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REVIEW

Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress

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Abstract

Insulin resistance and pancreatic β-cell dysfunction are major pathological mechanisms implicated in the development and progression of type 2 diabetes (T2D). Beyond the detrimental effects of insulin resistance, inflammation and oxidative stress have emerged as critical features of T2D that define β-cell dysfunction. Predominant markers of inflammation such as C-reactive protein, tumor necrosis factor alpha, and interleukin-1β are consistently associated with β-cell failure in preclinical models and in people with T2D. Similarly, important markers of oxidative stress, such as increased reactive oxygen species and depleted intracellular antioxidants, are consistent with pancreatic β-cell damage in conditions of T2D. Such effects illustrate a pathological relationship between an abnormal inflammatory response and generation of oxidative stress during the

progression of T2D. The current review explores preclinical and clinical research on the pathological implications of inflammation and oxidative stress during the development of β-cell dysfunction in T2D. Moreover, important molecular mechanisms and relevant biomarkers involved in this process are discussed to divulge a pathological link between inflammation and oxidative stress during β-cell failure in T2D. Underpinning the clinical relevance of the review, a systematic analysis of evidence from randomized controlled trials is covered, on the potential therapeutic effects of some commonly used antidiabetic agents in modulating inflammatory makers to improve β-cell function.

Key Words: Type 2 diabetes; Insulin resistance; β-cell dysfunction; Inflammation; Oxidative stress

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Core Tip: Elevated markers of inflammation and oxidative stress are related to β-cell dysfunction, the intracellular defense (antioxidant) mechanisms responsible for ameliorating some of these effects are significantly depleted during type 2 diabetes (T2D). Thus, beyond lowering glucose levels like most antidiabetic drugs, future research should invest in developing therapeutic agents to ameliorate inflammation and oxidative stress to improve blood control in patients with T2D.

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INTRODUCTION

Type 2 diabetes (T2D) is among the leading causes of death worldwide[1]. Latest global estimates indicate that one in ten adults are currently living with diabetes, of which over 90% of cases are attributed to T2D[2]. Insulin resistance and β-cell dysfunction are considered the major pathophysiological derangements in T2D. Insulin resistance is primarily associated with T2D, however, people with T1D have also been shown to develop insulin resistance mainly because of certain genetic factors or lifestyle modifications[2,3]. Generally, β-cell dysfunction indicates a compromised state of insulin secretion, while insulin resistance refers to the inability of insulin to exert its effects on target organs[3]. In a complex mechanism, insulin resistance and β-cell dysfunction promote elevated blood glucose levels and further drive the pathogenesis of T2D[4]. Changes in β-cell function occur during the early stages of diabetes development (the prediabetic stage) and gradually become worse with disease progression[5,6]. Thus, it has become imperative to delineate the pathological mechanisms driving β-cell dysfunction to alleviate complications linked with T2D, including those that implicate inflammation and oxidative stress.

Inflammation has long been considered the main component of diabetes[7,8]. During T2D, elevated blood glucose levels lead to an undesired inflammatory response, which may be exacerbated by inflammatory intermediaries produced by adipocytes and macrophages in adipose tissue[9]. This process may initiate the low-grade, chronic inflammatory state that induces injury to the pancreatic β-cells, subsequently causing inadequate insulin production, and leading to hyperglycemia[9]. As a result, uncontrolled inflammation has been positioned among the foremost factors in the pathogenesis of T2D [7,8]. Several reviews on the role of inflammation during β-cell dysfunction in T2D have been conducted. For example, Jo and Fang[10] reviewed evidence indicating that malfunctioning of the essential components of the inflammation, including helper T cells, cytotoxic T cells, and regulatory T cells may underpin pancreatic β cell failure in T2D. Sun *et al*[11] recently discussed that aberrant epigenetic signatures, including DNA methylation, chromatin accessibility, histone alteration, and non-coding RNAs orchestrate β-cell malfunction during embryonic growth and postnatal development, thus contributing to β cell dysfunction. These findings further highlight the pathological link between impaired metabolic function and alterations in molecular mechanisms that may lead to β cell dysfunction in T2D[11-13].

Oxidative stress is another factor that is consistently associated with β-cell destruction during the development of T2D[14,15]. Oxidative stress normally arises due to the excessive production of free radicals, especially reactive oxygen species (ROS) that severely affect the neutralizing capacity of intracellular antioxidants[14,15]. Generally, oxidative stress may induce its destructive effects through

causing damage to DNA, proteins, and lipids. In fact, due to the dyslipidemic features of most patients with T2D, uncontrolled oxidative stress is associated with clustering of interconnected plasma lipid and lipoprotein anomalies that may aggravate diabetic complications[16]. Notably, due to the inherent low expression of antioxidant enzymes in pancreatic islets[17], the consequences of oxidative stress can have devastating effects on driving β-cell dysfunction during the development of diabetes[18]. Obesity or excessive fat accumulation within the pancreas are some of the major mechanisms that promote oxidative stress, insulin resistance and β-cell dysfunction in T2D[19,20]. Enhancement of intracellular antioxidants can be targeted to alleviate oxidative stress and improve β-cell function to combat diabetes-associated complications[21,22]. In fact, the pathological relationship between inflammation and oxidative stress can have devastating outcomes leading to the progression of T2D. These complications are distinctively linked with worsening of T2D-related abnormalities, including retinopathy, neuropathy, nephropathy, and damage to tissues[23].

The current review updates and critically discusses literature on the pathological implications of inflammation and oxidative stress during the development of β-cell dysfunction in T2D. Preclinical and clinical research, elucidating the mechanisms that orchestrate the link between inflammation and oxidative stress during the development and progression of T2D are discussed. Firstly, an overview on the link between insulin resistance and β-cell dysfunction is covered to highlight its detrimental effect during the worsening of T2D. Thereafter, different biomarkers of inflammation and oxidative stress are discussed for their relevance in monitoring disease severity. This information also remains important to develop therapeutic targets to alleviate β-cell dysfunction in T2D. To further contribute to the novelty and relevance of the discussed information, a systematic analysis of evidence from randomized controlled trials (RCTs) on the therapeutic effects of antidiabetic agents in modulating inflammatory or oxidative stress to improve β-cell function is also covered.

LITERATURE SEARCH AND CLINICAL STUDY SELECTION

Findings from preclinical studies, especially animal models, remain important to accurately decipher or characterize pathological mechanisms implicated in the development of disease. Consistent with the main objective of the current review, this infers describing the potential biological processes and molecular mechanisms involving inflammation and oxidative stress during pancreatic β-cell dysfunction in T2D. However, it also remains important to uncover clinical data on the therapeutic effects of commonly used antidiabetic drugs like metformin in modulating inflammation and oxidative stress to protect against β-cell dysfunction in T2D.

Thus, a systematic search of major electronic engines and databases was done from inception until 18 November 2022 for relevant RCTs. To prioritize clinical relevance of the review, the search was restricted to RCTs reporting on the link between inflammation or oxidative stress and β-cell function in T2D. Medical Subject-Heading and text words such as "inflammation", "oxidative stress", "β-cells", and "type 2 diabetes", including their analogous synonyms and related words were tailored for the individual search engine or database. There was no restriction on the type of antidiabetic drug, with all RCTs reporting on the modulation of these drugs on inflammation or oxidative stress markers in patients with T2D included. The search focused on inflammatory markers such as C-reactive protein (CRP), fibrinogen, interleukins (IL)-6/IL-1β, and tumor necrosis factor alpha (TNF-α) as well as oxidative stress indicators like ROS, glutathione peroxidase (Gpx), superoxide dismutase (SOD), thioredoxin, and catalase (CAT) that have been linked with β-cell dysfunction in T2D.

INSULIN RESISTANCE AND PANCREATIC B-CELL DYSFUNCTION IN T2D

The pancreatic β-cells have the important function of producing and secreting insulin, a vital hormone that is necessary for the regulation of metabolism. Indeed, insulin is critical for the metabolic regulation of key energy substrates such as carbohydrates, lipids, and proteins. Insulin is required for the absorption of glucose from the blood stream into different cells, including cells from adipose tissue, skeletal muscle, and the liver. Thus, exploring the role of insulin in a broad spectrum of physiological processes including its production and regulation has relevance in understanding the development of T2D[24]. Notably, disturbances in insulin signaling through the inhibition of the insulin receptor substrate protein, phosphoinositide-3-kinase, and protein kinase B (AKT) leads to insulin resistance[25]. The latter is consistently associated with obesity, a major risk factor for T2D. Abnormal adipose tissue expansion causes elevated circulating levels of non-esterified fatty acids, glycerol, markers of oxidative stress, and pro-inflammatory cytokines, subsequently leading to the development of insulin resistance in individuals with obesity[26,27]. In fact, there is a close association between insulin resistance, obesity, and T2D[28]. Insulin resistance, obesity and pancreatic β-cell dysfunction are complex pathological mechanisms implicated in the progression of T2D (Figure 1). Both pathogenic states induce hyperglycemia and therefore increases insulin demand. Subsequently, β-cell dysfunction arises from insufficient glucose sensing to stimulate insulin secretion, hence increased glucose levels persist. This

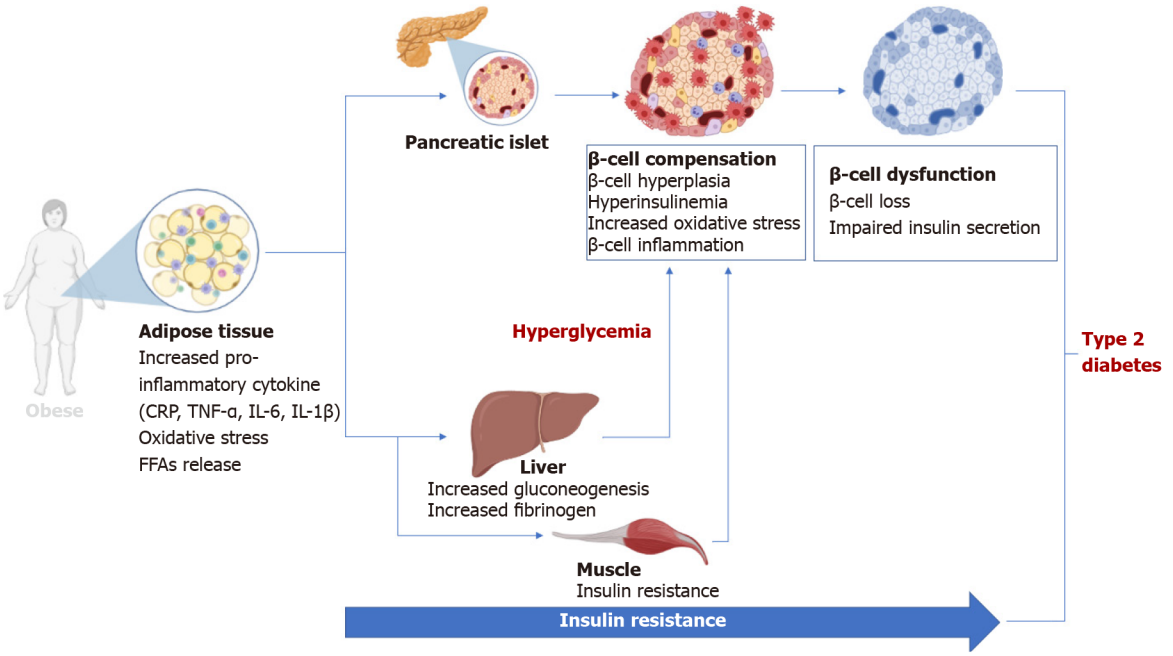

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Figure 1 An overview of the pathological implications of adipose tissue hypertrophy and insulin resistance during the development and progressive loss of β-cell function in conditions of obesity to type 2 diabetes. Briefly, adipose tissue expansion (usually seen in obesity or type 2 diabetes) is associated with enhanced secretion of pro-inflammatory markers and generation of oxidative stress that directly or indirectly cause pancreatic β-cell loss, leading to impaired insulin secretion. CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; FFAs: Free fatty acids.

process leads to the development of insulin resistance, increased glucose concentrations beyond the physiological state, thereby resulting in the manifestation of hyperglycemia. As a result, β-cells compensate for insulin resistance by hypersecretion of insulin, ultimately leading to β-cell failure[29]. β-cell dysfunction follows insulin resistance during the development and progression of T2D. In fact, both pathological states influence each other and likely synergistically worsens diabetes[29]. Maintaining β-cell function and insulin signaling in patients with T2D is vital for controlling glucose homeostasis. As such, alleviating the detrimental effects of inflammation has become a critical feature to protect and maintain β-cell function in conditions of T2D[4,30].

INFLAMMATION AND PANCREATIC B-CELL DYSFUNCTION IN T2D

Inflammation is generally classified as a localized response to cellular or tissue injury that is consistent with increased blood flow, leucocyte intrusion, and enhanced production of diverse chemical mediators. This response is necessary to prompt the removal of toxic agents and the restoration of injured tissue. It is now well accepted that chronic inflammation is coupled with insulin resistance and β-cell dysfunction in patients with T2D[4,30]. Adipose tissue expansion is known to play a major role during this process, with inflammation characterized by enhanced levels of macrophages and increased secretion of inflammatory cytokines[31,32]. Briefly, TNF-α, as well as IL-1β, and IL-6 are considered some of the prominent pro-inflammatory markers in the pathogenesis of T2D[31-33]. Beyond the elevated markers of inflammation, immune dysfunction is also an essential component of inflammation that has been implicated in β-cell failure in T2D.

CRP and β-cell dysfunction in T2D

Epidemiologic studies have reported a close relationship between elevated biomarkers of inflammation and the worsening of T2D and its complications[34,35]. Obesity, which is common in T2D, is well-acknowledged to be the main driver of the pathological consequences inflammation[36]. Obesity is responsible for the initiation of chronic systemic inflammation, with this feature characterized by the activation of the innate immune system in adipose tissue. This outcome prompts the systemic acute-phase response which is distinguished by elevation of acute-phase protein levels. For example, CRP is considered one of the predominant markers of systemic inflammation. Indeed, previous research have indicated that elevated levels of high-sensitive CRP (hs-CRP) are strongly associated with advanced β-cell dysfunction and insulin resistance in patients with T2D[37,38]. Although considered of hepatic origin, macrophages and T cells are known to be the main activators CRP levels in response to inflammation. Conventionally exploited as an indicator of infection and cardiovascular events[39], accumu-

lating evidence show that CRP plays a vital role in diverse inflammatory mechanisms including the complement pathway, cell death, autophagy, nitric oxide modulation, and the production of cytokines, especially IL-6 and TNF-α[40-42]. Serum concentrations of CRP and other pro-inflammatory cytokines like IL-6 and TNF-α, have been found to be significantly elevated in rats with T2D[43]. Interestingly, such effects occurred concurrently with damage to islets, islet atrophy and β-cell failure in these diabetic animals. Mechanistically, CRP has been reported to promote tissue injury and accelerate apoptosis, through inducing pro-inflammatory mechanisms involving toll-like receptor 4, nuclear factor kappa B (NF-κB), transforming growth factor-β, and the extracellular signal-regulated kinase (ERK) pathway in preclinical models of diabetes[44,45]. Although not directly reporting on β-cell failure, studies in humans have linked enhanced circulatory levels of CRP with systemic inflammation, development and progression of T2D[46,47]. For example, Weber and colleagues showed that worsened low-grade inflammation (through increased levels of hs-CRP) and poor glycemic control were accompanied by reduced β-cell function in patients with T2D[48].

Fibrinogen and β-cell dysfunction in T2D

It has been more than two decades since it was reported that increased plasma levels of fibrinogen are associated with clinical complications of T2D[49]. Fibrinogen is a glycoprotein secreted by the liver and its levels in circulation depict systemic inflammation and tissue injury[50]. The secretion of this protein is crucial for coagulation, revascularization and wound restoration, and this process is mainly facilitated through its enzymatic conversion to fibrin by thrombin. In T2D, fibrinogen levels are positively associated with vascular complications[51-53]. Patients with T2D display elevated levels of fibrinogen, which is linked with poor blood glucose control and increased cardiovascular risk[54,55]. Beyond its role in systemic inflammation[56], fibrinogen levels are increased in rats treated with streptozotocin, a chemical substance known to destroy pancreatic β-cells[57]. Fibrinogen directly promotes profibrogenic and proinflammatory functions in pancreatic stellate cells[58]. These effects are consistent with the activation of pro-inflammatory mechanisms such as activation of NF-κB, three classes of mitogen-activated ERK, c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) in pancreatic cells. Although clinical evidence directly implicating fibrinogen in β-cell dysfunction is limited, enhanced levels of this protein (hyperfibrinogenemia) has been identified in patients with diabetes[59,60].

IL-6 and IL-1β and β-cell dysfunction in T2D

ILs are known for their diverse biological functions and are of pathological importance during the development of many diseases including T2D. Different interleukin family members have been studied and increasing evidence indicate the significance of these proteins in connecting innate immunity with diverse diseases including inflammatory conditions[41]. Varied IL, including both IL-6 and IL-1β, play a central role in modulating inflammatory responses, especially during the development of metabolic disease[61,62]. Briefly, IL-1β, which is produced by stimulated macrophages is crucial for innate immune regulation (which is considered the first line of defense against invading pathogens). Through its interaction with pattern recognition receptors, the 1β-processing platform is vital for initiating signaling pathways that induce the inflammatory response and regulates adaptive immunity[63]. Notably, IL-6 can induce differentiation of naïve CD4+ T cells, further playing a major role in modulating the acquired immune response[61]. Abnormally regulated levels of both IL-6 and IL-1β are associated with interruption of immunological tolerance and is thus pathologically implicated in the development of autoimmune and chronic inflammatory diseases[62,64-66].

Evidence suggests that IL-6 protects β-cells against oxidative damage through the effective modulation of autophagy and enhancing the antioxidant response. In fact, it was demonstrated that IL-6 couples' autophagy to antioxidant responses leading to the reduction of ROS in β-cells and human islets [67]; whereas β-cell-specific blockage of IL-6 signaling *in vivo* causes mice to be more vulnerable to oxidative damage and cell death in response to exposure to selective β-cell toxins such as streptozotocin and alloxan[67]. Similarly, others have reported that pretreating β-cells with IL-6 blocks apoptosis induced by pro-inflammatory cytokines, mainly through effective regulation of autophagy[68]. These results are also consistent with reduced IL-6 pathway signaling in islets from donors with T2D[68]. Although such protective effects are noted, others argue that β-cell specific production of IL-6 is consistent with the development of diabetes, downplaying the potential advantage of targeting IL-6 as a therapeutic target for diabetes[69]. However, unlike IL-6, IL-1β has been associated with the inhibition of β-cell function and activation of fatty acid synthase-triggered apoptosis in part by interacting with the transcription factor NF-κB[70]. IL-1β-secreting β cells were identified in pancreatic sections of patients with T2D but not in nondiabetic control subjects[70].

TNF-α and β-cell dysfunction in T2D

A landmark study by Hotamisligil *et al*[71] was instrumental in demonstrating the close relationship between TNF-α and the progression of diabetes. Their results showed that elevated levels of TNF-α within adipose tissue of rats was consistent with the development of insulin resistance, while the inhibition of this pro-inflammatory cytokine was associated with improved glucose control and insulin

sensitivity. TNF-α belongs to a superfamily of type II transmembrane proteins comprising of the TNF homology domain and is acknowledged to play a major role in diverse cellular functions, especially the processes of immune response and inflammation. In various preclinical models of diabetes, including the genetically modified mouse model of T2D (*db/db*), the pancreatic islet cells display increased levels of chemokines and pro-inflammatory cytokines like TNF-α, when compared to nondiabetic controls [72]. In a Kurdish population, genetic polymorphisms of TNF-α have been linked with genetic predisposition to T2D[73]. Recombinant human TNF-α administration has been shown to acutely reduce basal plasma insulin levels but does not affect glucose-stimulated insulin secretion in patients with T2D[74]. Therapeutic targeted reduction in TNF-α levels has been associated with improved insulin sensitivity in patients with T2D[75]. More importantly, it is evident that TNF-α-activated pathways are responsible for inducing apoptotic cell death in pancreatic β-cells. Stephens *et al*[76] demonstrated that caspase activation is the prevailing mechanism of TNF-α-induced cell death in NIT-1 cells (an insulin-secreting mouse cell line). Others have shown that TNF-α, in combination with another pro-inflammatory cytokine, interferon-γ (IFN-γ) can induce pancreatic β-cell apoptosis by destructing highly controlled B-cell lymphoma 2 member proteins that are essential for efficient mitochondrial function[77]. Preclinical studies have laid an important foundation to clarify the pathological role of TNF-α in causing β-cell dysfunction in T2D[78], and such information is consistent with insulin resistance and progression of diabetes in clinical settings[79,80]. Although evidence on the detrimental effects of IL-1β, together with other pro-inflammatory markers like IFN-γ and TNF-α in pancreatic β-cell dysfunction is acknowledged [78,81].

T-cells and β-cell dysfunction in T2D

It is acknowledged that both innate and adaptive immune cells play a major role during pancreatic islet inflammation[82]. Innate immune cells produce cytokines that directly and indirectly modulate insulin secretion, whilst also stimulating inflammatory reactions. Macrophages and neutrophils, which physiologically inhabit the pancreatic tissue, can also partake in tissue homeostasis, including harmful activation of immune responses[82,83]. T cells are one of the significant white blood cells of the immune system and are crucial in the adaptive immune response. T-cells consist of two main subtypes, which are CD8+ "killer" and CD4+ "helper" T cells[84]. Regulatory T cells are yet another different subset of T cells that are required to support the mechanism of tolerance, whereby immune cells can recognize and differentiate between parent and invading cells. It is well known that diabetes impairs T cell function [85,86], although the precise mechanisms involved remain to be fully established. In fact, activated T-helper (TH)1 CD4+ T cells and CD8+ cytotoxic T cells have long been implicated in the destruction of pancreatic β-cells in diabetes[87]. Apparently, CD4+ T cells can be activated by IL-12 produced from macrophages and dendritic cells, and this consequence occurs as part of a vicious process involving cytotoxic T cells and recruitment by the pancreatic islets[87]. Notably, CD4+ T cells are instrumental in improving immune responses and their activation can lead to their differentiation into specific subtypes depending on the disease state[84]. Well-known subsets of CD4+ T cells include TH1, which are understood to promote β-cell damage by accelerating apoptosis[88]. Using electron microscopy, it was demonstrated that CD4+ T helper cells exhibit a much higher arrest (a cell jamming process) in the exocrine tissue than islet specific CD8+ T cells in diabetic mice[89]. With the overwhelming evidence supporting the notion that, like autoimmune diabetes, CD4+ (TH1 cell)-mediated inflammation and apoptosis may be the prominent features responsible for β-cell dysfunction and the aggravation T2D-associated complications[86,88,90,91]. Figure 2 highlights some of the pathophysiological mechanisms implicated in immune and T-cell activation during inflammation-mediated β-cell dysfunction in conditions of T2D.

ANTIDIABETICS AND OTHER AGENTS POTENTIALLY REGULATE INFLAMMATORY MARKERS TO IMPROVE B-CELL FUNCTION

It remains important to decipher the therapeutic mechanisms through which commonly used antidiabetic agents alleviate β-cell insult in conditions of T2D. Table 1 summarizes evidence from RCTs reporting on the effects of antidiabetics and other agents on β-cell function in patients with T2D. Here, the systematic search was focused on establishing the therapeutic link between β-cell function and regulation of circulating levels of prominent inflammatory makers, including hs-CRP, fibrinogen, IL-6, TNF-α, and T-cells. It emerged as early as in 1993 that metformin administration (up to a maximum of 850 mg three times a day for 12 wk) could improve glycemic control and β-cell function but had no effect on plasma fibrinogen concentrations and platelet function in patients with T2D[92]. Metformin is the most used antidiabetic drug with widely reported pleiotropic effects against complications linked with T2D[93,94]. Interestingly, predominantly included RCTs in Table 1 reported on the therapeutic effects of metformin in controlling basic metabolic profiles together with improving β-cell function and modulating inflammatory markers in patients with T2D. Evidence from different research groups published over the years (2006-2018) has indeed confirmed that metformin administration (from a dose between 1700-2000 mg/d) for a treatment duration of at least 6 mo could improve glycemic control,

Table 1 Effects of antidiabetics and other agents on β-cell dysfunction in type 2 diabetes through the regulation of inflammatory markers

Ref.	Study population	Intervention	Findings
Nagi and Yudkin[92], 1993	Patients with T2D (*n* = 27), with an average age between 48 and 56 yr	Received metformin up to a maximum of 850 mg three times a day, for 12 wk	Improved glycemic control and β-cell function, while ameliorating insulin resistance and risk factors for cardiovascular disease, including plasminogen activator inhibitor-1. But had no effect on plasma fibrinogen concentrations and platelet function
Tsunekawa *et al*[102], 2003	Patients with T2D (*n* = 17), with an average age of 67 yr	Received glimepiride started from 1 mg daily and increased up to 6 mg daily for 12 wk	Alleviated insulin resistance by decreasing plasma TNF-α levels and reducing those of adiponectin
Dominguez *et al*[103], 2005	Patients with T2D (*n* = 10), with an average age of 53 yr	Received etanercept treatment at 25 mg subcutaneously twice weekly for 4 wk	Reduced plasma levels of CRP and interleukin-6 decreased, while also improving β -cell function
Pfützner *et al* [37], 2006	Patients with T2D (*n* = 4270), with an average age of 64 yr	Received a combination therapy of peroxisome proliferator activated receptor g agonists and metformin. Disease duration was 5.4 ± 5.6 yr	Increased hs-CRP levels were associated beta-cell dysfunction but showed no correlation with disease duration or glucose control. Patients receiving combination therapy presented the lowest hs-CRP mean values
Hamann *et al* [95], 2008	Patients with T2D (*n* = 294), with an average age of 58 yr	Received maximum tolerated doses of rosiglitazone 8 mg plus metformin 2 g/d during the first 12 wk of double-blind treatment for 52 wk	Fixed-dose combination therapy with rosiglitazone/metformin lowered glycated HbA1c and hs-CRP levels over one year of treatment. This was followed by improved beta-cell function suggest and glycaemic control
Pfützner *et al* [96], 2011	Patients with T2D (*n* = 146), with an average age of 59 yr	Received a fixed dose combination of 15 mg of pioglitazone with 850 mg of metformin given twice daily for 24 wk	Improved biomarkers of lipid metabolism, β-cell function, activity of the visceral adipose tissue, and chronic systemic inflammation. This was consistent with reduced hs-CRP and increased adiponectin levels
Bellia *et al* [104], 2012	Patients with T2D (*n* = 27), with an average age of 56 yr	Received receive either rosuvastatin 20 mg daily or simvastatin 20 mg daily for 6 mo	Effectively reduced hs-CRP levels, but significantly diminished glycemic control and insulin secretion, without affecting insulin sensitivity
Derosa *et al* [97], 2012	Patients with T2D (*n* = 167), with an average age of 53 yr	Received metformin gradually titrated until a mean dosage of 2500 ± 500 mg/d was reached for 8 ± 2 mo. Thereafter, patients were randomly assigned to take, vildagliptin at 50 mg twice a day for 12 mo	A combination of metformin and vildagliptin showed better effect in reducing body weight, glycemic control, Homeostatic Model Assessment for Insulin Resistance and improving β-cell function. However, no significant effect was observed for TNF-α levels
Brooks-Worrell and Palmer [105], 2013	Patients with T2D (*n* = 26), with an average age of between 54 and 58 yr	Received rosiglitazone at 4 mg once/day and increased to twice/day if glycaemic control (HbA1c 70%) not achieved. Glyburide was at 2.5 mg and increased to twice per day up to a maximum of 10 mg twice/day if glycaemic control not achieved	Rosiglitazone reduced islet-specific T cell responses and improved glucagon-stimulated-β-cell secretion, consistent to decreasing in interferon gamma production. This was accompanied by increased adiponectin levels in comparison to glyburide-treated patients
Gagnon *et al* [106], 2014	Patients with T2D (*n* = 35), with an average age of 54 yr	Received a combination of calcium carbonate (1200 mg) and cholecalciferol [2000-6000 IU to target 25(OH)D 0.75 nmol/L] for 6 mo	Treatment did not affect glucose tolerance, inflammatory markers (including hs-CRP levels) and β-cell function in patients with T2D, but improved insulin sensitivity in subjects with prediabetes
Zografou *et al* [98], 2015	Patients with T2D (*n* = 64), with an average age between 52 and 56 yr	Received metformin at 1700 mg/d plus vildagliptin at 100 mg/d for 6 mo	A combination of metformin and vildagliptin reduced hs-CRP and improved glycemic control and β-cell function
Tao *et al*[99], 2018	Patients with T2D (*n* = 21), with an average of 29 yr	Received metformin at 2000 mg/d or saxagliptin at 5 mg/d for 24 wk	Treatment was comparatively effective at reducing body mass index and hs-CRP levels. This was parallel to improved glycemic control, lipid profiles and β-cell function
Zakerkish *et al* [107], 2019	Patients with T2D (*n* = 50), with an average of 55 yr	Received Iranian propolis extract at 1000 mg/d for 90 d (3 mo)	Reduction on hs-CRP corresponded with beneficial effects of the extract in decreasing post prandial blood glucose, serum insulin, insulin resistance, and other inflammatory cytokines like TNF-α

T2D: Type 2 diabetes; TNF-α: Tumor necrosis factor-alpha; hs-CRP: Highly sensitive C-reactive protein; HbA1C: Hemoglobin A1C; CRP: C-reactive protein.

lipid profiles and β-cell function in part by reducing pro-inflammatory markers like hs-CRP and TNF-α in patients with T2D[37,95-99]. Notably, evidence from these RCTs suggest that metformin may be most effective in improving β-cell function in patients with T2D when combined with other antidiabetic drugs such as rosiglitazone, pioglitazone and vildagliptin (Table 1). This highlights the potential enhanced effects of metformin when combined with other therapies in treating compilations of T2D, as discussed elsewhere[100,101].

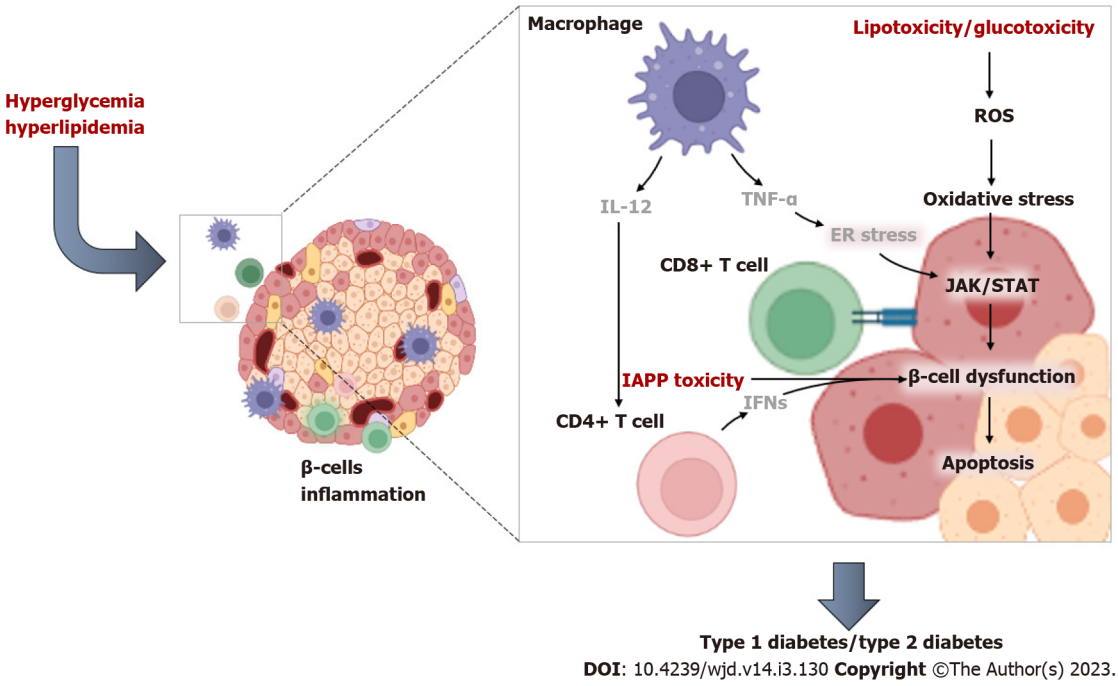

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Figure 2 An overview of the pathological mechanisms linking impaired immune function and inflammation during β-cell dysfunction in conditions of type 2 diabetes (characterized by hyperglycemia and hyperlipidemia). Briefly, CD4+ T cells can be activated by interleukin-12 produced from macrophages and dendritic cells, and this consequence occurs as part of a vicious process involving cytotoxic T cells and recruitment by the pancreatic islets. Notably, elevated levels of tumor necrosis factor-alpha are linked with activation of pro-inflammatory signals such as Janus kinase/signal transducer and activator of transcription that promote β-cell failure. IL-12: Interleukin-12; TNF-α: Tumor necrosis factor-alpha; INFs: Interferons; IAPP: Islet amyloid polypeptide; ROS: Reactive oxygen species; ER stress: Endoplasmic reticulum stress; JAK/STAT: Janus kinase/signal transducer and activator of transcription.

Furthermore, evidence summarized in Table 1 indicate that other antidiabetic therapies can also improve β-cell function while modulating inflammatory markers in patients with T2D. For example, Tsunekawa *et al*[102] showed that administration of glimepiride (started from 1 mg daily and increased up to 6 mg daily for 12 wk) could ameliorate insulin resistance by decreasing plasma levels of TNF-α in patients with T2D. Dominguez *et al*[103] demonstrated that the TNF-α blocker, etanercept (received at 25 mg subcutaneously twice weekly for 4 wk) could reduce plasma levels of CRP and IL-6 to improve β-cell function in patients with T2D. Such potential beneficial effects in improving β-cell function through the modulation of pro-inflammatory markers (especially hs-CRP and TNF-α) were confirmed through daily administration of other therapeutic drugs like rosiglitazone (at 4 mg), rosuvastatin or simvastatin (at 20 mg), a combination of calcium carbonate (at 1200 mg) and cholecalciferol (at 75 nmol/L), and even extracts like Iranian propolis extract (at 1000 mg) in patients with T2D[104-107]. These studies further indicate that interventions that block pro-inflammatory markers, especially hs-CRP and TNF-α levels, are likely to improve β -cell function in patients with T2D.

OXIDATIVE STRESS AND PANCREATIC B-CELL DYSFUNCTION IN T2D

Oxidative stress has emerged as a critical feature involved in health (physiology) or disease (pathophysiology)[108]. Oxidative stress is caused by the excessive production of free radical molecules (especially ROS) in response to severely diminished intracellular antioxidants. While ROS may be necessary for intracellular signaling[109], even during pathological conditions like cancer[110], this process is associated with unprecedented damage to many cellular processes during conditions like diabetes[23]. If uncontrolled, excess production of ROS can cause damage to DNA, cellular lipids and proteins, resulting in deteriorated metabolic function[14]. Although it can be sourced from different cellular compartments, the mitochondrial electron transport chain remains the major source of ROS within preclinal models and human systems[111]. The pancreatic β-cells contain mitochondria, which is vital for the regulation of glucose-stimulated insulin release by coupling glucose metabolism to insulin exocytosis[112]. Sustained exposure to hyperglycemic conditions has been associated with impaired β-cell dysfunction through diverse biochemical and molecular mechanisms that implicate impaired oxidation phosphorylation, enhanced production of advanced glycation end products, and abnormal activation of protein kinase C, as well as the polyol and hexosamine pathways[14]. Defects in mitochondrial function are consistent with impaired metabolic function, which can ultimately result in accelerated apoptosis and β-cell death[111,113,114]. Likewise, severely depleted levels of intracellular

antioxidants, such as Gpx, SOD, thioredoxin, and CAT have been linked with β-cell dysfunction in T2D, as highlighted in Figure 3.

Elevated markers of oxidative stress linked with β-cell dysfunction in T2D

Pancreatic β-cells are susceptible to oxidative damage through enhanced production of ROS. Glucose exposure can significantly increase ROS production and in turn cause damage to cultured β-cell-derived cells[115]. These effects were linked with activation of pro-inflammatory mechanisms involving JNK and MAPKs, leading to accelerated apoptosis and reduced β-cell mass[115]. This outcome further highlights the strong association between oxidative stress and inflammation during β-cell insults in conditions such as glucotoxicity. Diverse ROS molecules are actively studied for their detrimental effects in aggravating diabetes-associated complications, and these include superoxide ($O_2^{\cdot-}$) and hydroxyl ($^{\cdot}$OH) radicals, as well as hydrogen peroxide (H_2O_2)[14,108]. These ROS can cause chain activation of other free radicals, further driving the pathological features of oxidative stress. Nicotinamide adenine dinucleotide phosphate oxidases (NOX), existing in different isoforms depending on the specific type of tissue, is the prominent enzyme responsible for the generation of ROS, especially $O_2^{\cdot-}$, although H_2O_2 can also be produced[116]. Previous evidence indicated that NOX-derived ROS generation was responsible for accelerated apoptosis in cultured pancreatic β-cells (NIT-1 cells)[117]. Consistent with other findings[115], these effects were associated with inflammatory pathways involving activation of JNK and inhibition of AKT, which are required for insulin signaling. In fact, through its interaction with mammalian target of rapamycin complex 1, AKT plays a major role during β-cell cycle development in part by regulating the activity of cyclins D2, D3 and cdk4/cyclin D[118]. Other findings have supported the detrimental effects of ROS in mediating pancreatic β-cell death, especially through the activation of stress-activated protein kinases, mitochondrial dysfunction, p38 and JNK, and MAPKs resulting in reduced glucose-stimulated insulin secretion[119-121].

Several studies have investigated the correlation between markers of oxidative stress and β-cell dysfunction in individuals with T2D or related metabolic complications. To highlight the close association between inflammation and oxidative stress, it was demonstrated that markers of Th1/Th2 cytokines and oxidative stress markers were significantly increased in patients with T2D when compared to controls[122]. These findings were consistent with reduced levels of nuclear factor-erythroid factor 2-related factor 2 (Nrf2) and its downstream targets in peripheral blood mononuclear cells of diabetic patients. In many experimental models of T2D, Nrf2 is considered a master regulator of cellular survival, and its increased levels are instrumental to counteract the damaging effects of oxidative stress[123,124]. Reviewed evidence have further indicated that Nrf2 is essential for maintenance of β-cell mass to support the survival, function, and proliferation of β-cells[125]; whereas activation or upregulation of Nrf2 is necessary to diffuse inflammation, improve insulin sensitivity, decrease body weight, and protect against β-cell insult[125]. Thus, different therapeutic agents are entering clinical trials and being tested for their beneficial effects on β-cell survival and function by lowering markers of oxidative stress and promoting the antioxidant response in patients with metabolic disease and T2D[126-129].

Impaired levels of intracellular antioxidants linked with β-cell dysfunction in T2D

Pancreatic β cells are known to exhibit intrinsically low intracellular antioxidative capacity when compared to other tissues within the body[130]. Notably, Gpx, SOD, thioredoxins, and CAT are some of the prominent intracellular antioxidants that are important in protecting against oxidative insults to pancreatic β-cells[21]. The reduced expression of these antioxidants within the pancreas is pathologically implicated in ROS-induced β-cell damage. Importantly, it has been demonstrated that increasing intrinsic antioxidant defenses, through over-expressing Gpx-1 could protect β-cells from *db/db* mice against hyperglycemic insult[131]. Gpx is known for its high affinity to neutralize lipid hydroperoxides, with its low serum levels linked with oxidative stress and the progression of T2D[132]. The other isoforms of this enzyme, like Gpx-4, can salvage pancreatic β-cell death by reducing pro-inflammatory cytokines in pancreatic islets isolated from rats[133]. Over-expression of this glutathione-derived enzyme was very useful in alleviating dysregulated islet insulin production and secretion, mainly though acting on pancreatic and duodenal homeobox 1 (PDX-1) and uncoupling protein 2 (UCP-2), in high fat diet-fed mice[134]. PDX-1 is a transcriptional factor necessary for pancreatic development while UCP-2 is important for the detoxification of ROS through improved mitochondrial function. All these findings, highlight the significant role Gpx plays in detoxifying oxidative stress to improve β-cell function and insulin secretion under hyperglycemic conditions[135]. Ultimately, the genetic elimination of both Gpx-1 and SOD-1 can exert different influences on murine islet function and pancreatic integrity [136]. Even worse, this results in significantly reduced plasma insulin concentrations and islet β-cells mass, which also correlate with increased blood glucose, and blocked glucose-stimulated insulin secretion. These effects are orchestrated mainly through elevation of ROS levels within the pancreatic islets, especially the concentrations of $O_2^{\cdot-}$ and H_2O_2, leading to p53 phosphorylation[136]. While this is related to the diminished role of SOD, known for its neutralizing effects on ROS by eliminating $O_2^{\cdot-}$; phosphorylation of p53 has evolved the capability to incorporate unique environmental signals that facilitate DNA damage[137].

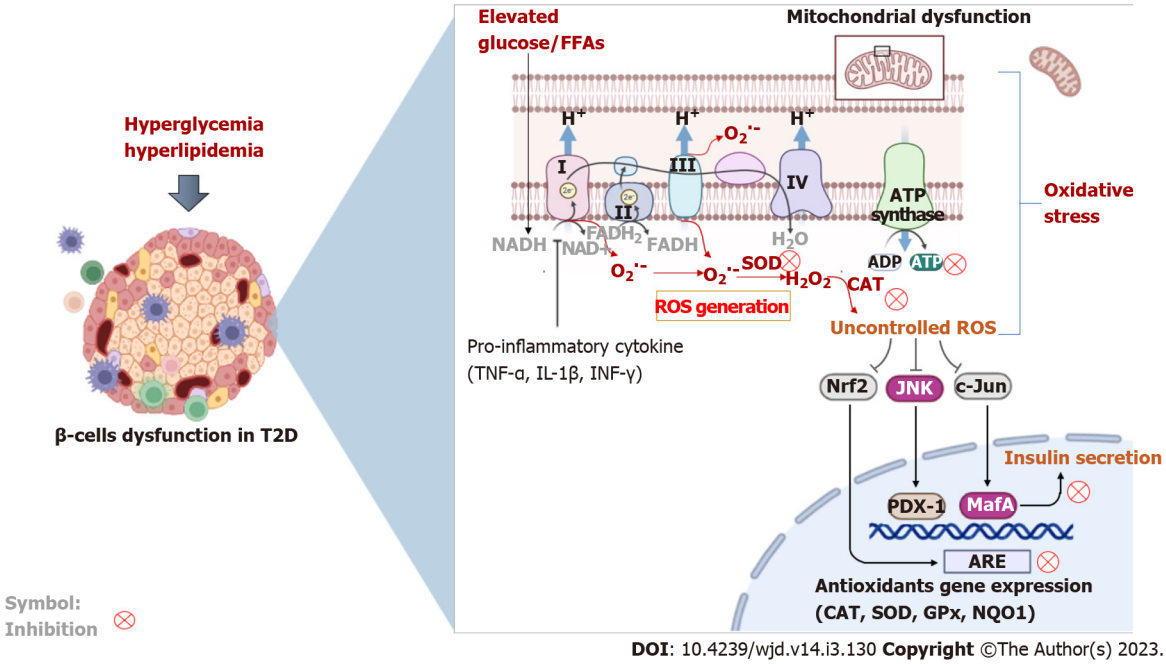

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Figure 3 An overview of some pathophysiological mechanisms that highlight the interrelated link between inflammation and oxidative stress during β-cell dysfunction in type 2 diabetes. Briefly, elevated levels of glucose (hyperglycemia) and lipids (hyperlipidemia) are consistent with an abnormal inflammatory response (due to increased levels of tumor necrosis factor-alpha, interferon-gamma, and interleukin 1 beta) and impaired mitochondrial electron transport chain that causes enhanced generation of reactive oxygen species implicated in β-cell dysfunction. Both inflammation and oxidative stress are responsible for activating cellular destructive mechanisms such as the c-Jun N-terminal kinase pathway and suppressing intracellular antioxidant responses (*e.g.*, nuclear factor erythroid 2-related factor 2, catalase, superoxide dismutase and others), leading to accelerated β-cell injury. ROS: Reactive oxygen species; SOD: Superoxide dismutase; CAT: Catalase; Gpx: Glutathione peroxidase; NQO1: NAD(P)H quinone dehydrogenase 1; NAD(H): Nicotinamide adenine dinucleotide; FADH: Flavin adenine dinucleotide; Nrf2: Nuclear factor erythroid 2-related factor 2; JNK: c-Jun N-terminal kinase; PDX-1: Pancreatic duodenal homeobox 1; ARE: Antioxidant response element; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin 1 beta; INF-γ: Interferon-gamma; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; ROS: Reactive oxygen species; T2D: Type 2 diabetes; FFAs: Free fatty acids.

Beyond the effects of Gpx1 and SOD, the thioredoxin reductase-dependent mechanism is another essential mechanism necessary for the detoxification of H_2O_2-induced β-cell dysfunction[138]. Thioredoxins mainly act by reducing oxidized cysteine residues, with elevated levels of this enzyme linked to increased levels of circulating non-esterified fatty acids in patients with T2D[139]. Other findings indicate that elevated thioredoxin-interacting protein (TXNIP) levels correlate with increased β-cell apoptosis[140]; whereas TXNIP deficiency safeguards against T2D by promoting β-cell survival [141]. In fact, TXNIP is considered essential for the regulation of pancreatic β-cell function and other complications of T2D[142,143]. Another important enzyme, CAT, has long established to protect transgenic mouse β-cells by neutralizing H_2O_2[144]. Indeed, CAT mainly acts by converting H_2O_2 to water and oxygen. Accumulating evidence indicate that increased levels of this enzyme is important for pancreatic β-cell protection, while maintaining insulin secreting function in conditions of T2D[144-146]. Such evidence is consistent with other reviews highlighting the susceptibility of islets to oxidative damage, and the importance of intracellular antioxidant enzymes in protecting β-cells against diabetic insults[21,147].

CONCLUSION

Currently, diverse pathological mechanisms are acknowledged to be involved in the development and progression of T2D. Although both T1D and T2D are associated with β-cell dysfunction, insulin resistance and obesity are the prominent characteristic features for T2D. During a state of obesity, adipose tissue expansion is linked with the production of an array of pro-inflammatory markers that are involved in accelerating β-cell dysfunction. Such effects are consistent with impaired immune response, further driving insulin resistance and elevated blood glucose levels. Oxidative stress also concurrently occurs with inflammation and can cause havoc in many biochemical processes leading to pancreatic β-cell death. Even worse, while sustainably elevated markers of inflammation and oxidative stress are related to β-cell dysfunction, the intracellular defense (antioxidant) mechanisms responsible for ameliorating some of these effects are significantly depleted during T2D. There is limited clinical evidence supporting the beneficial effects of commonly used antidiabetic therapies in enhancing

intracellular antioxidants to protect against β-cell dysfunction in T2D. The systematic analysis of RCTs supports the potential beneficial effects of metformin (especially when used in combination with other antidiabetic therapies like rosiglitazone, pioglitazone and vildagliptin) in improving β-cell function in part by reducing pro-inflammatory markers like hs-CRP and TNF-α in patients with T2D. Thus, beyond improving blood glucose control like with most antidiabetic drugs, future research should invest in developing therapies that can promote intracellular antioxidants and reduce markers of inflammation and oxidative stress to limit pancreatic β-cell failure in patients with T2D.

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FOOTNOTES

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