporter 4.

Box 2: Mechanisms of action of TNFα that promote insulin resistance.

TNFα promotes insulin resistance by:

- inducing the synthesis of SOCS3, an inhibitor of the insulin signaling pathway;
- decreasing the expression of the insulin receptor IRS-1 and of the glucose transporter Glut4;
- inhibiting the synthesis of peroxisome proliferator-activated receptor gamma (PPARγ), which plays a key role in adipogenesis and, therefore, in insulin sensitivity;
- stimulating adipose tissue lipolysis, thus increasing the concentrations of free fatty acids, which inhibit the cellular effects of insulin;
- diminishing the circulating levels of adiponectin, an adipocyte-specific cytokine that normally increases sensitivity to insulin;
- increasing fat mass at the expense of lean mass, thereby promoting the development of insulin resistance.

of cardiovascular disease and makes a major contribution to the development of diabetes type II [20].

3. Diabetes and rheumatoid arthritis

The prevalence of diabetes worldwide was estimated at 8.3% in 2012 [21]. In a British cohort of 11,158 patients with RA followed-up from 1986 to 2010, diabetes had an incidence rate of 6.3/1000 person-years [21]. After adjustment for age, gender, BMI, smoking history, alcohol consumption, glucocorticoid therapy, and comorbidities, the hazard ratio (HR) of developing diabetes in patients with RA compared to age- and sex-matched controls was 0.94 (95% confidence interval [95% CI]: 0.84–1.06) [21]. Thus, the development of diabetes in patients with RA is chiefly ascribable to obesity and lifestyle factors (smoking and alcohol use) [21].

Whether associations with RA differ between diabetes type I and type II deserves discussion. Diabetes type I has been estimated to affect 2.8% of patients with RA. This prevalence is higher in patients with anti-citrullinated peptide antibodies (ACPAs) (odds ratio [OR]: 7.3; 95% CI: 2.7–20.2) [22]. This association between two autoimmune diseases suggests the existence of shared

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