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Beyond blood sugar: exploring the anti-inflammatory frontier of antidiabetic medications to alleviate diabetic complications

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Abstract

Background and objective. *Inflammation is closely correlated with diabetes and diabetic complications. Research has shown that individuals with diabetes exhibit an upregulation of circulatory proinflammatory cytokines, resulting in a chronic state of low-grade inflammation. The participation of inflammation in the pathogenesis of diabetic complications, particularly cardiovascular and renal complications, is well-established. Targeting inflammation may produce prominent effects in improving the clinical condition of diabetic patients, reducing the progression of complications, and promoting glucose uptake by insulin-sensitive tissues. This review article aimed to explore the anti-inflammatory effect of antidiabetics beyond their hypoglycemic action and the potential effects of such antidiabetics in reducing diabetic complications.*

Materials and methods. *Based on relevant online publications using the terms anti-diabetics, anti-inflammatory, diabetic complications, and inflammatory mediators up to February 2024 on PubMed and Google Scholar were utilized to construct this review.*

Results. *The majority of antidiabetic drugs pose an indirect effect on inflammation through the hypoglycemic effect. However, many antidiabetics have an additional anti-inflammatory mechanism independently of their hypoglycemic effects, which augments their anti-inflammatory effects.*

Conclusion. *Suppression of the inflammatory response by anti-diabetics and achieving homeostatic control is an effective approach for preventing diabetic complications.*

Keywords: anti-diabetes, anti-inflammatory effects, diabetes, diabetic complications, inflammation, inflammatory mediators

Abbreviations:

AGEs – advanced glycation end products
AG-I – alpha-glucosidase inhibitors
Akt – protein kinase B
AMPK – adenosine monophosphate-activated protein kinase
CRP – C-reactive protein
CVD – cardiovascular disease
DM 2 – diabetes mellitus type 2
DPP-4-I – dipeptidyl peptidase-4 inhibitors
ESKD – end-stage kidney disease
GLP-1-Ra – glucagon-like peptide-1 receptor agonists
IKK-β – IKappa B kinase-β
IL – interleukins
InRs – insulin resistance
IRS-1 – insulin receptor substrate-1
JNK – c-Jun N-terminal kinase
MCP-1 – monocyte chemoattractant protein-1
MMP-9 – matrix metalloproteinase-9 (MMP-9)

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NAFLD – nonalcoholic fatty liver disease
NF-kappa B – nuclear factor kappa B
NLRP3 – nucleotide-binding domain, leucine-rich-containing family, and pyrin-containing-3
NO – nitric oxide
PAI-1 – plasminogen activator inhibitor-1
PPAR – peroxisome proliferator-activated receptors
RAGE – receptors for advanced glycation end products
ROS – reactive oxygen species
SGLT2-I – sodium-glucose cotransporter inhibitors
TAZDs – thiazolidinediones
TGF-β1– transforming growth factor-β1
TLRs – tool-like receptors
TNF-α – tumor necrosis factor α

INTRODUCTION

Insulin resistance (InRs) results when cells are unable to respond normally to insulin. This leads to an increase in the risk of diabetes mellitus type 2 (DM 2) development. A combination of genetics and environmental factors including obesity leads to InRs and consequently, DM 2 [1]. InRs could be caused by an inflammatory response resulting from immune system activation. This Inflammation has the potential to aggravate diabetes and other medical conditions. Circulating proinflammatory cytokines are upregulated in DM 2, leading to a persistent inflammatory state in a low-grade [2]. Therefore, inflammation has been proposed as a potential mechanism to explain the pathophysiology of DM 2. According to this mechanism, local stressful circumstances promote the production of cytokines and other proinflammatory signals including interleukins (IL), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and angiotensinogen. Adipocyte-secreted adipokines, including resistin, leptin, and adiponectin, can also impact DM 2 and inflammation [3].

Complications of DM 2 are aggravated by the inflammatory responses. The elevated inflammatory mediators in the presence of hyperglycemia participate in increasing prostaglandin synthesis, promote leukocyte and macrophage recruitment, upregulate fibronectin, increase the permeability of vascular endothelial cells and stimulate the renin-angiotensin system (RAS) [4].

The pathophysiology of diabetic complications, especially those related to the heart and kidneys are highly contributed to the activated immune system in diabetics. DM 2 is a condition that plays a major role in endothelial dysfunction that is developed in atherosclerosis [5]. The disruption of nitric oxide (NO) bioavailability and the promotion of reactive oxygen species (ROS) generation from vascular endothelial cells occurs due to the overexpression of advanced glycation end products (AGEs) and their receptors, receptors for advanced glycation end products (RAGE) [6]. This leads to cross-linking of proteins and changes in their conformations, altered extracellular matrix composition, accelerated atherosclerosis, and dysfunction of the endothelial tissues [7]. In addition, the excessive production of AGEs and ROS facilitates the recruitment of monocytes, oxidation of low-density lipoproteins, and finally the development of foam cells [8].

Renal inflammation significantly contributes to the pathophysiological processes leading to the progression of diabetic kidney disease. The inflammatory condition is aggravated hyperglycemia and elevated levels of AGEs, leading to the subsequent release of damaged molecules and the activation of pattern recognition receptors including RAGE and toll-like receptors (TLRs) [9]. As evidenced by kidney biopsies, macrophages attack glomeruli and renal interstitial tissues due to the recruitment and differentiation of bone marrow-derived monocytes. The extent of macrophage accumulation has also been linked to progression towards end-stage kidney disease (ESKD) [10]. In addition to macrophages, individuals with DM 2 have elevated levels of activated T cells in the renal concentration, which can be attributed to the presence of proteinuria. High levels of CRP is strongly correlated with diabetic nephropathy among individuals of African-American in the Jackson Heart Study [11].

In the course of diabetic retinopathy, early in the course of diabetes, there is increased mRNA expression for TNF-α and IL-1 in the retina. Moreover, it has been demonstrated that TNF-α inhibition helps to avoid early diabetic retinopathy. Higher levels of pro-inflammatory cytokines, which have been associated with the occurrence and progression of retinal injury, have been found in the vitreous fluid of individuals with proliferative diabetic retinopathy. According to these findings, persistent low-grade subclinical inflammation is a major contributing factor to the development of diabetic retinopathy [12]. The precise physiological mechanism that initiates inflammation in InRs is not fully understood. One theory is related to adipose tissue as a pathogenic site of InRs, expansion of adipose tissues leading to hypertrophy and hyperplasia of adipocytes that impede local oxygen supply and initiate stress conditions [13].

Local stressful circumstances promote the production of cytokines and other proinflammatory signals. Generally, the elevated levels of the inflammatory mediators associated with adiposity can interfere with either of two major pathways that interfere with insulin signaling, the c-Jun N-terminal kinase (JNK) or IKappa B kinase-β (IKK-β)/Nuclear factor kappa B (NF-kappa B) pathways [14]. JNK pathway results in the phosphorylation of serine residues of insulin receptor substrate-1 (IRS-1), inhibiting the activation of protein kinase B (Akt), which mediates insulin action, while the activa-

tion of the IKK β/NF-Kappa B pathway results in releasing NF-Kappa B from the cytoplasm to the nucleus which stimulates the transcription of inflammatory mediators. Proinflammatory cytokines such as TNF-α and IL-1-β activate JNK and IKK β/NF-Kappa B by pattern recognition receptors, known as surface proteins that recognize foreign substances such as the TLRs and the RAGE as shown in (Figure 1), which further worsen InRs [15].

TARGETING INFLAMMATION IN DIABETIC PATIENTS

As inflammation plays a significant role in the pathophysiology of DM 2 and InRs, targeting inflammation may produce prominent effects in improving the clinical condition of diabetic patients, reducing the progression of complications, and promoting glucose uptake by insulin-sensitive tissues. Therefore, it is considered that lowering the inflammatory response to diabetes and achieving homeostatic control is an effective approach to prevent diabetic complications [16]. Since chronic hyperglycemia is strongly correlated with the activation of inflammatory mediators both directly or indirectly through the formation of free radicals and oxidative stress, the majority of antidiabetic drugs pose an indirect effect on inflammation through the hypoglycemic effect [17]. However, many antidiabetics have an additional anti-inflammatory mechanism independently of their hypoglycemic effects, which augments their anti-inflammatory effects and subsequently, further reduces diabetic complication risk [18].

This review article aimed to explore the anti-inflammatory effect of antidiabetics beyond their hypoglycemic action and the potential effects of such antidiabetics in reducing diabetic complications.

ANTIDIABETICS WITH ANTI-INFLAMMATORY PROPERTIES

Metformin

Adenosine monophosphate-activated protein kinase (AMPK) is a significant potential target of metformin. Beyond the glycemic control, metformin may have other actions including anti-inflammatory action. Such effects may be useful in preventing diabetic vascular complications [19]. The exact mechanism by which metformin produces an anti-inflammatory effect is not fully understood. Metformin produces an anti-inflammatory effect by either direct or indirect effects. The indirect action of metformin on inflammation is the consequence of the main action of glycemic control and weight loss, both have favorable effects in reducing

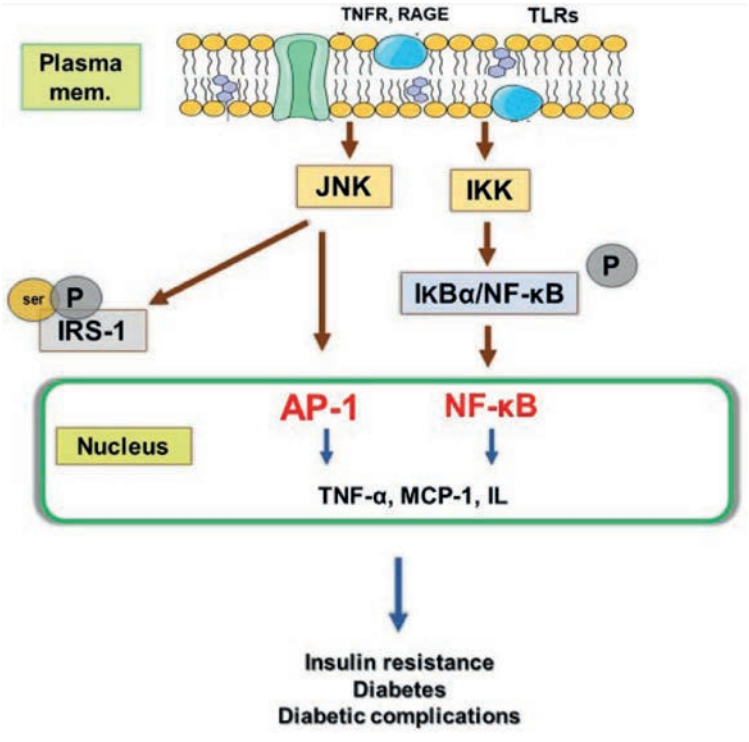

FIGURE 1. *Inflammatory pathways linking inflammation to InRs [15]. Serine kinase phosphorylation of IRS results from activation of the JNK and NF-κB pathways. This may block insulin signaling and ultimately induce IR. Furthermore, proinflammatory cytokines are produced by the JNK and NF-κB pathways, and these cytokines may then function as activation stimuli for the pathways.*
Mem – membrane; TLRs – tool-like receptors; TNF-α – tumor necrosis factor alpha TNFR, tumor necrosis factor receptor; RAGE – receptor for advanced glycation end products; JNK – c-jun N-terminal kinase; ROS – reactive oxygen species; IKB – inhibitor of NF-kappaB; IKK-β – IKappaB kinase β; NF-κ-B – nuclear factor-kappa-B; IRS-1 – insulin receptor substrate 1; AP-1 – activating protein 1; MCP-1 – monocyte chemoattractant protein-1; IL– interleukin

inflammation in diabetic patients. Direct effects can occur through various mechanisms. Direct inhibition of NF-Kappa B through activation of AMPK seems to be the most important mechanism [20].

Additionally, metformin improves the formation of NO, reduces ROS, and has inhibitory effects on the formation of AGEs, which are known to stimulate inflammation and ROS production as shown in (Figure 2) [21]. Metformin protects against cardiovascular disease (CVD) that are related to inflammatory stress. It causes anti-inflammatory and anti-angiogenic effects by increasing thrombospondin-1, which in turn lowers plasminogen activator inhibitor-1 (PAI-1) concentrations and increases fibrinolytic activity [22]. Patients with chronic kidney disease frequently have persistent systemic inflammation. Metformin prevents kidney damage by reducing inflammation triggered by a variety of stressors, according to preclinical research. Despite the renal protective properties of metformin, there is still a considerable amount of caution about therapeutic application in kidney disorders due to the risk of lactic acidosis. Thus, metformin, renal damage, and lactic acidosis all interact in complex manners [23].

Regarding the neuroprotective action of metformin, the effect on neurological diseases is variable and condition-specific. However, metformin shows promising effects as a potential candidate in the management of Alzheimer's disease [24].

Thiazolidinediones (TAZDs)

TAZDs act as a selective antagonist for peroxisome proliferator-activated receptors (PPAR-γ), decreasing insulin resistance and enhancing glucose uptake. The TAZDs exhibit significant anti-inflammatory properties [25]. The TAZDs have been observed to exert a direct inhibitory effect on inflammation through the inhibition of macrophage activation and the reduction of production and release of several proinflammatory mediators, including C-reactive protein (CRP), matrix metalloproteinase-9 (MMP-9), PAI-1, IL-1, and IL-6, as shown in both *in vitro* and *in vivo* studies. Evidence from in vitro studies suggests that TAZDs can affect the inflammatory response by influencing the activities of monocytes and macrophages [26].

In vivo, TAZDS therapy reduces blood levels of NF-kappa B while raising inhibitors of nuclear factor kappa B (IKB) expression in the same cells. Moreover, in both the overweight and the diabetic, therapy with TAZDs reduces plasma levels of CRP, MMP9, PAI-1, and a soluble cluster of differentiation-40 (sCD40). The activation of PPAR-γ agonist led to a reduction in urine albumin excretion and improvement in glomerulosclerosis [27].

Furthermore, it was found that pioglitazone therapy resulted in a subsequent reduction in inflammation, fibrosis, and matrix accumulation in the diabetic kidney. Additionally, pioglitazone treatment improves the recovery from behavioral abnormalities during neuropathic pain associated with transection of the tibial and sural nerves, as well as inflammation caused by carrageenan, damage to sparing nerves, and neuropathy caused by transection of the L5 nerve [28]. In addition, by suppressing glial activation and TLR-4 expression, pioglitazone exhibited an antiallodynic effect in a rat model of neuropathic pain. This, in turn, prevented the release of proinflammatory cytokines. As a result,

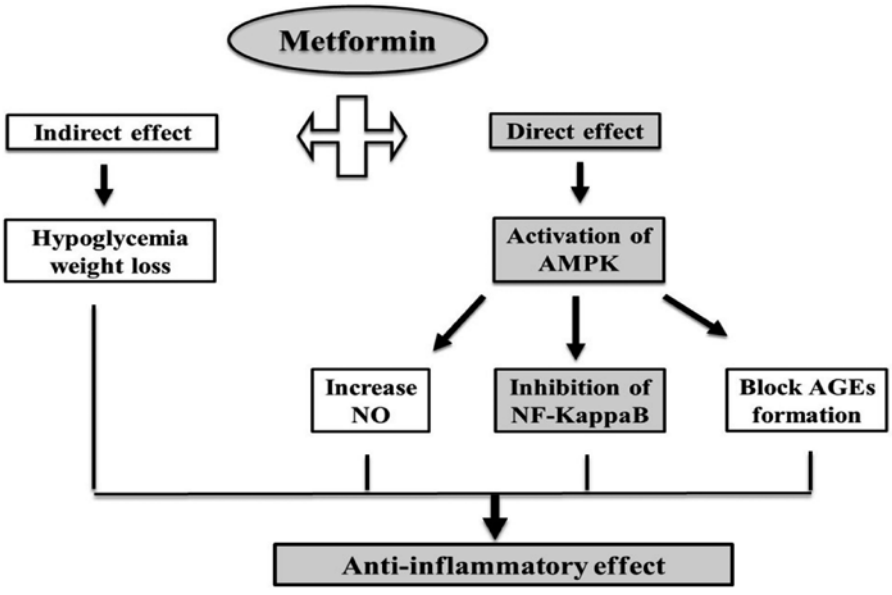

FIGURE 2. *Potential anti-inflammatory mechanisms of metformin [21]. Metformin affects inflammation either by direct or indirect effects. Direct effect can be achieved through the activation of AMPK that results in inhibition of NF-KappaB, blocks AGEs formation increases the level of nitric oxide, and reduces oxidative reactants. Indirect effects occur by improving glycemic control and weight loss. The grey pathway represents the main anti-inflammatory mechanism.*

AMPK – AMP-activated protein kinase; AGEs – advanced glycation end products; NO – nitric oxide; NF-KappaB – nuclear factor Kaapa B

PPAR-γ agonists could be considered a novel therapeutic approach for the management of neuropathic pain by inhibiting the production of hyperalgesia [29].

Sulfonylurea and meglitinides

Sulfonylurea stimulates the beta cells to secrete more insulin by blocking ATP-sensitive potassium channels. Sulfonylureas have been shown to have direct and indirect anti-inflammatory effects. In this regard, the increased expression of potassium channels in monocytes and macrophages could provoke inflammatory responses by the mitogen-activated protein kinase (MAPKs)/NF-kappa B-dependent pathway. Therefore, sulfonylureas may decrease inflammatory response by blocking these channels [17]. Sulfonylureas may also have an anti-inflammatory effect due to their antioxidant properties and by blocking the nucleotide-binding domain, leucine-rich–containing family, and pyrin–containing–3 (NLRP3) inflammasome. Despite their anti-inflammatory properties, sulfonylureas have not been shown to improve vascular outcomes for DM patients [30]. When compared to metformin and pioglitazone, the anti-inflammatory effect of sulfonylurea is less potent despite having some effects on the production of cytokines [31]. Meglitinides bind to the potassium ATP channel on the pancreatic beta cell to act as sulfonylureas. Meglitinides do not appear to have any anti-inflammatory properties [32].

Sodium-glucose cotransporter inhibitors (SGLT2-I)

SGLT2-I blocks SGLT2, which are responsible for glucose reabsorption in renal proximal convoluted tubules, leading to glycosuria and reduction in blood glucose levels. SGLT2-I has been shown to reduce inflammation in both direct and indirect ways. Direct way involves inhibition of the production of inflammatory mediators such as MCP-1, IL-6, TNF-α, transforming growth factor-β1 (TGFβ-1), and CRP. Additionally, they can decrease adipokine-induced inflammation, modify the redox state, and impact the RAS and hemodynamics to suppress inflammation [33].

The anti-inflammatory characteristics of SGLT2-I have been linked to their significant reno-protective effect. Studies on diabetic mice indicated that empagliflozin reduces albuminuria and glomerular hyperfiltration and blocks the production of inflammatory markers in the kidneys [34]. Studies in Akita mice have shown that dapagliflozin has protective effects on the kidneys, as it increases renal macrophage tissue accumulation and decreases interstitial fibrosis compared to insulin [35]. Furthermore, the anti-inflammatory effect of SGLT2-I is believed to be accountable for the cardioprotective effects. In addition, improvement in nonalcoholic fatty liver disease (NAFLD) indices has been documented [36].

Regarding diabetic retinopathy, SGLT2-I-induced low-grade ketonemia, thus produces enhanced fuel energetics and reduced hypoxia, and also through the anti-inflammatory and antioxidative stress characteristics of ketones. Also, by improving glycemia and lowering blood pressure, SGLT2-I could impact the progression of diabetic retinopathy [37].

Dipeptidyl peptidase-4 inhibitors (DPP-4-I) and glucagon-like peptide-1 receptor agonists (GLP-1-Ra)

DPP-4-I are effectively reducing blood glucose levels by inhibiting the inactivation of GLP-1. The administration of GLP-1-Ra results in improved action of GLP-1 [38]. Both DPP-4-I and GLP-1-Ra possess modulatory properties that influence inflammatory responses. The inhibition of DPP-4 by sitagliptin effectively reduced inflammation in adipocytes and liver cells [39].

Additionally, the GLP-1-Ra exendin-4 was shown to suppress inflammation, particularly in adipocytes. Results from studies have demonstrated the strong anti-inflammatory effects of GLP-1-Ra in both *in vitro* and *in vivo* experiments [35,40]. Clinical studies have demonstrated that GLP-1-Ra successfully repressed the progression of diabetic nephropathy and enhanced renal function by suppressing inflammatory responses within the kidneys [41,42]. Similar findings were observed with DPP-4-I, which reduced early kidney damage and minimized albuminuria in a rat model of diabetes through the suppression of inflammatory responses. DPP-4-I exerts a direct inhibitory effect on the generation of inflammatory cytokines by suppressing the activity of NF-kappa B in the renal glomeruli. Another possible effect might arise from their antioxidative characteristics, which could lead to a reduction in inflammation [43].

The anti-inflammatory properties of GLP-1-Ra may be used to treat neurodegenerative disorders. Recent research on Alzheimer's disease shows that liraglutide treatment can suppress inflammation in the brain while also having restorative benefits [44]. The inhibitory impact of exendin-4 on microglial activation was emphasized by Kim et al., indicating its potential therapeutic application in the management of Parkinson's disease [45]. DPP4-I also appears to lessen peripheral endothelial dysfunction and arterial stiffness as measured by pulse wave velocity [46]. Regarding retinopathy, no available large randomized clinical trials are focusing on the effect of DPP-4-I and GLP-1-Ra on diabetic retinopathy [47].

Alpha-glucosidase inhibitors (AG-I)

AG-I acts effectively by suppressing the activity of alpha-glucosidase inside the brush border of the gut.

TABLE 1. *Comparison of the anti-inflammatory effect of anti-diabetics and correlation with complications*

Drug Group	Complications correlation with anti-inflammatory effect	Anti-Inflammatory strength	Reference
TAZDs	Kidney complications reduction Novel therapeutic strategy for neuropathic pain	Potent	[25]
Biguanides	Cardiovascular complications reduction	Moderate	[20]
SGLT-2 inhibitors	Kidney complications reduction Cardiovascular complications reduction Eye complications reduction Improvement of NAFLD	Moderate	[40]
DDP-4 inhibitors	Kidney complications reduction Cardiovascular complications reduction	Moderate	[40]
GLP-1 receptor agonists	Kidney complications reduction Improvement of neurodegenerative diseases	Moderate	[40]
α-glucosidase inhibitors	No direct evidence of a correlation	Moderate	[48]
Sulfonylurea	No direct evidence of a correlation	Weak	[17]
Meglitinides	No direct evidence of a correlation	Weak	[32]

Several studies have shown that miglitol can inhibit the production of IL-1β, TNF-α, and other inflammatory cytokines in peripheral leukocytes of rats with diabetes, this observation implies a potential decrease in inflammation. Currently, there is no available evidence on the clinical effect of AG-I on inflammation in vascular tissue and the kidney (Table 1) [17,48].

CONCLUSIONS

Individuals with diabetes have an activated immune system with elevated levels of inflammatory mediators and pro-inflammatory cytokines.

Diabetes and its related complications could be worsened by such inflammation. Targeting inflammation may produce obvious effects in improving the clinical condition of diabetic patients and reducing the progression of complications. The majority of antidiabetic drugs pose an indirect anti-inflammatory effect through the hypoglycemic effect. However, many antidiabetics have an additional anti-inflammatory mechanism independently of their hypoglycemic effects, which augments their anti-inflammatory effects and subsequently, further reduces the risk of diabetic complications. To sum up, TAZDs have a potent anti-inflammatory effect and are recommended for diabetic nephropathy. In addition, a novel therapeutic approach for the management of neuropathic pain is the production of hyperalgesia by PPAR-γ agonists. The anti-inflammatory action of metformin is prominent and effective in reducing the risk of CVD in diabetic patients with high risk of CVD. Otherwise, actions on the kidney and the nervous system fail to produce clinical benefits in such patients, and further investigations are required. The anti-inflammatory characteristics of SGLT2-I, DPP-4-I, and GLP-1-Ra are less potent than those of TAZDs. SGLT2-I have been linked to their significant protective effect on the kidney, and it is effective in reducing ocular and cardiovascular complications. DPP-4-I are useful in reducing renal and cardiovascular complications. GLP-1-Ra reduces the risk of neurodegenerative and renal diseases. Regarding sulfonylurea, meglitinides, and α-glucosidase inhibitors, the lack of large trials is a major limitation in drawing safe conclusions about the effectiveness of their anti-inflammatory characteristics in reducing diabetic complications.

Author's contributions:
Khalil A. Hadid: writing – review & editing; writing – original draft preparation; and Conceptualization. Fawaz A. Alassaf: Supervision, Project administration, Formal analysis, and Conceptualization. Mohammed N. Abed: Supervision, Project administration, Formal analysis, and Conceptualization.

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