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REVIEW

Anti-inflammatory properties of antidiabetic agents

Eleni Xourgia, Eleni-Margarita Tzouganatou, Athanasia Papazafeiropoulou, Andreas Melidonis

ORCID number: Eleni Xourgia (0000-0001-5766-3209); Eleni Margarita Tzouganatou (0000-0002-3074-652X); Athanasia Papazafeiropoulou (0000-0002-7596-4942); Andreas Melidonis (0000-0003-0505-5708).

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Eleni Xourgia, Eleni-Margarita Tzouganatou, Athanasia Papazafeiropoulou, Andreas Melidonis, 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Athens 18536, Greece

Corresponding author: Athanasia Papazafeiropoulou, MD, MSc, PhD, Attending Doctor, Research Scientist, 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, 1 Zanni and Afentouli Street, Athens 18536, Greece.
pathan@ath.forthnet.gr
Telephone: +30-697-996483

Abstract

The reciprocal relationship between hyperglycemia and inflammation in the setting of diabetes mellitus has been the subject of extensive research. Insulin resistance, the hallmark of diabetic metabolic dysregulation, has been linked to the inflammatory cascade occurring mainly in adipose tissue. The main pathophysiologic processes facilitating the aforementioned interplay, is a phenotype switch of macrophages to the M1 class following gluco- and lipotoxicity and gut microbial remodeling. Given the correlation between inflammation and metabolic abnormalities, the elucidation of the exact mechanisms linking the two along with exploring the possible role of modulation of one in order to alter the other, could open up the possibility of novel therapeutic approaches for diabetes mellitus and its complications. Therefore, the aim of this review is to summarize the growing body of evidence concerning the molecular basis and results of pro-inflammatory processes in diabetic subjects along with the effect of current antidiabetic treatment options on tissue inflammation.

Key words: Inflammation; Adipose tissue; Anti-inflammatory; Type 2 diabetes mellitus; Antidiabetic drugs

Core tip: In this review, we aim to create a concise overview of the interplay between hyperglycemia and inflammation, while describing the immunomodulatory potential of each antidiabetic drug and its effects exerted in the inflammatory cascade in subjects with type 2 diabetes.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is currently considered a worldwide epidemic. It is regarded as one of the most important chronic conditions because of the high disease prevalence and its debilitating chronic complications, responsible for elevated indexes of morbidity and mortality. According to World Health Organization, the number of people affected by diabetes in 2014 has approximately quadrupled since 1980, worldwide. In detail, the age-standardized prevalence of diabetes in adults has nearly doubled since 1980, reaching 8.5%[1].

While the development of diabetes and its complications is a multifactorial process, the interplay between innate and acquired immunity in the pathogenesis of metabolic diseases has been attracting increasing research interest, mainly in the context of seeking novel treatment approaches and, ultimately, a causative therapy. Inflammation has been speculated to play an important role, central to the pathophysiologic dysregulation of the pancreatic islet in type 1 diabetics. Furthermore, growing evidence suggests that inflammation also affects the pathogenetic process of T2DM, modulating processes like obesity-related insulin resistance, impaired insulin secretion, and diabetes-related vascular dysfunction[2]. Furthermore, it is now understood that inflammation plays a major role in the pathogenesis of cardiovascular disease with ongoing research in the field of prevention of coronary artery disease by use of anti-inflammatory drugs[3-6]. Therefore, the purpose of this review is to discuss the potential anti-inflammatory effects of currently available antidiabetic medications in relation to the disruption of metabolic homeostasis.

TYPE 2 DIABETES AND INFLAMMATION

Adipocytes are the main site of interplay between inflammation and insulin resistance in T2DM. The immunomodulatory role of adipose tissue has now been well-described, as adipocytes not only produce various adipocytokines that can interfere with insulin production and sensitivity but interact in close communication with the immune cells surrounding them[7]. Adipose tissue macrophages affect tissue remodeling and metabolic balance through presenting with an M2 phenotype in lean fat[8]. The activity and expression patterns of M2 macrophages depend heavily on cytokine signaling cascades, namely those including interleukin (IL)-4 and IL-13. Macrophages shifted to the M2 phenotype produce arginase and IL-10[9]. In obesity, macrophages proliferate and shift to the M1 phenotype, activated by pro-inflammatory cytokines. M1 macrophages express CD11c and produce tumor necrosis factor-α (TNF-α), IL-6, and reactive oxygen species (ROS)[9]. The accumulation of M1 macrophages is incremental in the development of insulin resistance[7]. Adipose tissue inflammation can also be induced by localized decreased oxygen perfusion in tissues rapidly expanding with disproportional to the proliferation vascular adaptation[10].

In diabetes, hyperglycemia and elevated levels of free fatty acids (FFAs) may act as proinflammatory stimulants through the induction of glucose utilization and modulating the process of oxidative phosphorylation[11,12]. Such metabolic dysregulation has been shown to induce a proinflammatory shift in adipose, islet and vascular tissue-related anti-inflammatory cells[7-9]. Glucotoxicity and lipotoxicity fuel processes induce oxidative and endoplasmic reticulum stress, further initiating inflammation by activation of thioredoxin-interacting protein and the NLR family, pyrin domain containing 3 (NLRP3) inflammasome, which increase the release of active IL-1β[11-14]. IL-1β plays an important initiator role in the inflammatory cascade, recruiting macrophages and other cells of the immune response ("auto-stimulation")[14]. The same interplay between metabolic dysregulation and inflammation occur between other tissue and cell types in the pancreas and circulatory system[13,14]. In T2DM, amyloid depositions in pancreatic islets induce inflammation through NLRP3 inflammasome formation and the production of IL-1β[15]. Increasing stress and inflammation, instigated in a positive-feedback manner, trigger cellular pro-apoptotic cascades and β-cell impairment, insulin resistance, and arterial atheromatosis.

Additionally, obesity is associated with alterations in the gut microbiome leading to

functional changes of inherent gut homeostasis, with bacterial wall lipopolysaccharides (endotoxins) further promoting tissue inflammation[16]. Endotoxins, FFAs and cholesterol have a pro-inflammatory capacity through the activation of Toll-like receptor (TLR) pathways and, subsequently, nuclear factor-κB (NF-κB)-mediated cytokine and chemokine signaling including TNF-α, IL-1β, IL-8, and monocytes chemoattractant protein-1 (MCP-1) promoting immune cell attraction in several tissue types[17]. It has recently been reported that in obesity, gut microbiota aberrant growth patterns might affect the innate and acquired immune system responses, thereby promoting insulin resistance[18].

The interplay of metabolism and inflammation could justify the theory that metabolic dysfunction amelioration through lifestyle modification and pharmaceutical intervention could attenuate inflammation. Current antidiabetic treatments induce normoglycemia by acting on several different pathways. Many of these treatments also exert anti-inflammatory effects that might be mediated *via* their hypoglycemic and hypolipidemic capacities or by directly modulating the immune system. Below, we gather and discuss the current data on the anti-inflammatory properties of antidiabetic medications.

ANTIDIABETIC TREATMENT AND INFLAMMATION

Metformin

Metformin is considered a first-line treatment for T2DM in almost all guidelines and expert recommendations issued worldwide. The molecular mechanisms behind the pharmacologic activity of metformin appear to be rather complex and remain controversial. However, it is universally accepted that metformin phosphorylates and activates AMP-activated protein kinase (AMPK)[19]. In the liver, the AMPK cascade activates fatty acid oxidation with inhibition of cholesterol and triglyceride synthesis[19]. Peripheral effects include the activation of fatty acid oxidation and glucose uptake in skeletal muscle as well as a systemic increase in insulin sensitivity[19].

It has been reported that metformin increased nitric oxide (NO) synthesis via activation of AMPK[20] and decreased ROS production through inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the respiratory mitochondrial chain[21]. Another study showed that metformin inhibited NFκB activation in the vessel wall and decreased serum C-reactive protein (CRP) level in high-fat-fed atherogenic rabbits[22]. Furthermore, Isoda *et al*[23] have reported that metformin inhibited NFκB activation through blockade of the phosphoinositide 3-kinase (PI3K)-Akt pathway in human vascular wall cells. Also, in lipopolysaccharide-activated macrophages, metformin inhibited production of the IL-1β precursor molecule and other pro-inflammatory cytokines, while it boosted induction of the anti-inflammatory cytokine, IL-10[24]. Another possible mechanism of the anti-inflammatory action of metformin is inhibition of advanced glycation end products (AGEs) formation. Metformin inhibits the formation of AGEs which promote inflammation and ROS (glycoxidation)[25].

Apart from the studies where the molecular effects of metformin were examined in vitro, there are also clinical studies. In the Diabetes Prevention Program (DPP) study, metformin slightly reduced the levels of CRP compared with placebo[26]. Similar results were provided by the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, in which metformin and/or a thiazolidinedione (TZD) led to lower plasma insulin, lower plasminogen activator inhibitor type 1 (PAI-1) antigen, lower CRP and lower fibrinogen levels compared with a sulphonylurea (SU) or meglitinide in a population of diabetic patients with coronary artery disease[27]. Krysiak *et al*[28] have reported that metformin reduced monocyte release of TNF-α, IL-1β, IL-6, MCP-1 and IL-8, as well as plasma CRP level in patients with impaired fasting glucose. On the other hand, in the LANCET Trial: A Trial of Long-acting Insulin Injection to Reduce C-reactive Protein in Patients with Type 2 Diabetes, metformin did not alter inflammatory biomarkers in patients with a short T2DM duration, in spite of glucose regulation[29]. In addition, it has been reported that metformin treatment did not change CRP or 8-iso-prostaglandin F2α(8-iso-PGF2α) level in subjects with normal glucose tolerance[30].

Overall, the various results are conflicting and even though metformin seems to have several anti-inflammatory pharmacologic properties *in vitro*, those are not always observed *in vivo*. Therefore, it remains uncertain whether the anti-inflammatory effect of metformin is due to its direct tissue-action or, induced indirectly, through the improvement of insulin sensitivity and hyperglycemia.

Sulphonylureas

Apart from the potent hypoglycemic effect of SUs, many studies have shown that they may have additional anti-inflammatory potential. Glyburide has been shown to inhibit the NLRP3 inflammasome and subsequent IL-1β activation in macrophages[31] while gliclazide, as compared with glibenclamide, decreased the serum levels of soluble intercellular adhesion molecule-1 (sICAM-1), sE-selectin and high sensitive CRP (hsCRP), in a population of diabetic patients[32]. Mu-Huo *et al*[33] showed that in an animal model of sepsis, glibenclamide pretreatment exerted protective properties on the lung parenchyma by inhibiting both the inflammatory responses and oxidative stress. In addition, glibenclamide reduces pro-inflammatory cytokine production by neutrophils in patients with diabetes in response to bacterial infection[34]. Mavridis *et al*[35] reported that T2DM patients treated with SU had significantly lower cytokine levels than the insulin-treated.

By contrast, in various head-to-head clinical trials, no significant changes in CRP and other inflammatory markers were observed with SU therapy, whereas significant reductions were found with TZD, pioglitazone and the glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1 RA) exenatide[36-38]. Also, in a recent 52-wk head-to-head study between metformin, gliclazide, and pioglitazone on pro-inflammatory biomarkers, coagulation, and endothelial function, no improvements were seen in the circulating levels of inflammatory markers selected (IL-1, IL-6, and TNF-α) with SU therapy when compared to the other treatment types, while glycemic control was comparamble among all treatment groups[39].

It is notable that while SU appears to have some effect in the expression of various inflammatory cytokines, its anti-inflammatory effect is less potent when compared to metformin or pioglitazone.

Alpha-glucosidase inhibitors

Alpha-glucosidase (α-glucosidase) inhibitors are a unique class of antidiabetic medications which, by competitive and reversible inhibition of intestinal alpha-glucosidases, delay carbohydrate digestion and thereby extend the total time of glucose absorption[40]. Given the research data suggesting that postprandial glucose load results in a biomarker profile consistent with systemic low-grade inflammation and endothelial dysfunction, with increased levels of hsCRP, IL-6, TNF-α, sICAM-1, soluble vascular cell adhesion molecule 1 (sVCAM-1), E-selectin, and metalloproteinases (MMPs) 2 and 9 in patients with T2DM compared to healthy patients[41], α-glucosidase inhibitors are expected to have anti-inflammatory potential, justified by their mechanism of action.

Osonoi *et al*[42] suggested that miglitol depresses the production and release of inflammatory cytokines/cytokine-like factors in peripheral leukocytes by flattening glucose level fluctuation curves in Japanese patients with T2DM, incrementally more than other α-glucosidase inhibitors. Emoto *et al*[43] studied patients with T2DM and coronary artery disease on a 3-mo regimen of miglitol and demonstrated an improvement in both the insulin resistance index and CRP. Derosa *et al*[44] evaluated effects of acarbose in patients with T2DM and found it to be effective in reducing the post-oral-fat-load peaks of various parameters including inflammatory markers such as hsCRP, after 7 mo of therapy.

In a randomized double-blind, placebo-controlled crossover study, acarbose-induced normoglycemia did not affect adiponectin, insulin sensitivity, or pro-inflammatory circulating biomarkers (MCP-1, IL-6, and IL-1β)[45]. Similarly, a comparison of pioglitazone *vs* voglibose by Fujitaka *et al*[46] showed an improvement in serum adiponectin, hsCRP levels and insulin resistance assessment through the homeostatic model only in the pioglitazone group.

While, α-glucosidase inhibitors may have some indirect anti-inflammatory properties mainly *via* lowering the post prandial glucose levels, they do not seem to have further immunomodulatory potential.

Thiazolidinedione

Rosiglitazone and pioglitazone, also known as TZDs, are selective agonists of nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ).

There is plenty of scientific evidence that TZDs act not only as hypoglycemic medications but as anti-inflammatory agents as well. Specifically, PPAR-γ is mainly expressed in adipocytes and appears to attenuate pro-inflammatory biomarkers in visceral adipose tissue (VAT) deposits, steatotic liver, atherosclerotic plaques and plasma. Furthermore, in vitro results demonstrate that the anti-inflammatory activity of TZDs is partially resulting from their modulatory properties in glucocorticoid nuclear translocation activation, in a PPAR-γ-independent manner[47].

TZDs have been shown to decrease inflammatory markers in visceral adipose tissue, liver, atherosclerotic plaques, and circulating plasma[48]. Pioglitazone treatment

decreased invasion of adipose tissue by proinflammatory macrophages and increased hepatic and peripheral insulin sensitivity in obese subjects[49]. Patients with insulin resistance had a decreased total adipose macrophage population, with a decrease in M1 macrophages and an increase in M2 macrophages with pioglitazone treatment[50]. Also, treatment with TZDs attenuated inflammation in nonalcoholic steatohepatitis and in atherosclerotic lesions[51,52].

The notion that PPAR-γ activation by TZDs can modulate monocyte and macrophage activity and have an impact on the inflammatory process is supported by *in vitro* research data. Further evidence of this is provided by studies *in vivo*, both in animal models and in humans. Haffner *et al*[53] in their study of approximately 300 T2DM patients on a 26-wk rosiglitazone treatment regimen, reported a reduction of at least 20% in plasma CRP levels and MMP-9 and approximately 12% in total white blood cell count. A reduction in MMP-9 was also observed by Marx *et al*[54] along with a concomitant decrease in plasma sCD40 levels (another emerging marker of inflammation and cardiovascular risk) in T2DM patients with established cardiovascular disease, following rosiglitazone treatment.

In addition, a recent meta-analysis of 27 randomized controlled trials, found that circulating levels of hsCRP, monocyte chemoattractant protein-1, von Willebrand factor, fibrinogen, and E-selectin were significantly decreased after TZD therapy. However, IL-6, MMP-9, sCD40 ligand, PAI-1 and ICAM-1 were not significantly affected[55]. In the PERISCOPE trial, treatment of diabetic patients with known coronary artery disease with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis and a decrease in hsCRP levels, compared with glimepiride[56].

Nonetheless, one could argue that all the aforementioned anti-inflammatory actions of TZDs can be attributed to their effect on glucose lowering. Satoh *et al*[57], following pioglitazone treatment in T2DM, observed a decrease in CRP levels of the same magnitude both in patients who responded to therapy (defined as an improvement in glucose control) and in non-responders. Also, Nitta *et al*[58] showed that, compared with glimepiride, pioglitazone reduced coronary arterial inflammation in patients with T2DM or impaired glucose tolerance, even though both agents decreased glucose-control related parameters such as HbA1c and fasting plasma glucose.

TZDs appear to be potent modulators of the inflammatory cascade, independently of their glucose lowering effect. Currently, various studies examine their potential use as immunomodulators outside the setting of diabetes, in normoglycemic subjects with rheumatic and other auto-immune diseases[59,60].

SGLT-2 inhibitors

Sodium–glucose cotransporter (SGLT) 2 inhibitors improve glycemia by inhibiting reabsorption of glucose in the proximal tubule of the kidney, inducing glucosuria and lowering plasma glucose levels, without inducing hypoglycemia.

In T2DM mice, the SGLT-2 inhibitor ipragliflozin was shown to improve hyperglycemia, insulin secretion, hyperlipidemia, and liver levels of oxidative stress biomarkers and reduce markers of inflammation including IL-6, TNF-α, MCP-1, and CRP levels[61]. In another study, short-term luseogliflozin treatment normalized the expression of inflammation-related genes such as F4/80, TNFα, IL-1β, IL-6, ICAM-1, platelet endothelial cell adhesion molecule-1 (PECAM-1), MMP2 and MMP9 in apolipoprotein-E deficient knockout (ApoE KO) mice, while markedly attenuating the progression of atherosclerosis[62]. Another study in mice treated with empagliflozin provided similar results[63]. Furthermore, empagliflozin reduced M1-polarized macrophage accumulation while inducing the anti-inflammatory M2 phenotype of macrophages within adipose tissue and liver, lowering plasma TNFα levels and attenuating obesity-related chronic inflammation in diet-induced obese mice[64]. Also, empagliflozin, alone or in combination with linagliptin, attenuated (nonalcoholic steatohepatitis) NASH development in diabetic mice, through reducing hepatic expression of inflammatory genes (TNF-α, IL-6, and MCP-1)[65]. Dapagliflozin also reduced mRNA levels of various cytokines and attenuated the development of diabetic cardiomyopathy in diabetic mice[66].

Moreover, there is evidence that the important renoprotective effect of SGLT-2 inhibitors is partly due to their anti-inflammatory properties. Vallon *et al*[67] showed that administration of empagliflozin in diabetic mice not only attenuated glomerular hyperfiltration, albuminuria, but also inhibited diabetes-induced renal expression of inflammation markers, such as NF-κB and IL-6. Hatanaka *et al*[68] reported that the administration of dapagliflozin to Akita mice induced an incremental renal macrophage tissue accumulation and attenuated interstitial fibrosis when compared with insulin, despite glycemic control being equally efficient in the two groups, indicating that dapagliflozin exerts renoprotective effects beyond glucose reduction. In addition, studies using cultured proximal tubular cells support the notion that a

decrease in the expression and circulation of pro-inflammatory molecules, such as transforming growth factor-β, MCP-1, osteopontin, and ICAM-1, oxidative stress, NADPH oxidase 4 (Nox4) expression and ROS production underlie the major actions of dapagliflozin[69].

In a small study with 32 male diabetic patients empagliflozin and canagliflozin lowered interferon-λ, TNF-α, IL-6[70]. Sato *et al*[71] studied the effect of dapagliflozin on epicardial adipose tissue and observed that treatment with dapagliflozin resulted in a slight reduction of serum PAI and a greater reduction of serum TNF-a in T2DM patients with coronary artery disease. Okamoto *et al*[72] studied the effects of dapagliflozin on several biomarkers using a population of 27 obese T2DM patients and showed that dapagliflozin treatment led to a significant increase in serum adiponectin and a mild decrease in CRP. A small decrease in CRP with dapagliflozin treatment was also observed in another study[73]. In a post-hoc exploratory analysis of the CANTATA-SU study, changes from baseline in serum leptin, adiponectin, IL-26, TNF-a, CRP, PAI-1, VCAM-1 and MCP-1 were measured in T2DM patients taking metformin, but also receiving either canagliflozin or glimepiride. Canagliflozin shifted the balance of appetite-related hormones, significantly decreasing median serum leptin and increasing median serum adiponectin when compared to glimepiride. Median serum IL-6 was accordingly decreased as well accompanied by a trend towards a slight reduction in hsCRP which, however, contrasted with a modest increase in median serum TNF-a in the canagliflozin group over glimepiride. Despite changes in serum leptin being associated with changes in body weight, there were no notable correlations between changes in adiponectin, IL-6, TNF-a and CRP levels and alterations in body weight and HbA1c[74].

The majority of studies that have been discussed above used animal models. Evidence from clinical trials in human subjects is limited and as a result it is not safe to reach a conclusion regarding the anti-inflammatory effect of this particular category.

DPP-4 inhibitors

Dipeptidyl peptidase (DPP)-4 inhibitors reduce DPP-4 activity in peripheral plasma, preventing the inactivation of the incretin hormone GLP)-1[75]. The ubiquitous tissue localization of DPP-4 (monocytes, natural killer cells, macrophages, epithelial and endothelial cells, lung, spleen, pancreas, kidney, liver and intestinal cells) could play a role in explaining the immunomodulatory role of this enzyme. DPP-4 hormone production in macrophages, especially in visceral adipose tissue depots, binds to adenosine deaminase, facilitating, *via* nonenzymatic function, T-cell proliferation and activation. Also, CD26, which can partially act as an *in vivo* DPP-4 mimic, serves as a signaling molecule in T-cell activation and immunoregulation [76].

The DPP-4 inhibitor alogliptin can attenuate TLR-4 mediated extracellular signal regulated kinase (ERK) activation and ERK-dependent expression of MMPs in histiocytes, and inhibit TLR4-mediated IL-6 and IL-1-beta production[77]. In human macrophages cultured *in vitro*, the DPP-4 inhibitor sitagliptin significantly increased GLP-1 induced the levels of cyclic adenosine monophosphate (cAMP) in the cytosol, resulting in hindering of NF-κB p65 nuclear translocation and suppression of pro-inflammatory mediator production in response to lipopolysaccharide (LPS)[78]. Treatment with linagliptin notably suppressed the activation of the fibrotic process in an experimental model of autoimmune myocarditis mice and was associated with reduced inflammatory cytokine (IL-2, TNF-α, IL-1β, and IL-6) gene expression[79]. Another study indicated that sitagliptin treatment of obese insulin-resistant mice was associated with an improved metabolic phenotype and concurrent reduction of inflammation in pancreatic islets and adipose tissue[80]. In diabetic rats, sitagliptin decreased circulating levels of CRP, MCP-1, TNF-α, IL-6, PAI-1, and suppressed vascular smooth muscle cells proliferation[81].

Surface expression of CD26 on CD4+ and CD8+ T-cells was found to be higher in T2DM patients when compared to healthy controls[82]. In a recent study concerning the production of inflammatory mediators, treatment with sitagliptin for 12 wk reduced mRNA expression of CD26, TNF-α, TLR2, TLR4, proinflammatory kinases c-Jun N-terminal kinase-1 and inhibitory κB kinase, and inhibitor of chemokine receptor CCR-2 in mononuclear cells, as well as of plasma CRP, IL-6, and FFAs[83]. Similarly, another study showed that sitagliptin reduced the expression of inflammatory cytokines and improved the unfavorable M1/M2 phenotypes of peripheral blood monocytes in Japanese diabetic patients[84]. Treatment with sitagliptin or vildagliptin lowered plasma IL-6, IL-18, TNF-alpha and nitrotyrosine levels compared with baseline in T2DM patients[85]. Furthermore, in a study of subjects with coronary artery disease and uncontrolled T2DM, sitagliptin significantly improved endothelial function and inflammatory state beyond its hypoglycemic action[86]. In hemodialysis patients with T2DM, linagliptin decreased levels of prostaglandin E2, IL-6, hsCRP, glycated

albumin, and blood glucose which was associated with an increase in active GLP-1[87]. However, on a model of sitagliptin or metformin as add-on therapy to a pioglitazone regimen in patients with poorly controlled T2DM demonstrated that only metformin led to a decrease of body weight and to a faster and superior improvement of insulin resistance and inflammatory parameters, such as adiponectin and TNF-a[88].

In summary, research suggests that all currently available DPP-4 inhibitors have multiple immunomodulatory effects, in a way that is independent of their glucose lowering effect.

GLP-1 receptor agonists

GLP-1 receptor agonists have been shown to activate GLP-1 receptor to increase the intracellular concentration of cAMP in acinar cells of the pancreas, resulting in an increased insulin secretion and decreased glucagon secretion.

In patients with T2DM, treatment with GLP-1 analogs appears to modulate the pro-inflammatory activity of the innate immune system, leading to reduced pro-inflammatory activation of macrophages and consequently the expression and secretion of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6 and increased adiponectin. This effect is not dependent on the glycemic or body weight effects of GLP-1[89]. With regard to the effects of GLP-1 analogs on CRP, a small placebo-controlled study demonstrated a significant reduction in CRP levels with exenatide[90]. Also, in a 12-mo comparative study, exenatide demonstrated a significant decrease in hsCRP compared with SU[37].

Treatment of cultured human islets with exendin-4, a GLP-1 RA, suppressed the expression of inflammatory genes such as NFκB1(p105), NFκB2(p100), RelA (also termed p65), TNF receptor superfamily member 1A, and receptor-interacting serine/threonine kinase 2[91]. In addition, administration of a recombinant adenovirus producing GLP-1 to ob/ob mice reduced the macrophage population and production of TNF-α, MCP-1, and IL-6 in adipose tissue via inhibition of NF-κB activation and phosphorylation of ERK1/2 and c-Jun N-terminal kinases[92]. Also, Arakawa *et al*[93] observed that GLP-1 receptor agonists reduced monocyte/macrophage accumulation in the arterial wall by inhibiting the inflammatory response in macrophages, in C57BL/6 or apolipoprotein E-deficient mice apoE(-/-). In another study, exenatide significantly increased the level of IL-10 and decreased both TNF-α and IL-1β in LPS-treated monocytes/macrophages, via activation of protein kinase A[94].

Exendin-4 also prevented macrophage infiltration, and decreased protein levels of ICAM-1 and type IV collagen, as well as decreasing oxidative stress and NF-κB activation in kidney tissue, in a rat model of type 1 diabetes[95]. Furthermore, Kim *et al*[96], showed that exendin-4 had an anti-inflammatory, neuroprotective effect in mice after a stroke, through inhibition of COX-2 through modulating JNK signaling-mediated stimulation of islet brain 1. Moreover, exendin-4 treatment reduced hepatic expression of the inflammatory markers TNF-α, IL-1β, and IL-6 and macrophage markers, cluster of differentiation 68 (CD68), and F4/80 in the liver of mice fed a western-type diet[97,98].

In addition, exenatide plus metformin resulted in a significant reduction in CRP and TNF-α compared with baseline[99]. In another study, treatment of diabetic patients with exenatide for 1 year significantly reduced increased total adiponectin by 12% and reduced hsCRP by 61% and these changes were statistically independent of the change in total body fat mass and body weight[100]. Moreover, Daousi *et al*[101] showed that GLP-1 continuous infusion in patients with T2DM was associated with a significant reduction in circulating IL-6 at 120 and 180 min post-administration. In a retrospective analysis of 110 obese patients with T2DM treated with liraglutide, the mean concentration of CRP declined after treatment with liraglutide for a mean duration of 7.5 mo[102].

Overall, the results of a number of studies all agree that GLP-1 RAs present many anti-inflammatory properties via multiple molecular pathways. It is also important to underscore that these immunomodulatory effects seem to be independent of their metabolic effects in weight and glucose lowering.

Insulin

Insulin induces an attenuation of inflammatory processes through several mechanisms, including increased endothelial nitric oxide release and decreased expression of proinflammatory cytokines and immune mediators, such as NF-κB, ICAM-1, and MCP-1, as well as several TLRs[103].

In a randomized parallel-group study in patients with T2DM, serum concentrations of hsCRP and IL-6 were markedly reduced in insulin-treated patients compared with metformin, despite the achievement of similar glycemic control[104]. This may suggest that insulin reduces inflammation, irrespectively of its effects on glycemia. In another study, treatment of insulin in patients with poorly controlled T2DM reduced serum

hsCRP levels, without affecting plasma fibrinogen or serum MCP-1 levels[105]. In contrast, in the LANCET trial, treatment with insulin compared with a placebo or metformin did not reduce inflammatory biomarker levels despite improving glucose control[29]. Also, Jansen *et al*[106] observed that patients characterized by a pronounced insulin-associated weight gain had an influx of macrophages into the adipose tissue and higher protein levels of MCP-1, TNF-α and IL-1β after 6 mo of insulin therapy compared with those who had not gained weight.

Overall, the results of the various studies concerning insulin are rather conflicting. It is unclear both whether insulin has notable anti-inflammatory properties and whether or not they correlate with its hypoglycemic effect. The lack of large, randomized, double-blind, controlled trials on the subject, or head-to-head studies with other antidiabetic agents, is a major limitation in drawing safe conclusions.

CONCLUSION

The inflammatory process and its causal relationship with the pathophysiology of diabetes mellitus and its complications remains a rather complex matter due to the numerous intertwining pathways involved in various tissue types, along with the interpersonal multifactorial variation of the inflammatory response. While the antidiabetic agents and their indications in the treatment algorithm are mainly evaluated based on their glucose lowering attributes, their immu-nomodulatory potential, most importantly on M1 macrophages could carry great therapeutic benefit, especially in highly insulin resistant patients. Another point of great interest when discussing the aforementioned attributes of these agents is whether the attenuation of the inflammatory cascade activation is secondary to normoglycemia achievement or independent to glycemic regulation, a differentiation that significantly alters the appropriate setting in which they could be successfully introduced to a particular anti-inflammatory-oriented treatment regimen. Moreover, most of the research data on the subject derives from studies on animal subjects, with large, randomized, double-blind studies lacking at the moment, a fact that does not allow for safe conclusions to be drawn as far as clinical correlation of molecular changes is concerned. In conclusion, there is need for further research quantifying the immunomodulatory capacity of antidiabetic agents, elucidating the mechanisms by which those effects are induced and exploring whether those theoretical alterations in circulatory and tissue cytokine and cell-phenotype patterns can be translated into clinical benefit for diabetes and its complications.

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