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Antidiabetic effect of disease-modifying antirheumatic drugs

ABSTRACT

Disease-modifying antirheumatic drugs (DMARDs) form the mainstay of treatment for chronic arthritis, slow down progression of the disease and can lead to a state of remission. Most of these drugs are immunosuppressive preparations and biologics. There are reports on effects of these preparations in addition to their anti-inflammatory effect, including antidiabetic effect.

This paper aims to present the currently available results of studies and clinical observations indicating the potential for multidirectional effects of DMARDs, particularly a risk-reducing effect on the development of diabetes and diabetes-dependent complications.

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KEY WORDS: chronic arthritis; disease-modifying antirheumatic drugs; diabetes; treatment; antidiabetic effect

INTRODUCTION

Chronic arthritides, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), are systemic diseases with not only symptoms of musculoskeletal involvement but also symptoms associated with damage to extra-articular organs and tissues, which is caused by a chronic inflammatory process. The co-occurrence of chronic arthritis and cardiovascular diseases, diabetes or depression were observed [1]. It is estimated that diabetes is present in at least 10% of patients with RA, PsA or AS [1].

There is a growing body of data indicating a key role for the inflammatory process in the pathogenesis of type 2 diabetes (T2D) and T2D-dependent organ complications [2]. Findings indicate that a low-grade inflammatory process persists in T2D patients, and is associated with elevated serum levels of acute-phase proteins (e.g. C-reactive protein [CRP]), cytokines (e.g. tumour necrosis factor [TNF]), interleukin-1 (IL-1), interleukin-6 (IL-6), adipocytokines (e.g. visfatin, resistin) and reduced levels of anti-inflammatory adipocytokines that enhance insulin sensitivity (e.g. adiponectin, omentin) [2]. A state of pro-inflammatory responsiveness is observed even before the diagnosis of diabetes, during a period of persistent hyperglycaemia. Therefore, T2D is currently considered an inflammatory disease that is associated with ongoing chronic systemic inflammation and pancreatic islet inflammation, resulting in the development of insulin resistance and pancreatic islet β-cell dysfunction [2].

Insulin resistance, diabetes and other signs of the metabolic syndrome are more frequently observed in patients with chronic arthritis, compared to healthy control, which may be related to the persistence of chronic systemic inflammation and type of therapy used (e.g. glucocorticosteroids [GCs]) [2, 3].

The mainstay of treatment for chronic arthritis is the use of disease-modifying antirheumatic drugs (DMARDs) that slow down progression of the disease and can lead to a state of remission. Most of DMARDs are immunosuppressive preparations and biologics. With their increasing use, there are reports on additional effects of these preparations that can be used in the presence of comorbidities. It appears that DMARDs, in

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addition to their anti-inflammatory effect, may also have the antidiabetic effect by affecting metabolic pathways [2, 3].

This paper aims to present the currently available results of studies and clinical observations indicating the potential for multidirectional effects of DMARDs, particularly a risk-reducing effect on the development of diabetes and diabetes-dependent complications.

REVIEW OF THE RESULTS OF STUDIES AND CLINICAL OBSERVATIONS

The last two decades produced publications presenting the results of studies and clinical observations regarding the effect of DMARD therapy on the risk of developing diabetes in patients with chronic arthritis.

In a prospective, multi-centre observational study in a group of RA patients (approximately 5000 participants), there was an association between treatment with hydroxychloroquine (HCQ) and a reduced risk of developing diabetes. Diabetes risk reduction increased with duration of HCQ therapy. Patients treated with HCQ for more than 4 years had a relative ratio of 0.23 [4], compared to those not taking HCQ.

Several long-term studies found that treatment with TNF inhibitors (TNFi) was associated with improved insulin sensitivity [5, 6]. In RA patients after intravenous infusions (120 min after infusion) of infliximab (IFX), there was a rapid and significant reduction in serum insulin levels and insulin/glucose ratio, as well as a reduction in insulin resistance [5]. Both in RA patients and AS patients there were found improvements in insulin sensitivity as a result of IFX treatment [6].

In a retrospective study conducted among RA or PsA patients (approximately 14 000 participants), the frequency of newly diagnosed cases of diabetes was assessed in relation to the use of DMARD therapy. The hazard ratio (HR) of diabetes was 0.77 for patients treated with methotrexate (MTX), 0.62 for those treated with TNFi and 0.54 for those treated with HCQ — compared to patients treated with other non-biologic DMARDs. The results of an in-depth analysis indicated that initiation of MTX therapy was not associated with a statistically significant reduction in the HR of diabetes. A reduction in the HR of diabetes was confirmed for HCQ therapy and TNFi therapy [7].

In another large prospective study, RA patients (approximately 13 500 participants) were found to have an increased HR of diabetes compared to the general United States adult population. The HR of diabetes associated with DMARD therapy was (compared to MTX monotherapy): 0.67 for those treated with HCQ, 0.52 for those treated with abatacept (ABA). The HR of diabetes in patients treated with GCs was 1.31, while in those treated with statins it was 1.56. Combination treatment of GCs with HCQ did not result in a significant change in the HR of diabetes associated with HCQ treatment (HR = 0.69). Therapy with other synthetic or biologic DMARDs was not associated with a change in the HR of diabetes [3].

Based on data from population-based studies, a retrospective study was conducted in a large group of RA, PsA and AS patients (approximately 85 000 of participants) who started DMARD therapy. It was found that in patients with RA or PsA, compared to those treated with non-biologic DMARDs, the HR of diabetes was significantly lower in patients treated with TNFi in combination with HCQ (HR = 0.49) and those treated with HCQ in monotherapy (HR = 0.7). A reduced HR of diabetes was not reported in patients treated with TNFi in monotherapy (without HCQ) or in those treated with other non-biologic DMARDs, such as cyclosporine A. No reduced HR of diabetes was found in AS patients treated with TNFi and HCQ [8].

In another retrospective study conducted among RA, PsA, AS and diabetic patients (approximately 10 000 patients) who started TNFi, MTX or metformin therapy (positive control), changes in glycated haemoglobin (HbA1c) levels were compared during treatment. The largest reduction in HbA1c levels was found in patients who were on metformin therapy (–0.8) while a significant, but approximately half as large, reduction in HbA1c levels was observed in patients who were treated with MTX (–0.4) and TNFi (–0.35) [1].

A large observational study in RA patients (approximately 50 000 participants) compared the HR of diabetes in patients treated with biologic DMARDs or targeted synthetic DMARDs (tofacitinib [TOFA]). There was a significantly increased HR of diabetes among those who started treatment with adalimumab (ADA) (HR = 2.0), IFX (HR = 2.34) compared to those treated with ABA. The HR of diabetes for those treated with etanercept (ETA) was increased compared to those treated with ABA but not statistically significant

(HR = 1.65). Due to the small number of patients treated with other TNFi or TOFA, it was not possible to obtain a reliable assessment for these drugs [9].

In a large group of patients with RA and diabetes (approximately 10 000 participants) who started therapy with biologic DMARDs (TNFi, rituximab [RTX], tocilizumab [TCZ]) or TOFA, the HR of changing or intensifying diabetes treatment (e.g. by including insulin or another drug) was assessed. The HR of changing antidiabetic treatment was found to be similar for patients treated with ABA *vs.* TNFi (HR = 0.97), RTX (HR = 0.99), and TCZ (HR = 0.94), but lower for TOFA *vs.* ABA (HR = 0.67) [10].

One recent large population-based study conducted among RA patients (approximately 70,000 participants) assessed the HR of diabetes during DMARD therapy. There was a significantly increased HR of diabetes in those treated with statins, GCs (higher risk in the case of higher cumulative dose) and tacrolimus (odds ratio [OR] = 1.27). In contrast, a reduction in the HR of diabetes was found when taking DMARDs for more than 270 days: HCQ (OR = 0.76), MTX (OR = 0.81). Short-term therapy (≤ 90 days/year) with sulfasalazine (SS) or leflunomide (LEF) was associated with an increased HR of diabetes, however, this effect was not observed for long-term (> 270 days/year) treatment with SS or LEF [11].

CONVENTIONAL SYNTHETIC DISEASE--MODIFYING ANTIRHEUMATIC DRUGS

Conventional synthetic DMARDs (csDMARDS) are a group of drugs that are most commonly used in the treatment of chronic arthritis.

ANTIMALARIAL DRUGS

Hydroxychloroquine (HCQ)

Available literature data indicate that HCQ has an antihyperglycaemic effect, thus influencing glucose homeostasis in both non-diabetic and diabetic subjects [2, 12]. Results from observational studies indicate that the use of HCQ significantly reduces the HR of diabetes in patients with chronic arthritis (RA, PsA), systemic lupus erythematosus (SLE) and Sjögren's syndrome [3, 4, 7, 8].

HbA1c levels were assessed in a retrospective study conducted among HCQ- or MTX-treated patients with diabetes and rheumatic diseases. Over 12 months of therapy, there was a reduction in HbA1c levels by 0.11% in the MTX-treated group, while the HCQ-treated group had a reduction in HbA1c levels by 0.66% (by 54% — significantly higher — compared to MTX) [13].

Several short-term randomised trials conducted among T2D patients revealed that the addition of HCQ (at a dose of 400–600 mg/d) to sulfonylurea derivatives or insulin was associated with a significant reduction in HbA1c levels, without increasing the risk of hypoglycaemia [2]. In India, HCQ (400 mg/d) was licensed in 2014 for the treatment of T2D as a third-line drug in cases of poor diabetes control, despite lifestyle adjustments and combination therapy with metformin and sulfonylurea derivatives [2, 14]. As the hypoglycaemic effect increases, doses of insulin or other antidiabetic drugs may need to be reduced [2].

Moreover, HCQ therapy in T2D patients results in an improved lipid profile in the form of a significant reduction in total cholesterol and LDL cholesterol (low-density lipoproteins). Similar observations also apply to RA patients without diabetes, who already had a significant reduction in total cholesterol and LDL cholesterol after 8 weeks of treatment with HCQ at a dose of up to 6.5 mg/kg/day (maximum dose: 600 mg/d). However, the mechanism of HCQ's potential lipid--lowering effect remains unclear and may be due to HCQ's anti-inflammatory effect or may be related to other effects of the drug [12].

A recent meta-analysis found that treatment with HCQ induces improvements in glucose control by lowering fasting glucose levels, lowering glucose levels two hours after a meal and lowering HbA1c levels. There was no significant effect of HCQ on insulin values or the Homeostatic Model Assessment index [14]. Indications are that the mechanism of HCQ's hypoglycaemic effect may be related to inhibition of the dissociation of the insulin-receptor complex, which prolongs the half-life and enhances insulin action, as well as reduces insulin resistance and increases tissue sensitivity to insulin. Experimental studies reveal that HCQ reduces lysosomal degradation of insulin, resulting in an increase in insulin levels and a decrease in glucose levels. In addition, HCQ — by increasing intracellular pH — inactivates a proteolytic enzyme (insulinase), which consequently improves the biological activity of insulin [14].

The immunomodulatory and anti--inflammatory properties of HCQ, together

with a reduction in the production of pro-inflammatory cytokines, may be relevant to the treatment of T2D. Recently, it has been found that 48 weeks after the initiation of HCQ therapy in patients with T2D, glycaemic control was better (although not statistically significant) among patients with baseline higher hs-CRP levels (> 3 mg/L) compared to patients with low hs-CRP levels (≤ 3 mg/L) [15].

In a group of non-diabetic, obese or overweight patients, after approximately 13 weeks of treatment with HCQ (400 mg/d), not only were pancreatic β-cell function and insulin sensitivity improved, but serum adiponectin levels were also increased [16].

According to clinical observations, the tolerability of HCQ treatment is good, excluding gastrointestinal complaints when using an HCQ dose of 400 mg/day or higher. It should be noted that risk factors for adverse effects associated with HCQ therapy include a dose of more than 400 mg/day or more than 6.5 mg/kg of lean body mass/day; a cumulative HCQ dose of more than 1000 g; duration of HCQ use of more than 5 years; impaired liver or renal function; retinopathy preceding therapy or maculopathy [17].

When considering HCQ therapy as a hypoglycaemic drug, it is important to take into account the contraindications present in combination with T2D, such as pre-existing retinopathy or maculopathy, concomitant therapy with oculotoxic drugs, pre-existing cardiomyopathy and/or heart failure, myopathy and/or neuropathy, recurrent episodes of severe hypoglycaemia and/or malnutrition; glucose-6-phosphate dehydrogenase (G6PD) deficiency [2, 12].

Although the precise mechanism of HCQ's hypoglycaemic properties is not entirely clear and may differ between diabetic and non-diabetic patients, results from preclinical and clinical observations indicate that HCQ may have a multidirectional effect on glucose homeostasis. HCQ therapy may induce improved insulin sensitivity in peripheral tissues, increased insulin secretion, reduced hepatic clearance of insulin, reduced intracellular degradation of insulin and insulin-receptor complex, increased production of adiponectin (which has anti-inflammatory effects and improves insulin sensitivity), inhibition of systemic inflammation and/or inflammation-dependent insulin resistance in adipose tissue and skeletal muscle cells [2, 12].

It is likely that HCQ acts directly by stimulating β-cells (insulinotropic action) and/or improving insulin sensitivity (insulin-sensitising action) and indirectly by inhibiting pancreatic islet inflammation (anti-inflammatory action) [2]. The result is a significant reduction in HbA1C levels, fasting and postprandial glucose levels, as well as improvements in insulin levels and lipid profile, as observed in many studies [17].

Chloroquine

Back in the 1990s, it was observed that therapy with chloroquine (CQ) in T2D patients was associated with an increase in insulin levels by increasing insulin secretion and inhibiting insulin degradation, resulting in improved glucose metabolism [18]. According to experimental data, CQ produces a hypoglycaemic effect by inducing glucose uptake and glycogen synthesis in muscle cells via activation of Akt [19].

Studies proved that CQ in T2D patients can improve fasting glucose levels by increasing glucose consumption in peripheral tissues, decreasing hepatic insulin clearance, and increasing endogenous insulin secretion both during fasting and hyperinsulinaemia. CQ appears to exhibit a direct insulinotropic effect on pancreatic β-cells [12].

METHOTREXATE

A meta-analysis of studies revealed that in RA patients, MTX therapy is associated with a 52% reduction in the risk of developing T2D (relative ratio 0.48) compared to patients not treated with MTX. It was found that the greatest reduction in the risk of T2D occurred in MTX-treated patients who were older (> 60 years of age), with shorter duration of RA (≤ 2 years) and longer period of observation (> 5 years), which may be related to the longer duration of exposure to MTX and higher MTX levels in patients [20].

There are emerging data that patients with RA or PsA experience a reduction in HbA1c levels and improved glucose homeostasis as a result of MTX therapy [2, 20]. The mechanism of action of MTX may involve inhibition of the enzyme AICAR formyltransferase, resulting in the accumulation of AICAR substrate and metabolites that inhibit adenosine deaminase and adenosine monophosphate (AMP) deaminase. This leads to an increase in intracellular AICAR monophosphate (ZMP) and AMP levels; ZMP induces kinase (AMPK) on whose

activity the control of glucose homeostasis in diabetes depends. Therefore, by increasing ZMP accumulation and activating AMPK, MTX improves glucose homeostasis [20]. Like metformin, MTX can reduce hepatic production and intestinal absorption of glucose and improve peripheral tissue insulin sensitivity [20].

LEFLUNOMIDE

Leflunomide appears to be a potential insulin sensitivity-improving drug that may have applications in the treatment of patients with chronic arthritis and T2D. In experimental studies, the active metabolite of LEF — A77 1726 — enhanced insulin-stimulated glucose uptake in adipocytes and muscle cells. Moreover, treatment with LEF resulted in normalisation of blood glucose levels, overcoming insulin resistance [2]. These findings need to be confirmed in human studies.

In one population-based study conducted among RA patients (approximately 70 000 participants), LEF treatment with a total exposure time of no more than 90 days/year was associated with an increased risk of developing diabetes. However, this effect was not found for total exposure time of more than 270 days/year. This might have been related to high disease activity and/or the use of GCs in the initial period, shortly after diagnosis of RA [11].

SULFASALAZINE

There were reports of a reduction in HbA1c levels in T2D patients treated with SS, who achieved normoglycaemia after the initiation of this therapy [2]. However, later studies highlighted the association of reduced HbA1c levels with haematological changes observed during SS therapy. The cause of the "false" reduction in HbA1c levels is primarily due to haemolysis induced by SS therapy. In addition to the "false" reduction in HbA1c levels, unchanged serum glucose levels and fructosamine levels were reported at the same time, which are not affected by haemolysis or anaemia [2, 21]. Haemolysis is a known adverse event of sulfonamide drugs, and its severity can be subclinical, even without significant anaemia, with macrocytosis as the primary symptom suggestive of haemolysis. Haemolysis is associated with a reduction in HbA1c levels by shortening the lifespan of erythrocytes, with a reduction in the exposure time of haemoglobin to glucose, resulting in a reduction in glycation [21]. Therefore, the determination of HbA1c values is not a reliable method to assess diabetes control in patients treated with SS [21].

In one population-based study conducted among RA patients (approximately 70 000 participants), SS treatment with a total exposure time of no more than 90 days/year was associated with an increased risk of developing diabetes. However, this effect was not found for total exposure time of more than 270 days/year. This might have been related to high disease activity and/or the use of GCs in the initial period, shortly after diagnosis of RA [11].

BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS

The initiation of biologic therapies for use in patients with chronic arthritis represented a significant advance in the treatment of chronic arthritis due to the effective inhibition of the inflammatory process. There is a steady increase in the number of patients with chronic arthritis treated with bDMARDs to achieve and then maintain remission or low disease activity.

TUMOUR NECROSIS FACTOR INHIBITORS

TNF is known to exacerbate insulin resistance. In a large retrospectively evaluated group of patients with RA or PsA (approximately 14 000 participants), it was found that treatment with TNFi (IFX, ETA, ADA) was associated with a reduced risk of developing diabetes compared to patients treated with other DMARDs (HR = 0.62) [7]. It was found that TNFi therapy (IFX, ETA, ADA) in RA and non-diabetic patients was associated with a reduction in insulin resistance [2], while in patients with chronic arthritis – with a reduction in HbA1c levels [1].

In a 6-month randomised placebo-controlled clinical trial conducted among obese participants with signs of the metabolic syndrome, impaired glucose homeostasis and signs of subclinical inflammation, ETA was used (50 mg twice a week for 3 months, then 50 mg once a week for a further 3 months). ETA therapy resulted in a significant improvement in fasting glucose levels, an increase in the ratio of high-molecular-weight adiponectin to total adiponectin and a decrease in sICAM-1 (soluble intracellular adhesion molecule-1) levels [22].

Short-term observations in patients with chronic arthritis and T2D or metabolic syndrome found no effect of ETA on indices that

assess insulin secretion and insulin sensitivity [2]. Further studies in large groups of patients are needed.

INTERLEUKIN-6 INHIBITORS (TOCILIZUMAB)

First reports from 2011 indicated that initiation of TCZ therapy in RA and diabetic patients resulted in significant reductions in HbA1c levels after 1 month and 6 months of treatment (–0.8% and –1.2%, respectively) [2].

In a retrospective study conducted among RA patients with or without diabetes, treated with TNFi or TCZ, there was a significant reduction in HbA1c levels, both at month 1 and at month 3 after initiation of the therapy, and changes in HbA1c levels occurred independently of diabetes status. The analysis after 3 months of treatment revealed significantly lower HbA1c values in patients treated with TCZ compared to those treated with TNFi (5.8% *vs.* 6.1%), with significantly greater reductions in HbA1c levels in patients treated with TCZ *vs.* TNFi (0.4% *vs.* 0.1%). These results imply that in RA patients, TCZ results in a more significant reduction in HbA1C levels than TNFi [23].

ABATACEPT (ABA)

RA patients treated with ABA had a reduced risk of developing diabetes (HR = 0.52) compared to those treated with MTX monotherapy [3]. ABA therapy can slow down the loss of pancreatic β-cell function in the course of T1D. In contrast, the mechanism of action of ABA in the course of T2D is not clear. It appears that ABA may have a beneficial effect on insulin resistance by inhibiting the activation of T cells infiltrating the adipose tissue [2, 3].

CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (CSDMARDS)

Results from animal studies indicate that TOFA not only significantly reduces pro-inflammatory cytokines (TNF, IL-6), serum amyloid A (SAA) proteins, but also improves insulin secretion and insulin sensitivity when used in combination with aspirin [2].

In experimental models, baricitinib restored insulin action in liver and skeletal muscles through inhibition of the JAK2-STAT2 pathway [2].

A retrospective study conducted among patients with RA and T1D or T2D assessed the risk of intensification of diabetes treatment during taking ABA, TNFi, RTX, TCZ or TOFA. There were no significant differences when comparing ABA *vs.* TNFi, RTX, TCZ therapies, however, the risk was lower when taking TOFA [10].

OTHER DRUGS USED IN RHEUMATIC DISEASES

GLUCOCORTICOSTEROIDS

The increased risk of developing diabetes during treatment with GCs is well known. This was proved in a study conducted among RA patients (HR = 1.31) [3].

STATINS

The study conducted among RA patients found a significantly increased risk of developing diabetes associated with statin therapy (HR = 1.56). Similar observations were also made in the general population (increased risk by 9–87%) [3]. The mechanism of action of statins is not fully clear; statin-induced insulin resistance in skeletal muscles and liver or genetic variants of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase are considered [3].

CONCLUSIONS

It appears that DMARDs, through inhibition of the inflammatory activity of rheumatic diseases and additional mechanisms of action, may contribute to reducing metabolic disorders, improving control of diabetic parameters, preventing the development of diabetes-dependent complications. The antidiabetic effect of DMARDs should be taken into account when planning the treatment of patients with chronic arthritis. However, further studies and observations are needed to determine reliable antidiabetic effects of individual DMARDs.

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