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Review

Antidiabetic agents: Potential anti-inflammatory activity beyond glucose control

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Abstract

A growing body of evidence is emerging to show that abdominal obesity, the metabolic syndrome, type 2 diabetes, cardiovascular disease and microvascular diabetic complications are intimately related to chronic inflammation. These observations pave the way to the development of new pharmacological strategies that aim to reduce silent inflammation. However, besides specific anti-inflammatory agents, glucose-lowering medications may also exert anti-inflammatory effects that could contribute to improved outcomes in diabetic patients. Most studies have used metformin, an AMP-activated protein kinase (AMPK) activator, and thiazolidinediones (TZDs), which act as peroxisome proliferator-activated receptor-gamma (PPARγ) agonists. Both pharmacological classes (considered insulin-sparing agents or insulin sensitizers) appear to have greater anti-inflammatory activity than insulin-secreting agents such as sulphonylureas or glinides. In particular, TZDs have shown the widest range of evidence of lowered tissue (visceral fat and liver) and serum inflammation. In contrast, despite reducing postprandial hyperglycaemia, the effect of α-glucosidase inhibitors on inflammatory markers appears rather modest, whereas dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) and glucagon-like peptide-1 (GLP-1) receptor agonists appear more promising in this respect. These incretin-based therapies exert pleiotropic effects, including reports of anti-inflammatory activity. No human data are available so far regarding sodium-glucose cotransporter type 2 (SGLT2) inhibitors. Although they may have indirect effects due to reduced glucotoxicity, their specific mode of action in the kidneys does not suggest systemic anti-inflammatory activity. Also, in spite of the complex relationship between insulin and atherosclerosis, exogenous insulin may also exert anti-inflammatory effects. Nevertheless, for all these glucose-lowering agents, it is essential to distinguish between anti-inflammatory effects resulting from better glucose control and potential anti-inflammatory effects related to intrinsic actions of the pharmacological class. Finally, it would also be of major clinical interest to define what role the anti-inflammatory effects of these glucose-lowering agents may play in the prevention of macrovascular and microvascular diabetic complications.

Keywords: Inflammation; Gliptin; GLP-1 receptor agonist; Metformin; Thiazolidinedione; Type 2 diabetes mellitus

1. Introduction

Both chronic low-grade inflammation and activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance, the metabolic syndrome and type 2 diabetes mellitus (T2DM) [1–3]. In addition, as diabetic vascular complications are at least partly mediated by inflammatory processes [4], targeting inflammation may help to prevent, retard and alleviate complications such as retinopathy, nephropathy and cardiovascular diseases [5]. Many specific anti-inflammatory approaches have been investigated in recent years to treat T2DM and its associated vascular complications, but none has yet emerged for use in clinical practice [6]. The management of T2DM is evolving, and many therapies targeting insulin secretion, insulin resistance or other insulin-independent processes can be prescribed by physicians [7]. Among the currently used glucose-lowering agents, some also

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exert anti-inflammatory effects, which may contribute positively to patients' outcomes [8]. An emerging body of evidence also suggests that insulin suppresses the inflammatory process not only through preventing hyperglycaemia, but also by modulating key inflammatory molecules [9,10]. Also, these effects of glucose-lowering agents could potentiate the anti-inflammatory effects reported with other drugs commonly used in the overall risk approach for T2DM [11], including statins, fibrates and inhibitors of the renin-angiotensin-aldosterone system (RAAS) [8,12].

Our team recently published an extensive review describing the various anti-inflammatory strategies tested to prevent or treat T2DM and its associated metabolic disorders and vascular complications [6]. The aim of the present review is to describe the potential anti-inflammatory activities of commonly used antidiabetic agents and, thus, the oral glucose-lowering agents [metformin, sulphonylureas, glinides, α-glucosidase inhibitors, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter type 2 (SGLT2) inhibitors] and injectable glucose-lowering compounds [glucagon-like peptide-1 (GLP-1) receptor agonists and insulin] are successively considered. To identify the relevant studies, an extensive search of the literature from January 2000 to December 2014 in MEDLINE was performed, using the terms "inflammation" and "anti-inflammatory" combined with the names of each of the above-mentioned pharmacological classes of glucose-lowering agents or the generic names of any commercially available medications within each class. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

2. Oral glucose-lowering agents

2.1. Metformin

This is the first-choice drug for the management of T2DM [7] even in high-risk patients [13]. This biguanide acts, at least partially, as an AMP-activated protein kinase (AMPK) activator [14,15]. AMPK is a key regulator of energy balance and plays many roles in human diseases [16]. Activation of AMPK has a number of potentially beneficial antiatherosclerotic effects, including reducing inflammatory cell adhesion to blood vessel endothelium, reducing lipid accumulation and proliferation of inflammatory cells caused by oxidized lipids, stimulation of gene expression responsible for cellular antioxidant defences and stimulation of enzymes responsible for nitric oxide formation [17]. Metformin can inhibit proinflammatory responses and cytokine-induced nuclear factor kappaB (NF-kB) activation *via* AMPK activation in vascular endothelial cells [18,19], and also inhibit inflammatory responses *via* the AMPK–phosphatase and tensin homologue (PTEN) pathway in vascular smooth muscle cells [20]. By decreasing STAT3 phosphorylation through increased AMPK activity, metformin can also inhibit monocyte-to-macrophage differentiation [21], while other anti-inflammatory mechanisms have been proposed with lysosomes as a target of metformin [22]. Recently, this biguanide has proved effective for reducing YKL-40 (chitinase-3-like protein 1) concentrations, a novel marker of inflammation, and the effect seems to be independent of glycaemic control or reductions in high-sensitivity C-reactive protein (hs-CRP) [23]; it also lowered serum chemerin concentrations, a novel member of the adipocytokine family [24]. In addition, the pharmacology of metformin may include alterations of bile acid recirculation and gut microbiota, resulting in enhanced enteroendocrine hormone secretion [25]. Because of the known relationship between microbiota and silent inflammation [26], this ability may represent another mode of action to reduce silent inflammation, although this needs to be more carefully investigated.

However, in human studies, the effects of metformin on inflammatory variables were relatively small in patients with T2DM [27]. In the US Diabetes Prevention Program, metformin only slightly reduced CRP levels in patients with impaired glucose tolerance [28]. Interestingly, if incident diabetes developed, the durable effect of metformin to lower hs-CRP vanished [29]. Yet, in patients with recent-onset T2DM in the randomized LANCET trial, treatment with metformin compared with a placebo did not reduce inflammatory biomarker levels despite improving glucose control [30]. Also, head-to-head comparative trials in patients with T2DM showed less pronounced efficacy with metformin compared with TZDs in reducing various inflammatory markers, including hs-CRP levels [27,31,32].

Low-grade chronic inflammation underlies the pathogenesis of insulin-resistant disorders such as polycystic ovary syndrome (PCOS), and early application of metformin therapy has relieved chronic low-grade inflammation in women with PCOS in many studies [33–36]. However, the extent of the reduction in inflammatory markers was, again, less with metformin than with TZDs [36].

Because metformin may confer benefits in chronic inflammatory diseases [37] and cancers [38,39] independent of its ability to normalize blood glucose, there is now growing interest in identifying and exploiting AMPK anti-inflammatory effects with the development of new compounds that are currently under investigation [6,40].

2.2. Sulphonylureas

These agents stimulate insulin secretion by closing K(ATP) channels in the beta cells of islets of Langerhans. K(ATP) channels can stimulate inflammatory reactions through mitogen-activated protein kinase (MAPK)/NF-κB pathways in macrophages. Interestingly, K(ATP) channels in monocytes/macrophages are upregulated and correlate with increased inflammation in vulnerable plaques, whereas glibenclamide can rescue the progression [41]. However, another study found that oxidative stress (STAT-8-isoprostane) and inflammatory status (hs-CRP) were not significantly affected by adding glibenclamide to metformin-treated T2DM patients [42]. In two further comparative trials, no significant changes in CRP levels were observed with either glibenclamide [43] or glimepiride [44], whereas the active comparator pioglitazone was associated with significant reductions in CRP concentrations. In a head-to-head