World Journal of Diabetes

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DOI: 10.4239/wjd.v5.i5.697

World J Diabetes 2014 October 15; 5(5): 697-710
ISSN 1948-9358 (online)

REVIEW

Targeting inflammation in diabetes: Newer therapeutic options

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Author contributions: Agrawal NK and Kant S made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published.
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Received: December 27, 2013 Revised: April 24, 2014
Accepted: May 29, 2014
Published online: October 15, 2014

Abstract

Inflammation has been recognised to both decrease beta cell insulin secretion and increase insulin resistance. Circulating cytokines can affect beta cell function directly leading to secretory dysfunction and increased apoptosis. These cytokines can also indirectly affect beta cell function by increasing adipocyte inflammation.The resulting glucotoxicity and lipotoxicity further enhance the inflammatory process resulting in a vicious cycle. Weight reduction and drugs such as metformin have been shown to decrease the levels of C-Reactive Protein by 31% and 13%, respectively. Pioglitazone, insulin and statins have anti-inflammatory effects. Interleukin 1 and tumor necrosis factor-α antagonists are in trials and NSAIDs such as salsalate have shown an improvement in insulin sensitivity. Inhibition of 12-lipooxygenase, histone de-acetylases, and activation of sirtuin-1 are upcoming molecular targets to reduce inflammation. These therapies have also been shown to decrease the conversion of pre-diabetes state to diabetes. Drugs like glicazide, troglitazone, N-acetylcysteine and selective COX-2 inhibitors have shown benefit in diabetic neuropathy by decreasing inflammatory markers. Retinopathy drugs are used to target vascular endothelial growth factor, angiopoietin-2, various proteinases and chemokines. Drugs targeting the proteinases and various chemokines are pentoxifylline, inhibitors of nuclear factor-kappa B and mammalian target of rapamycin and are in clinical trials for diabetic nephropathy. Commonly used drugs such as insulin, metformin, peroxisome proliferator-activated receptors, glucagon like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors also decrease inflammation. Anti-inflammatory therapies represent a potential approach for the therapy of diabetes and its complications.

Key words: Inflammation; Insulin resistance; Diabetes; Neuropathy; Retinopathy; Nephropathy

Core tip: The burden of diabetes and its complications is increasing worldwide. To control this pandemic, drugs targeting different areas of the pathogenesis of diabetes and its complications are needed. Inflammation plays a key role in the natural history of diabetes during the progression from pre-diabetes to diabetes, including decreased beta cell secretory capacity and insulin resistance. Insulin resistance is an important part of the metabolic syndrome and plays a role in the pathogenesis of various macrovascular complications. Drugs targeting inflammatory pathways represent a fresh approach in the treatment of diabetes and its complications.

Agrawal NK, Kant S. Targeting inflammation in diabetes: Newer therapeutic options. *World J Diabetes* 2014; 5(5): 697-710 Available from: URL: http://www.wjgnet.com/1948-9358/full/v5/i5/697.htm DOI: http://dx.doi.org/10.4239/wjd.v5.i5.697

INTRODUCTION

The incidence of both diabetes and obesity is increasing worldwide and approaching epidemic proportions. Inflammation has been recognised as a common mechanism in the pathophysiology of both these conditions. Inflammation increases insulin resistance and islet cell inflammation, which leads to defects in beta cell secretion both of which lead to diabetes. Inflammation may also be the underlying mechanism in the increased risk of cardiovascular disease in subjects with diabetes and/or obesity. Hence, targeting inflammation may be a new therapy in the already expanding options for the management of diabetes mellitus and its complications. There is concern over many drugs used for diabetes which increase cardiovascular morbidity and/or mortality. Targeting inflammation in diabetes will theoretically lead to better glycemic control, and decrease both micro- and macrovascular complications including cardiovascular complications. Most therapies for type 2 diabetes mellitus (T2DM) target insulin resistance and drugs targeting inflammation may be a paradigm shift, wherein earlier recognition of the inflammatory status of the predisposed individual with type 2 diabetes, or at risk for the development of type 2 diabetes, would be evaluated and appropriate therapy initiated.The aim of this review is to elaborate on the drugs targeting inflammation in diabetes and its complications. Both previous studies and upcoming targets including their molecular mechanisms will be discussed in the review.

Inflammation in diabetes

A number of studies have demonstrated that markers of inflammation correlate with incident diabetes. Total leucocyte count which is a surrogate marker of inflammation, and more specifically the neutrophil count in the higher quartiles of the normal range, correlates with worsening of insulin sensitivity, and incident diabetes[1] and cardiovascular disease[2]. This suggests that a simple surrogate marker such as total leucocyte count may be a marker of insulin resistance.

Insulin resistance has been defined as a state of inflammation involving both innate and adaptive immunity[3]. Islet cell inflammation as a result of an autoimmune phenomenon has already been recognised in T1DM and has been increasingly implicated in the pathogenesis of T2DM. In fact, obesity has also been seen to modify the development of T1DM. Small human studies have demonstrated that anti-inflammatory therapy has improved glycemia and beta cell function in T2DM[4,5]. Thus, inflammation is recognised as one of the important pathways in the pathogenesis of T2DM and its complications.

The major cell involved in inflammation and insulin resistance in T2DM is the adipocyte. Insulin regulates glucose uptake and triglyceride storage by adipocytes. The adipocytokines in turn also affect insulin secretion and insulin resistance[6,7]. The various adipocytokines, especially leptin, adiponectin, omentin, resistin, and visfatin may contribute to beta cell dysfunction by increasing insulin resistance. Adipose tissue also secretes dipeptidyl peptidase-4 (DPP-4) which enhances the degradation of glucagon like peptide-1 (GLP-1) and has an insulinotropic effect on beta cells[8].

Circulating cytokines can affect beta cell function directly and indirectly by increasing adipocyte inflammation. Cytokines including tumour necrosis factor-alpha (TNF-α), interleukin beta (IL-1β), and interferon-gamma (IFN-γ) disrupt the regulation of intracellular calcium in the beta cells and hence insulin release. In addition, TNF-α increases the expression of islet amyloid polypeptide (IAPP, amylin) in beta cells leading to their accelerated death[9]. IAPP expression and deposition induces and increases beta cell inflammation[10,11]. Glucotoxicity and especially lipotoxicity increase the local level of free fatty acids (FFA) in the islets, and long chain fatty acids, particularly palmitic acid, cause oxidative stress and jun N-terminal kinase (JNK) activation[12]. This further leads to increased IL-1β, TNF-α, chemokine (C-C motif) ligand 2 (CCL2), IL-6, chemokine (C-X-C motif) ligand 1 (CXCL1), and IL-8 production, and activated nuclear factor-kappa B (NF-κB) in human islets leading to islet cell dysfunction[13]. Overall, this leads to a vicious cycle of inflammation-induced beta cell dysfunction which in turn again increases inflammation.

Oxidative stress is another pathway that leads to inflammation through activation of JNK, NF-κB, and p38 mitogen-activated protein kinase (p38MAPK)[14]. Palmitic acid causes endoplasmic reticulum (ER) stress, oxidative stress, ceramide production, and JNK activation, all of which provoke inflammatory responses. Pancreatic islets have low antioxidant defence and are hence vulnerable to oxidative stress. There is differential regulation of oxidative stress genes in T2DM donors compared with control subjects, implicating oxidative stress in islet dysfunction[15]. Divalent metal transporter 1 is another factor that increases IL-1β-induced insulin resistance[16]. These findings suggest that oxidative stress is an important factor in the pathogenesis of T2DM.

Endoplasmic reticulum stress also leads to increased cytokine expression and NF-κB activation causing dysfunction of beta cells[17]. Infact, cyclopiazonic acid-induced ER stress has been shown to cause beta cell dysfunction through increased levels of cytokines and NF-κB expression[18]. The levels of thioredoxin-interacting protein (TXNIP) increase rapidly in islets during ER stress provoked by thapsigargin (depletes calcium stores in the ER). Up-regulation of TXNIP results in IL-1β and IL-6 production through initiation of the inflammasome[19,20]. TXNIP also leads to induction of oxidative stress through its interaction with thioredoxin, which is a critical redox protein in cells. TXNIP expression is regulated by glucose in human islets and plays a role in glucose-induced β cell death.Therefore, TXNIP may well be a key transducer of glucotoxicity, oxidative stress, and ER stress, feeding into various inflammatory pathways in islets.

The gut may also be involved in the development of

diabetes mellitus. Increased lipopolysaccharide absorption from the gut causes activation of toll like receptor 4 and NF-κB leading to decreased insulin gene expression and insulin secretion in rat and human islets[21]. There is data to suggest that colonization of the gut by specific bacterial species alters the development of autoimmunity in NOD mice and can modify the cytokine and chemokine profile leading to islet cell inflammation[22].

With all this in mind, the search for anti-inflammatory therapies for diabetes was started. Lifestyle modification and drugs already in use for the management of diabetes also have additional anti-inflammatory effects. In the Diabetes Prevention Program (DPP), weight reduction decreased the levels of C-Reactive Protein (CRP) by 31%, whereas metformin decreased CRP by only 13%[23]. Similar results have been observed with surgical weight loss procedures[24]. This implies that lifestyle interventions, even without drug therapy, can decrease insulin resistance; and decrease the progression of pre-diabetes states to T2DM and can decrease the progression of diabetes mellitus (DM) and its complications by decreasing inflammation. Drugs like thiazolidinedione for the same degree of glucose reduction have been shown to reduce markers of inflammation to a greater extent compared to other therapies[25]. This may be the result of peroxisome proliferator-activated receptor-γ (PPAR-γ) transrepression of inflammatory-response genes[26]. This demonstrates that a reduction in inflammation adds to the beneficial effects of these drugs, which are independent of the effect on glucose levels and thus is a direct effect.

Insulin therapy by itself over the short-term has been associated with a decrease in inflammation. This effect is mediated by the decreased activity of NF-κB which is the master transcriptional regulator of the inflammatory response[27]. However, this effect of insulin is temporary and/or requires higher doses of intravenous insulin[28]. This may be one of the additional advantages of adding insulin early in the course of T2DM and may delay the progression of DM and its complications.

One class of drugs used widely in diabetes mellitus that also have anti-inflammatory effects are statins. Statins inhibit hydroxymethylglutaryl-CoA reductase, and hence, cause a reduction in cholesterol levels. In addition, statins have also been shown to reduce the levels of CRP by 25%-30%[29]. This is a class effect of all statins and is not dose-dependent. The decrease in CRP levels does not correlate with the decrease in lipid levels, which implies that this effect is a direct effect of statins. CRP is an independent predictor of cardiovascular events. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin trial assessed the effect of rosuvastatin on the rates of primary cardiovascular events in subjects with high CRP concentrations, but without hyperlipidemia (CRP > 2 mg/L; low density lipoprotein (LDL) < 130 mg/dL)[30]. The CRP concentration was reduced by 37%, however, the LDL concentration was reduced by 50%, therefore, it is uncertain whether the effects of statins are truly mediated *via* the anti-inflammatory process or are the result of its lipid-lowering effect. In addition, incident T2DM increased in the statin-treated patients, an effect seen with other agents in the statin class[31]. This finding demonstrated a divide in the association between inflammation, diabetes, and cardiovascular disease, which may be explained by the potent effects of statins on lipids. Apart from CRP, statins do not have any effect on any other markers of inflammation such as fibrinogen.

NEWER THERAPEUTIC TARGETS

The following drugs are in trials for targeting inflammation and are not yet available as prescription drugs for diabetes.

Etanercept

Etanercept (934 amino acids, 150 kilo Dalton) is a dimeric fusion protein with an extracellular ligand binding domain of the Human Tumor Necrosis Factor Receptor (TNFR) linked to the Fc component of human IgG1. It is produced by a recombinant DNA technique in Chinese Hamster Ovary cells.

Blockade of TNF-α receptor has been shown to decrease insulin resistance in obese rats[32]. A trial of etanercept failed to improve insulin sensitivity in subjects with the metabolic syndrome despite lowering CRP[33]. This may have been due to the fact that the concentration of TNF-α intracellularly is almost twice that in the extracellular space, and it is the intracellular TNF-α that is responsible for insulin resistance *via* paracrine effects which were not blocked by etanercept.

Anakinra

Anakinra (153 amino acids, 17.3 kilo Dalton) is a non glycosylated form of the Human IL-1 Receptor antagonist (IL-1Ra) from which it differs only by the addition of a single methionine residue at the amino terminus. It is produced by a recombinant DNA technique in *E. coli*.

IL-1 contributes to impaired insulin secretion, decreased cell proliferation, and apoptosis of pancreatic β cells. The IL-1Ra is endogenously produced, and its concentrations are reduced in the pancreatic islets of patients with T2DM. Anakinra was studied in T2DM and showed promise in increasing beta cell secretory function, and reducing glycemia and markers of systemic inflammation[34]. Definitive conclusions on the possible clinical utility of IL-1Ra in the prevention of diabetes are awaited from the large ongoing Canakinumab Anti-inflammatory Thrombosis Outcomes Study phase Ⅲ clinical trial[35]. The study is being conducted in more than 40 countries around the world and is specifically testing whether blocking the pro-inflammatory cytokine IL-1β with canakinumab, as compared to placebo, can reduce rates of recurrent myocardial infarction, stroke, and cardiovascular death among patients with a history of myocardial infarction who remain at high risk due to a persis-

tent elevation of the inflammatory biomarker hsCRP (≥ 2 mg/L) despite best medical care.

Salsalates

Salsalates belong to the class of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) which exert their anti-inflammatory effect through inhibition of prostaglandin G/H synthase, or cyclooxygenase.These enzymes catalyse the transformation of arachidonic acid to prostaglandins and thromboxanes. NSAIDs also inhibit the expression of cell adhesion molecules, which play a role in targeting circulating cells to inflammatory sites and directly inhibit activation and function of neutrophils.

Trials with high dose salsalates in rodents[36] and in subjects with diabetes[37] have shown that salsalate by inhibiting the inhibitor of nuclear factor kappa-B kinase subunit beta decreases glucose intolerance and increases insulin sensitivity. In an open label study, salsalate, a prodrug form of salicylate, reduced fasting and post-challenge glucose levels and increased glucose utilization in euglycemic, hyperinsulinemic clamp studies[37]. Circulating FFAs were reduced and adiponectin levels were increased. In another study, salsalate, when compared with placebo, reduced fasting glucose by 13% ($P < 0.002$), glycemic response after an oral glucose challenge by 20% ($P = 0.004$), and glycated albumin by 17% ($P < 0.0003$). Although insulin levels were unchanged, fasting and oral glucose tolerance test and C-peptide levels decreased in the salsalate-treated subjects compared with placebo ($P < 0.03$), consistent with improved insulin sensitivity and a known effect of salicylates to inhibit insulin clearance. Adiponectin increased by 57% after salsalate treatment compared with placebo ($P < 0.003$). Additionally,within the group of salsalate-treated subjects, circulating levels of CRP were reduced by 34% ($P < 0.05$)[38]. These findings prove that salsalate reduces glycemia and may improve inflammatory cardiovascular risk indices in overweight individuals. These data support the hypothesis that sub-acute to chronic inflammation contributes to the pathogenesis of obesity-related dysglycemia and that targeting inflammation may provide a therapeutic option for diabetes prevention. However, the effects of salsalate on inflammation are controversial as shown by another study in which salsalate did not change flow mediated dilatation in peripheral conduit arteries in patients with T2DM despite lowering HbA1c. This finding suggests that salsalate does not have an effect on vascular inflammation[39].

Vitamin D

Calcitriol exerts regulatory effects on molecular pathways involved in inflammation, such as inhibition of PG synthesis and actions, inhibition of stress-activated kinase signaling and the resultant production of inflammatory cytokines,such as inhibition of NF-κB signaling and the production of pro-angiogenic factors. Clinical trials investigating the effects of vitamin D supplementation on serum levels of inflammatory markers have provided inconsistent results, with no evidence of effects in most trials, or effects on selected markers in a few other trials[40]. Similarly, available trials have shown no convincing benefits of vitamin D supplementation on plasma glucose levels and insulin resistance[41,42]. This systematic review and meta-analysis showed that vitamin D supplementation resulted in a small improvement in fasting glucose and insulin resistance in subjects with diabetes or impaired glucose tolerance, but no effect on glycated haemoglobin among those with diabetes. Hence, the role of vitamin D supplementation requires further well planned trials.

Chloroquine

Chloroquine is a weak base and carries a positive charge at acidic pH. It is this property of the drug that makes it selectively accumulate in lysosomes and generate a concentration gradient of a high order. This lysosomatotrophic action is responsible for the hepatic retention of insulin. Another action of the drug is decreased degradation of insulin in the muscle tissue.

A retrospective study suggested that the use of chloroquine to treat rheumatoid arthritis is associated with a lower incidence of T2DM[43]. However, this study included a specific group of patients who required the drug for another indication. Prospective studies of chloroquine are ongoing and the results are awaited.

Diacerin

Diacerin is a semi-synthetic anthraquinone derivative which directly inhibits IL-1 synthesis and release *in vitro* and downregulates IL-1 induced activities. It has been shown to possess a disease modifying effect in osteoarthritis.

In a randomized double-blind, placebo-controlled trial, 2-mo treatment of drug-naive T2DM patients with diacerin increased insulin secretion without changes in insulin sensitivity[44]. This implies a direct effect of the drug on beta cell function.

Other emerging therapies

Inhibition of 12-Lipo oxygenase: Twelve-Lipo oxygenase (12-LO) produces pro-inflammatory arachidonic acid products and is upregulated in islets of both T1DM and T2DM patients[45] leading to insulin resistance and islet cell dysfunction. Hyperglycemia and inflammatory cytokines increase the expression of 12-LO[45,46]. The activation of 12-LO has also been implicated in causing adipose tissue inflammation and insulin resistance. In NOD mice (T1DM model), Zucker diabetic fatty rats (T2DM model), and diet-induced obese mice (T2DM model) gene deletion and pharmacological suppression of 12-LO prevented the development of diabetes[47,48]. These findings point towards inhibition of 12-LO being a promising target in both T1DM and T2DM for decreasing insulin resistance, β cell dysfunction and cardiovascular complications.

Histone de-acetylases inhibition: Histone de-acetylases (HDAC) Ⅰ, ⅡA, ⅡB, Ⅲ and Ⅳ are involved in inflam-

matory responses in a variety of conditions including diabetes. HDAC inhibitors cause acetylation of the p65 subunit of NF-κB leading to its inhibition and hence a decrease in the inflammatory response. To date, there are no human data, however, animal data support the role of HDAC inhibition in β cell preservation. Linkage analysis has also revealed that a locus in 6q21, associated with both T1DM and T2DM, lies near HDAC2. Beta cell mass expansion has been observed with HDAC Ⅱ A inhibitors. In streptozotocin (STZ)-induced diabetes, ITF2357 an orally active inhibitor against class I and Ⅱ HDAC, leads to the prevention of diabetes[49].

Sirtuin 1: Sirtuin 1 (Sirt1) is a NAD^+-dependent HDAC class Ⅲ deacetylase. Some of the SIRT1 deacetylation substrates (PGc1a, FoXo, p53, and the p65 subunit of NF-κB (10,41-43 proteins) are central regulators of cellular metabolism, energy expenditure, inflammation and stress response pathways in the cell. These may be an additional target in reducing inflammation. Activation of Sirt1 may have an antiinflammatory role to play in the islets. Sirt1 overexpression prevents NF-κB mediated cytokine-induced β cell damage and its expression has been shown to be reduced in pancreatic islets after cytokine exposure[50]. Nicotinamide mononucleotide, a metabolite that augments sirtuin action, rescues islets from reduced insulin secretion after IL-1β and TNF-α exposure[51].

Identification of the targets of each class of HDAC in human islets under inflammatory conditions will aid in the therapeutic application of this emerging class of agents.

FAT-1 transgene: Long-chain n-3 PUFAs act directly by replacing arachidonic acid as an eicosanoid substrate and inhibiting arachidonic acid metabolism indirectly by altering the expression of inflammatory genes through effects on transcription factor activation. In addition, they increase anti-inflammatory mediators such as resolvins. Thus, n-3 PUFAs are potent anti-inflammatory agents. The FAT-1 transgenic mouse, which expresses the Caenorhabditis elegans *FAT-1* gene encoding an n-3 fatty acid desaturase that converts n-6 to n-3 fatty acids (which is absent in mammals) showed augmented production of n-3 polyunsaturated fatty acids. This has been shown to be protective against the development of diabetes after multiple low dose STZ injections, and displays lower levels of IL-1β, TNF-α, NF-κB and 12-HETE[52]. This may be an additional target for inflammation in T2DM.

Recent studies have indicated that ELF5A-1, an ancient and poorly understood protein, is an important regulator of cytokine release and signalling. This protein is the only protein which contains the unique amino acid, hypusine,which is a modified amino acid lysine residue. Hypusine modification by the inhibitory enzymes, deoxyhypusine synthase and deoxyhypusine hydroxylase, is required for ELF5A-1 action in cytokine signalling. Therefore, this modification may well be a new therapeutic target for preventing beta cell decline in the setting of diabetes inflammation[53]. Anti-inflammatory therapeutic targets have been used to decrease the conversion from prediabetes to diabetes and the progression of T2DM. Anti-inflammatory therapies have also been used as treatment modalities for the complications of T2DM and are detailed as follows.

Therapeutic treatments targeting inflammatory mediators in diabetic neuropathy

The various proposed mechanisms of diabetic neuropathy include increased reactive oxygen species production, increased protein glycosylation, neurovascular disturbances, and decreased neurotrophic support.Mouse models have shown that NF-κB activation is associated with diabetic neuropathy. Toll-like receptors can also activate NF-κB and lead to increased expression of cytokines and chemokines. The levels of pro-inflammatory cytokines, chemokines and TNF-α have been shown to be increased in mouse and human models, although the pathogenesis is not yet clear. Rodent studies revealed that increased COX-2 expression leads to a decrease in sensory and motor nerve conduction velocities (NCV), endoneurial blood flow, and intraepidermal nerve fiber density in diabetic mice compared to non-diabetic mice. This led to trials of COX-2 inhibitors and other anti-inflammatory drugs in diabetic neuropathy.

Monocytes from T2DM patients demonstrated increased expression of TNF-α, IL-1, IL-6, and IL-8 as compared to healthy controls and T1DM patients; treatment of these monocytes with 1,25-dihydroxyvitamin D3 downregulated the mRNAs of these cytokines[54]. The natural flavonoid, curcumin, led to a dose-dependent decrease in serum TNF-α levels and attenuated thermal hyperalgesia in STZ-treated mice[55,56]. The beneficial effect of this treatment was further enhanced by the use of insulin[57]. Other agents capable of preventing inflammatory-mediated events in rodent models include glicazide and troglitazone both of which attenuate TNF-α levels. Both of these treatments also prevented decreases in myelinated fiber area, fiber density, and the axon/myelin ratio in the tibial nerve of diabetic rats[58,59].

The anti-oxidant, N-acetylcysteine, dose-dependently decreased TNF-α levels[60] which translated into a decreased incidence or severity of neuropathy.

The expression of COX-2 is increased in the peripheral tissues of diabetic neuropathy models. Piroxicam statistically improved STZ-induced decreases in sensory neuron action potential amplitude[61]. The non-selective inhibitors, sulindac and indomethacin, decreased losses in sural and caudal sensory nerve conduction velocity of diabetic rodents compared to control mice[62,63]. Some non-selective COX inhibitors are effective treatment options, and flurbiprofen alone decreased motor NCV (MNCV). In fact, flurbiprofen treatment mimicked STZ-induced changes and did not reverse/alter STZ-induced changes on MNCV[64]. These findings indicate that COX-1 maintains neural function in rodents. Following this observation, studies were planned to assess the efficacy of COX-2 inhibitors. It was found that

celecoxib treatment prevented the decrease in MNCV and sensory nerve conduction velocity (slowing)[65], and meloxicam was shown to protect against MNCV slowing and endoneurial blood flow deficits in diabetic rodents. Intrathecal administration of COX-2 inhibitors led to a dose-dependent attenuation of mechanical behaviour[66]. Selective inhibition of COX-2 *via* pharmacological or gene inactivation played a preventive role in the increased TNF-α expression in the sciatic nerve of STZ-induced diabetic rodents[67]. However, clinical studies with these drugs are lacking. Only one study evaluating NSAID treatment in diabetic patients has been carried out, which demonstrated an improvement in the neuropathy score with ibruprofen and sulindac treatment compared to placebo[68]. However, these results should be interpreted with caution as no healthy age-matched controls were included. The study only compared responders with non-responders. NSAIDS are a double-edged sword in that their long-term use requires caution due to their well-known side effects. Although selective COX-2 inhibitors do not result in gastrointestinal side effects, cardiovascular side effects are a concern, especially in patients with a high risk for cardiovascular disease, of which subjects with DM form a part. However, it is clear that the agents targeting inflammation in diabetic neuropathy are effective only if targeted very early in the course of neuropathy. Evidence demonstrating their effectiveness after the development of diabetic neuropathy in reversing symptoms such as reductions in nerve conduction velocities or nociceptive behaviour is lacking. Larger studies investigating the time course of anti-inflammatory therapeutics should be planned. Current studies have demonstrated no reversal of diabetic neuropathy and the benefits observed only occur after a treatment period of at least 12 wk[69,70]. Overall, more studies are needed to validate these findings.

Therapeutic treatments targeting inflammatory mediators in diabetic retinopathy

Hyperglycemia increases advanced glycation endproduct (AGE) formation, reactive oxygen species and leads to nitric oxide synthatase dysregulation resulting in activation of NF-κB followed by an increase in cytokines (IL-1, IL-6, TNF-α), chemokines such as CCL-2, 58, 10, 12 and adhesion molecules like intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). This leads to activation of endothelial cells, recruitment of inflammatory cells, increased levels of vascular endothelial growth factor (VEGF) and Angiopoietin 2. These factors are involved in the pathogenesis of increased capillary permeability, capillary dropout and neo-vascularization.

The various therapies used as anti inflammatory therapies in diabetic retinopathy hence target VEGF, Angiopoietin 2, various proteinases and chemokines.

The most important factor, which has been extensively investigated in the alteration of the blood retinal barrier (BRB), is VEGF. Levels of VEGF are significantly elevated in patients with diabetic macular edema (DME) as compared to non-diabetic eye diseases[71,72]. VEGF is a potent vasoactive cytokine which increases vascular permeability. The major effect of VEGF is on endothelial tight junction proteins, leading to extravasation of fluid and hence retinal edema. It also induces the phosphorylation of VE-cadherin, occludin, and ZO-1, causing disruption of the barrier[73].

In addition, it also stimulates increased leukostasis in the microvasculature of the retina, which also leads to breakdown of the BRB[74,75].

Therefore, most of the clinical trials on retinopathy have targeted VEGF. Direct VEGF inhibitors include the anti-VEGF aptamer, pegaptanib, the monoclonal antibody fragment, ranibizumab, and the full length antibody bevacizumab. Other drugs include soluble VEGF receptor analogs, VEGF-Trap, small interfering RNAs (siRNAs) bevasiranib, and rapamycin (sirolimus). Some studies have shown that after two years, the mean change in the visual acuity letter score from baseline was 3.7 letters greater in the ranibizumab and prompt laser group, 5.8 letters greater in the ranibizumab and deferred laser group, and 1.5 letters worse in the triamcinolone and prompt laser group[76]. However, it is important that response to the anti-VEGF treatments in DME is variable, and is not as robust as in proliferative diabetic retinopathy or neovascular glaucoma. This implies that the pathogenesis of DME is multifactorial and anti-VEGF therapy is only one player in the overall pathogenesis.

Angiopoietins are another class of inflammatory growth factors that are important modulators of angiogenesis. The levels of angiopoietin-2 (Ang-2) are significantly elevated in patients with clinically significant macular edema[77], indicating that it alters the BRB. In another study increased expression of Ang-2 mRNA and protein has been demonstrated in the retina of diabetic animals[78]. Even in non-diabetic rats, intra-vitreal injection of Ang-2 led to a three-fold increase in retinal vascular permeability. Ang-2 also induces phosphorylation and loss of VE-cadherin[78]. Recent data have suggested that Ang-2 sensitizes endothelial cells to TNF-α-induced ICAM-1 expression and hence monocyte adhesion. This implies that Ang-2 is an autocrine regulator of endothelial cell inflammatory responses. Therefore, Ang-2 plays a permissive role in the augmentation of pro-inflammatory cytokines[79]. This molecule maybe an important therapeutic target in DME. Ang-2 inhibitors in various tumor models have been found to be effective in preventing tumor growth through the modulation of monocyte infiltration and angiogenesis[80]. Matrix metalloproteinases (MMPs) are major regulators of innate and acquired immunity[81]. Knockout mouse models have shown that these molecules play an important role in both acute and chronic inflammation[82]. It has also been shown that MMPs are important for the proteolytic alteration and hence activation of chemokines. They cleave many members of the CCL/monocyte chemoattractant protein (MCP) family of chemokines rendering them proactive,

which amplifies the inflammatory response. Furthermore, MMPs organise the recruitment of leukocytes as an essential component of tumor-associated inflammation[83]. It is now evident that MMPs also play an important role in the pathogenesis of diabetic retinopathy (DR). The vitreous level of proteinases, such as MMP9, are higher in diabetic subjects with DR than without DR[84]. Both MMP2 and MMP9 are elevated in the retina of animal models with early DR[85]. The retinal vascular permeability in diabetic animals is significantly increased which is a result of a decrease in cell-cell junctional protein and VE-cadherin. MMP inhibitors can decrease this vascular permeability[86]. This implies that the proteolytic degradation of VE-cadherin contributes to the BRB breakdown. This is evidence for the role of extracellular proteinases in the alteration of the BRB seen in DR[87]. Hyperglycemia can activate many soluble mediators such as AGE, reactive oxygen species (ROS), and inflammatory cytokines, which can increase MMP levels and activity in the diabetic state. Retinal inflammation leads to increased leukocyte infiltration in the retina, which by binding to endothelial cells activates cellular proteinases such as elastase, followed by removal of VE-cadherin and its associated protein from the cell surface, resulting in alterations in the endothelial monolayer[88]. These studies indicate an important role for these proteinases in DR.

The levels of many chemokines have been shown to be elevated in various studies.The most common chemokine found to be elevated in serum and vitreous is CCL2[89,90]. CCL2, also known as MCP-1, plays an important role in vascular inflammation by inducing leukocyte recruitment and activation. Hyperglycemia increases CCL2/MCP-1 generation in retinal vascular endothelial cells, pigmented epithelial cells and Muller's glial cells[91]. Furthermore, the gene polymorphism of CCL2 has been indicated as a potential risk factor for DR[92].

Studies have shown that genetic knockout of the CCL2 gene in diabetic mice plays a preventive role in alteration of the BRB[93], and that selective inhibition of the CCL2 gene can prevent alteration of the BRB in diabetes. Further studies using selective inhibitors of CCL2 and CCR2 are in progress.

Genistein, a tyrosine kinase inhibitor, has been shown to be effective in reducing diabetes-induced retinal inflammation by interfering with inflammatory signaling (ERK and P38 MAPKs) in activated microglia. This beneficial effect of genistein may represent a new intervention therapy for modulating early pathological pathways long before the occurrence of vision loss in diabetics[94].

Therapeutic treatments targeting inflammatory mediators in diabetic nephropathy

Inflammation activated by the metabolic, biochemical and haemodynamic derangements may play a key role in the development and progression of diabetic nephropathy. Cytokines such as IL-1, IL-6 and TNF-α stimulate the expression of cell adhesion molecules and profibrotic growth factors, increase endothelial permeability, promote mesangial proliferation, glomerular hypertrophy and the production of ROS. Chemokines like Protein kinase C (PKC)-dependent ICAM-1, VCAM-1 and MCP-1 facilitate leukocyte-endothelial adhesion and infiltration into diabetic kidneys. Adiponectin is protective in that it reduces oxidative stress, the production of TNF-α, and leukocyte-endothelial adhesion. Adiponectin has also been shown to interfere with receptor activation of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF). Increased mammalian target of rapamycin (mTOR) activity has been shown to cause glomerular hypertrophy and hyperfiltration in diabetic subjects.

Adenosine is a potent autocrine anti-inflammatory and immunosuppressive molecule that is released from cells into the extracellular space at sites of inflammation and tissue injury. The levels of adenosine, an endogenous purine nucleoside, released from various tissues and organs are decreased in diabetic nephropathy (DN)[95]. DN was more severe in A_{2A} receptor knockout mice than in wild-type mice, which suggests that endogenous adenosine may contribute to kidney protection due to diabetes in a similar manner to that in kidney ischemia-reperfusion injury[96]. MCP-1/CCL2 inhibition by propagermanium ameliorated diabetic glomerulosclerosis and is another target for DN[97]. However, clinical inhibitors of CCL2 have shown only partial effects[98]. Even with CCL2 knockout, only a reduction in albuminuria was observed[99].

Pentoxifylline inhibits the expression of TNF-α mRNA levels[100]. In combination with angiotensin-converting enzyme inhibitors and AT1 receptor blockers (ARB), pentoxifylline decreased albuminuria in DN[101,102].

In a prospective, randomized, double-blind, placebo-controlled study, pentoxifylline (1200 mg daily) for 12 mo, in 34 patients with incipient or established DN had a reno-protective effect determined by a significant reduction in urinary albumin excretion in both incipient and established ($P < 0.01$) DN patients. This effect was attributed to a reduction in CRP, IL-6, TNF-α and serum leptin levels ($P < 0.01$)[103].

The results from 7 animal studies and 13 randomized controlled trials on diabetic kidney disease consistently demonstrated that short-term use of pentoxifylline produced a significant reduction in proteinuria and microalbuminuria in patients with diabetic and non-diabetic kidney diseases. The reports on long-term studies also showed that urinary protein excretion was considerably reduced in patients treated with pentoxifylline; however, as these results were mostly based on small clinical trials it is not clear whether the additive anti-proteinuric effect of pentoxifylline is sustained over time. Large scale clinical trials are needed to establish the long-term use of pentoxifylline as a pharmacological alternative for delaying or preventing the development of end-stage renal disease.

Adiponectin has been shown to suppress inflammatory markers including TNF-α, and receptor activation for PDGF, EGF and FGF. Adiponectin has also been shown to preserve nephrin, decrease the expression levels of TGF-β, and reduce albuminuria.

Inhibition of NF-κB in kidney using PPAR-γ[104],

ARB[105], or pentosan polysulfate[106] has been shown to ameliorate DN in animal models. However,the efficacy of inhibition of NF-κB in delaying progression of DN has not been reported.

HMG-CoA reductase inhibitors (statins) have a controversial role in DN. In a subanalysis of the Treating to New Targets study, treatment with 10 mg and 80 mg atorvastatin was found to increase estimated glomerular filtration rate (eGFR)[107], while in the Prevention of Renal and Vascular End-Stage Disease Intervention Trial, treatment with 40 mg pravastatin did not result in an increase in eGFR[108].

The mTOR is a serine/threonine kinase that mediates cell proliferation, survival, size, and mass[109]. Rapamycin decreases hyperglycemia-induced increase in mTOR activity and thus decreases renal changes in DN, including mesangial expansion and glomerular basement thickness[110]. Rapamycin also significantly reduces the influx of monocytes and macrophages associated with the progression of DN[111,112]. It has also been shown to decrease the release of pro-inflammatory cytokines or chemokines including MCP-1, regulate normal T cell expression and secreted, IL-8, and fractalkine[111,112]. Thus, rapamycin represents a new and valuable anti-inflammatory target in DN.

A recent study showed that aspirin decreased albuminuria in patients with DN[113]. In combination with AT1 receptor blockers (ARB) it led to a further decrease in the progression of DN and inflammatory markers compared to when used alone[114]. This effect of COX-2 inhibitors is postulated to occur as a result of the effects on renal hemodynamics and decrease in profibrotic cytokines[115]. However, in another study, treatment with 200 mg/d COX-2 inhibitor for six weeks did not decrease DN[116]. Thus, the overall data for COX-2 inhibitors in DN remains controversial.

PKC is induced by hyperglycemia and insulin resistance. This PKC activation then alters cell signaling molecules including inflammatory cytokines such as NF-κB, IL-6, TNF-α, and plasminogen activator-1 (PAI-1) in endothelial and mesangial cells[117-119]. Ruboxistaurin (RBX), a PKCβ isoform selective inhibitor, has been shown to prevent DN in rodent DN models by inhibiting mediators of extracellular matrix accumulation, TGF-β and amelioration of insulin signalling[120]. Diabetic PKCβ null mice showed decreased albuminuria and mesangial expansion[121]. A phase Ⅱ clinical trial with RBX significantly decreased albuminuria and maintained a stable eGFR[122]. Recently, it was shown that hyperglycemia itself can activate PKCβ isoforms, which increased the detrimental effects of Ang-2 on glomerular endothelial cells and decreased the glucagon-like peptide-1 (GLP-1) receptor, leading to resistance to GLP-1 treatment in DN[123]. Recent findings suggest that hyperglycemia also activates PKCβ and p38 mitogen-activated protein (MAPK) to increase Src homology-2 domain-containing phosphatase-1 and causes VEGF resistance and independent NF-κB activation to induce podocyte apoptosis in DN[124] which may be new targets of treatment.

Exogenous insulin has been shown to inhibit the activation of TNF-α in animal models[125]. Furthermore,insulin inhibits MCP-1 expression and activation of NF-κB in endothelial cells[126]. Recent studies in patients with T2DM have shown that insulin treatment decreases the expression of inflammatory cytokines, such as MCP-1, ICAM-1, soluble VCAM-1 (sVCAM-1), TNF-α, and IL-6[127,128].

Insulin can increase endothelial nitric oxide (NO) production by rapid post-translational mechanisms, mediated by the PI3K/Akt signaling pathway, leading to vasodilatation, an antithrombotic effect, and anti-inflammatory actions[129-131]. Insulin not only stimulates NO production, but also increases the expression of endothelial NO synthase (eNOS)[132]. Recent data indicate that vascular endothelial cell specific insulin receptor knockout mice had decreased eNOS expression in the aorta[133]. Thus, insulin resistance in vascular tissue could contribute to DN. However, to date, the efficacy of exogenous NO donor remains unclear. Insulin and metformin were studied in a trial for 14 wk. Despite substantially improving glucose control, neither insulin nor metformin reduced inflammatory biomarker levels including hsCRP, IL-6, and sTNFR2, which were the main effects evaluated in comparisons between the individual treatment groups (placebo metformin only; placebo metformin and insulin; active metformin only; or active metformin and insulin)[28].

PPARs regulate insulin sensitivity, lipid metabolism, adipogenesis and cell growth[134-137]. Recent studies indicated that a PPAR-γ agonist decreased the expression of inflammatory markers such as PAI-1, ICAM-1, and NF-κB in the kidney in DN and ameliorated renal function[138].

Analysis of the GLP-1 receptor (GLP-1R) has revealed its expression in endothelial cells and kidney[139,140]. In endothelial cells, GLP-1 inhibits the expression of TNF-α and VCAM-1[141]. GLP-1 acts on the glomerular endothelial cells and decreases the signaling pathway of Ang-2 at phospho-c-Raf (Ser338)/phospho-Erk1/2 *via* phospho-c-Raf (Ser259) activated by the cAMP/PKA pathway. Administration of GLP-1 in DN decreases inflammatory markers including PAI-1, CD68, IL-6, TNF-α, NF-κB, and CXCL2 in the kidney[117].

DPP-4 inhibitors provide vascular protection by increasing the bioavailability of GLP-1and its action. They have also been reported to decrease the levels of MCP-1. In addition, they have vasotropic actions and a possible reduction in DN[142]. A recent large phase Ⅲ study showed that linagliptin significantly reduced albuminuria in DN by 30%[143]. However, the role of DPP-4 inhibitors in the regulation of inflammatory cytokines and vasotropic actions remains largely unexplored and open to further trials.

DIABETES, THE METABOLIC SYNDROME AND NON-ALCOHOLIC FATTY LIVER DISEASE

Type 2 diabetes mellitus is part of the metabolic syn-

drome and non-alcoholic fatty liver disease (NAFLD) shares insulin resistance as a common pathophysiology with T2DM. More recently, NAFLD has been proposed, but not yet accepted, as a criterion for defining the metabolic syndrome[144]. Hepatic insulin resistance has a key role to play in the pathogenesis of NAFLD and adiponectin, an abundant adipocytokine, decreases both hepatic and systemic insulin resistance by decreasing inflammation[145]. Hence, adiponectin and its agonists may be promising targets to reduce both hepatic and systemic insulin resistance[146,147]. Exercise, in addition to its benefits in reducing weight and insulin resistance also reduces the levels of inflammatory cytokines implicated in diabetes-associated NAFLD[148]. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been used in NAFLD and lead to a significant reduction in the expression of pro-inflammatory molecules (TNF-α and IL-6) and of reactive oxygen species[149]. Inhibition of Bcl-2 (B-cell lymphoma 2), the first member of the Bcl-2 family of apoptosis regulatory proteins encoded by the *Bcl-2* gene, leads to intensification of inflammation in NAFLD[150]. Serum Bcl-2 concentrations in overweight-obese subjects with NAFLD have been shown to be reduced and may represent an additional target for therapy[151]. JNK, insulin resistance and inflammation represent possible links between NAFLD and coronary artery disease. There are few studies on anti-inflammatory drugs such as aspirin, anti-IL-6 receptors, immune-modulators (calcineurin inhibitors), substances which enhance the expression of heat shock proteins (which protect cells from endoplasmic reticulum stress-induced apoptosis), and anti-c-Jun amino-terminal kinases in NAFLD and these require further study[152]. Thus, NAFLD is a chronic low grade inflammation that leads to insulin resistance due to the increased levels of cytokines[153,154], and anti-inflammatory therapies may help decrease the burden of NAFLD and T2DM.

Thus, inflammation has a role to play both in the pathogenesis of diabetes and its complications and it represents a potential target for treatment in both diabetes and its complications.

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