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REVIEW ARTICLE

# Potential Anti-inflammatory Role of Anti-Diabetic Agents

**Raj Kumar,Navreet Kaur,Nagma Bansal,Kanav Mehta**

**Abstract**

Many current studies show an association of diabetes and secondary complications with chronic inflammation. Evidence of these immunological changes include altered levels of cytokines and chemokines, changes in the numbers and activation states of various leukocyte populations, apoptosis, and fibrosis during diabetes. Therefore, correcting inflammation may be beneficial to stop, impede, and improve diabetes status and its associated complications. Apart from anti-inflammatory drugs, various hypoglycaemic agents have also been found to reduce inflammation that could contribute to improved outcomes in diabetic patients. Various studies have been carried out with thiazolidinediones, dipeptidyl peptidase-4 inhibitors and Metformin showing moderate-to-strong anti-inflammatory action. Sulfonylureas and alpha glucosidase inhibitors exert modest anti-inflammatory effects, while the injectable agents, insulin and glucagon-like peptide-1 receptor agonists, may improve secondary complications due to their anti-inflammatory potential. Currently, there is paucity of human clinical data on anti-inflammatory effects of sodium-glucose cotransporter type-2 (SGLT) inhibitors. Nevertheless, it is essential to distinguish between anti-inflammatory effects resulting from better glucose control and effects related to intrinsic anti-inflammatory actions of the glucose-lowering agents. Also, it is important to define what role the anti-inflammatory effects of these anti-diabetic agents may play in the prevention of macrovascular and microvascular diabetic complications.

**Key Words**

Glucose-lowering Agents, Diabetic Complications, Inflammatory Mediators/ Markers, Interlukin-6 (IL-6), hs-CRP, ESR.

## Introduction

Diabetes mellitus is one of the non-communicable diseases which has become a major global health problem with a prevalence of 382 million human cases, and the incidence is expected to increase to 592 million by 2035. According to the Centres for Disease Control, diabetes incidence suggests one in three Americans will be diagnosed with diabetes by the year 2050. [1] Majority of diabetic patients (90%-95%) suffer from type 2 DM (T2DM), whereas type 1 DM accounts for only 5%-10%. Prevalence of diabetes among Asian Indian population is 12.6%. India is one of the topmost countries which has high prevalence of diabetes. [1] According to WHO, the underlying metabolic cause of T2DM can be attributed to an impairment of insulin-mediated glucose disposal (insulin resistance) and a progressive defect in insulin secretion by pancreatic Beta-cells. [2] Type 1 DM, on the other hand, is a multifactorial, organ-specific autoimmune disease, in genetically susceptible individuals, characterized by a selective and progressive loss of insulin-producing Beta-cells. [3] Insulin resistance persists the entire period, from early stage of pre-diabetes to later stage of overt T2DM. Obesity, aging, Beta-cell dysfunction (hyperglycaemia), tissue lipid accumulation (dyslipidaemia), oxidative stress, endoplasmic reticulum stress (ER-stress) in Beta-cells, tissue inflammation, and physical inactivity are the most commonly known factors linked to insulin resistance which progress T2DM [*Fig1*].Once T2DM occurs, it imparts long-term

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consequences (microvascular or macrovascular complications) which may include atherosclerosis, neuropathy, nephropathy, retinopathy, myopathy and nephropathy. These complications are associated with considerable morbidity, mortality, and with an economic health care burden, which may be addressed by appropriate therapeutic and preventive strategies. [4] Recently, studies have changed the perspective of diabetes mellitus from a metabolic disease to an inflammatory condition. Current literature recognizes that chronic low-grade subclinical inflammation is a part of insulin resistance and strongly related to the features of metabolic syndrome. It's also contributing to the foreseen diabetes complications including both macro and microvascular. [5]

***Association between Inflammation and Hyperglycemia in Type II Diabetes Mellitus***

Many studies have been conducted in order to develop the relationship between various inflammatory mediators and T2DM. Literature has shown increased concentration of markers of acute phase response (including CRP), serum amyloid-A, Sialic acid, white blood cells, plasma level of coagulation factors (fibrinogen, plasminogen activator inhibitor-1), pro-inflammatory cytokines (TNF alpha, IL-1B, IL-6) and chemokines in patients with type 2 diabetes mellitus. In terms of pathogenesis, glucolipotoxicity is one an essential determinant of T2DM. Glucolipotoxicity is a common term used in combination for glucotoxicity and lipotoxicity as both are known to progress simultaneously. [6] Glucotoxicity refers to constantly elevated levels of blood glucose (hyperglycaemia), that have damaging effects on normal functioning of Beta-cells and finally decreases insulin secretion. Similarly, lipotoxicity term refers to constant elevated levels of lipids including free fatty acids (FFAs) and Adipokines. Chronically elevated plasma levels of FFAs and Adipokines may also leads to chronic low-grade inflammation in adipose tissue and Beta-cell dysfunction .[7,8] The term over-nutrition is a frequent over consumption of nutrients relative to the normal amounts. Chronic exposure of hyperglycaemia and dyslipidaemia due to over-nutrition leads to the production of oxidative stress and/or Endoplasmic reticulum stress (ER-Stress) via activation of reactive oxygen species (ROS).

Anti-oxidative enzymes (Cu/Zn superoxide dismutase, Mn (Manganese) superoxide dismutase, Catalase and glutathione peroxidase) are not sufficiently present in Beta-cells, these cells are highly vulnerable to oxidative stress. [9] Both oxidative stress and ER-Stress potentiate each other's effect. Once, oxidative stress occurs within the body, because of imbalance between the production of reactive oxygen species (ROS) and anti-oxidative defence mechanism against the production of ROS, it leads to the activation of various Stress-signalling pathways such as JNK pathway and transcriptional mediated pathways such as p38, JNK, IKK-beta and/or NF-B. IKK-beta also induces the activation of NF-kB. p38, JNK and IKK-beta, further activates the serine phosphorylation of insulin receptor substrate-1 (IRS-1). On the other side, activation of NF-kB further activates the expression of iNOS which also induces the S-nitrosylation of IRS-1. Both S-nitrosylation and serine phosphorylation of IRS-1 suppress the tyrosine phosphorylation of insulin signalling pathways which ultimately results into the induction of insulin resistance in liver, adipocytes and skeletal muscles, which further leads chronic hyperglycaemia. [10] Hence, Transcriptional mediated pathways (p38, JNK, IKK-beta and/or NF-kB) and JNK pathway not only induce Insulin resistance by altering the insulin-mediated glucose uptake by tissue, insulin signalling, but also altered the upregulation of various Pro-inflammatory mediators such as TNF-alpha, IL-1B, IL-6, hs-CRP [*Fig 2*].

***Antidiabetic Agents and their Potential Anti-inflammatory Action***

**Biguanides (Metformin):** Metformin is an oral hypoglycaemic agent which is most widely used as first-line therapy for T2DM. An important possible target of metformin is AMP activated protein kinase (AMPK). AMPK is a key regulator of energy balance and plays many roles in human diseases. [11] A cellular energy sensor is activated under metabolic stress. The activation of AMPK, inhibits hepatic glucose production, improves insulin sensitivity and glucose uptake by muscles, and induces fatty acids oxidation. Recent preclinical and clinical studies have suggested that Metformin not only improves hyperglycaemia and insulin resistance but also has been shown to have anti-inflammatory, anticancer, and antiaging effects and to improve other cardiovascular risk factors, such as an overweight state or obesity, atherogenic dyslipidaemia, blood pressure, procoagulant state, and carotid intima-media thickness . [12] Metformin inhibits pro-inflammatory responses and cytokine-induced nuclear factor kappa B (NF-kB) activation through AMPK-dependent and independent pathways. Metformin also activates AMPK to inhibit NF-kB via PI3K-AKT (PTEN pathway) pathway in human vascular smooth muscle cells for anti-inflammatory action. Metformin also reduces levels of nitric oxide (NO) synthesis activation of AMPK [13] pathway and decreased reactive oxygen species (ROS) production through inhibition of nicotinamide adenine dinucleotide phosphate [NAD(P)H]

oxidase and the respiratory mitochondrial chain in vascular endothelial cells thus leading to suppression of inflammatory response. In addition, other possible mechanism of anti-inflammatory action of metformin is inhibition of advanced glycation end products (AGEs) formation as well as expression of receptor for AGE (RAGE). [12] All above potential anti-inflammatory action collectively reduce the production of NO, ROS, Prostaglandin E2, and pro-inflammatory cytokines through inhibition of NF-kB activation in macrophages. [12]

**Sulfonylureas**

Sulfonylureas is one of the groups of drugs recommended alternate to Metformin. These agents target the ATP-sensitive potassium (KATP) channels in Beta-cells of pancreas. They work by inhibiting ATP-sensitive potassium channels in pancreatic Beta-cells and stimulate insulin secretion. Recent studies have suggested that glibenclamide possesses anti-inflammatory activity. [14] Possible mechanisms include inhibition of the IL-4/ IL-13 signalling pathways and reduced NLRP3 inflammasome activation, leading to decreased production of TNF- alpha, IL-1beta, hs-CRP and ROS. [15-16]

**Glinides**

These drugs act via a similar mechanism as sulfonylureas, they bind to ATP-dependent potassium channels on pancreatic Beta-cells, leading to insulin secretion. But they have a weaker binding affinity and dissociate faster from the sulfonylurea receptor-1 (SUR-1) binding site. Although the anti-inflammatory effects of repaglinide have been demonstrated in non-diabetic animals, the high doses required for an efficacious effect. [17] Whereas, one study showed significant reduction on reduce levels of plasminogen activator inhibitor type-1 (PAI-1), hs-CRP and urinary 8-hydoroxydeoxyguanosine, when treatment (glucose lowering therapy) was changed from glimepiride to repaglinide in Japanese T2DM patients. They nevertheless suggest that Repaglinide can reduce inflammation and oxidative stress by minimizing glucose fluctuations. [18] Another study has showed that controlling postprandial hyperglycaemia with mitiglinide significantly improved a cluster of oxidative stress (reduces ntrotyrosine, malondialdehde, and oxidized low-density lipoprotein levels) and inflammatory markers (decreases IL-6, IL-1B and TNF).

**Thiazolidinediones (PPAR-gamma Agonists)**

These drugs are also known as PPAR-gama agonists. Peroxisome proliferator-activated receptors (PPARs), especially PPAR-gamma, have potential implications in molecular pathways of insulin resistance, T2DM, and atherosclerosis. [19, 20] Rosiglitazone and pioglitazone are two main TZDs, also known as selective agonists of nuclear transcription factor PPAR-gamma. This class of antidiabetic drugs works by activating PPAR-gamma, which stimulates increased storage of FFAs in adipocytes. Because of this, cells utilize more carbohydrates for their energy requirements, thus decreasing circulating glucose levels. PPAR-gamma is mainly expressed in adipose tissue and has been shown to reduce inflammatory markers in visceral adipose tissue (VAT), steatotic liver, atherosclerotic plaques, and circulating plasma. [21] Treatment of Pioglitazone in patients with T2DM reduced ATM content and activity, and was associated with a decrease in inflammatory markers. Recently, a unique population of VAT-resident regulatory T cells was implicated in control of the inflammatory state of adipose tissue and necessary for complete restoration of insulin sensitivity. [21]

**Dipeptidyl peptidase-4 inhibitors (DPP-4 Inhibitors)**

DPP-4 inhibitors, commonly referred to as gliptins, improve glucose metabolism through inhibition of degradation of endogenous GLP-1, which causes the elevation of GLP-1 receptor signalling, leading to increased insulin secretion and suppressed glucagon secretion in the pancreas. [22] DPP-4 also inhibitors offers clinical advantages including beneficial effects on the cardiovascular system without risk of hypoglycaemia and weight gain. Also, DPP-4 inhibitors can exert antiatherogenic effects which include lowered systolic blood pressure, improved postprandial lipid parameters, reduced silent inflammation, reduced oxidative stress, and improved endothelial dysfunction. Previous data consistently suggested that DPP-4 inhibitors positively influence a variety of cardiovascular risk factors, including inflammatory markers. [23] DPP-4 inhibitors were found to suppress NLRP3 gene, toll-like receptor-4 (TLR-4) and IL-1 in human macrophages through inhibition of protein kinase C (PKC) activity. All above findings provide novel insights into the mechanism of inhibition of the inflammatory state and immune response in atherosclerosis by these agents .[24] Commonly used DDP-4 inhibitors are linagliptin, tinigliptin, sitagliptin and vildagliptin. Sitagliptin is the most extensively studied DPP-4 inhibitor in terms of its potential effect on inflammatory processes. Its potent and rapid anti-inflammatory effect has been reported in patients with T2DM and may potentially contribute to inhibition of atherosclerosis. [25] In addition, treatment with sitagliptin inhibits mononuclear mRNA expression of CD26, pro-inflammatory cytokines, TNF-alpha, endotoxin receptors, TLR-4, TLR-2 and pro-inflammatory kinases, c-Jun N-terminal protein kinase-1 (JNK-1), inhibitory nuclear factor kappa-B kinase subunit beta (IKKbeta) and inhibitor of

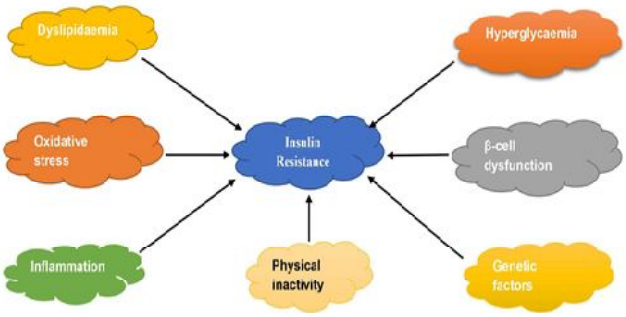


***Fig. 1 Factor Linked to Insulin Resistance***

C-C chemokine receptor type-2 (CCR-2), in T2DM patients. Anti-inflammatory activities have been reported with other DPP-4 inhibitors, too. The anti-inflammatory, anticoagulant and antithrombotic mechanisms of vildagliptin were recently reviewed. [23] Vildagliptin was found to be superior compared to Sitagliptin in reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with T2DM.The anti-inflammatory effects of linagliptin monotherapy were also reported in diabetic haemodialysis patients, a population at high risk of cardiovascular disease. Linagliptin decreased levels of prostaglandin E2, IL-6, hs-CRP, glycated albumin, and blood glucose which was associated with an increase in active GLP. [25]

***Sodium-glucose Cotransporter-2 inhibitors (SGLT2 Inhibitors)***

SGLT2 inhibitor is the newest oral approach for the management of T2DM. Dapagliflozin, canagliflozin, empagliflozin, and ipragliflozin are commonly used drugs in many countries, and others are in the late phases of development. SGLT2 inhibitors may also exert metabolic effects beyond increased glucosuria, it also reduces hyperglycaemia (without inducing hypoglycaemia), promote weight loss, and exert a modest diuretic effect with blood pressure reduction. Although, few clinical data are available (animal data are reported more) to suggest anti-inflammatory effect or role of SGLT2 inhibitors on markers of inflammation. [26] Ipragliflozin was found to reduce hyperglycaemia, dyslipidemia, oxidative stress and plasma, inflammatory markers (IL-6, TNF-alpha, MCP-1, and CRP) in high-fat diet and streptozotocin-nicotinamide-induced type-2 diabetic mice and in rats with streptozotocin-induced type-1 diabetes. [27]

## Conclusion

There is a growing body of evidence that over-nutrition and obesity can lead to various metabolic disorders including diabetes mellitus type II and cardiovascular diseases. Chronic exposure to hyperglycaemia and

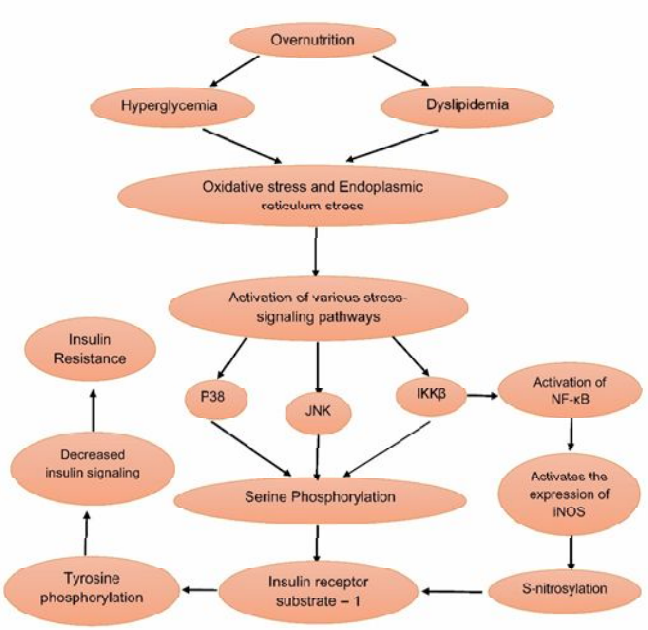


***Fig. 2 Mechanism of Oxidative stress and Endoplasmic Reticulum Stess induced insulin Resistance***

dyslipidemia due to over-nutrition cause further activation of the innate immune system in various tissues. As a result, it causes elevation of pro-inflammatory markers, while anti-inflammatory factors get decreased in T2DM patients. The most popular inflammatory marker is hs-CRP. Antidiabetic agents have dual action that is improving the glycaemic level and inflammatory markers in T2DM. Thus, these agents are quite effective in managing of diabetes cases having subacute complications involving inflammation. This review article has explored studies that make it evident that available antidiabetic agents exert anti-inflammatory actions which may contribute to improve T2DM patients' outcomes. There is further need to investigate the role of other glucose-lowering agents to explore the anti-inflammatory effects and / or inflammatory markers which may help in the overall management of patients with T2DM.

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