IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Quantitative Evaluation Of Antioxidants And ROS Profile In Type 2 Diabetes

[1]Pritam Singha, [2]Md.asif Iquebal

[1]Department of Pharmacy Practice, Parul Institute of Pharmacy, Parul University, Vadodara, Gujarat, India, 391760.

[2]Calcutta institute of pharmaceutical technology and AHS Maulana Abul Kalam Azad University of technology, Banitabla, Uluberia, Howrah, West Bengal, 711316.

Abstract

This review article examines the quantitative evaluation of antioxidants and reactive oxygen species (ROS) profiles in type 2 diabetes mellitus (T2DM). T2DM is characterized by progressive insulin resistance and impaired insulin secretion, leading to increased oxidative stress due to chronic hyperglycemia. Elevated ROS levels can damage pancreatic beta cells, impairing their function and exacerbating insulin resistance. The article highlights the critical role of antioxidants in counteracting oxidative stress, noting that pancreatic islets have a lower abundance of antioxidant enzymes compared to other tissues, making them particularly vulnerable to oxidative damage. Furthermore, it discusses the dual role of ROS in glucose-stimulated insulin secretion and the potential therapeutic benefits of antioxidant supplementation to enhance cellular defense mechanisms. By exploring the relationship between oxidative stress, antioxidant status, and metabolic dysfunction in T2DM, this review aims to provide insights into novel biomarkers and therapeutic strategies for managing oxidative stress-related complications in diabetic patients.

Keywords: Type 2 diabetes mellitus, chronic hyperglycemia, Insulin resistance, ROS, Antioxidant

Introduction

Diabetes mellitus is a multifaceted metabolic disorder characterized by a gradual decline in the pancreas's ability to secrete insulin and the body's resistance to its effects [1]. In healthy individuals, pancreatic β-cells respond robustly to nutrient intake and the insulin resistance that often accompanies obesity by producing excess insulin, which helps maintain normal glucose levels [2]. However, in individuals with type 2 diabetes, these β-cells fail to sustain this compensatory insulin secretion, leading to detrimental consequences for their function [3].

Research indicates that prolonged high glucose levels can generate reactive oxygen species (ROS), which contribute to increased oxidative stress within β-cells. This oxidative stress can impair both insulin secretion and action by causing direct damage to cellular components such as DNA, proteins, and lipids [4-6]. Additionally, ROS can activate various stress-sensitive pathways that are associated with insulin resistance and reduced insulin secretion [7]. To combat oxidative stress, cells possess antioxidant defense mechanisms; however, β-cells have a notably lower concentration of key antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase compared to other tissues. This deficiency means that excessive ROS can lead to significant oxidative stress during β-cell dysfunction [8-10]. Consequently, administering antioxidant supplements may enhance the capacity of islet cells to manage oxidative stress. Interestingly, there is emerging evidence that hydrogen peroxide (H2O2) may facilitate glucose-stimulated insulin secretion (GSIS) [11]. Studies suggest that boosting the intrinsic antioxidant capacity of β-cells can diminish ROS signaling and subsequently lower GSIS [12,13]. Therefore, an imbalance between ROS signaling and antioxidant defenses appears to play a crucial role in the dysfunction of β-cells associated with diabetes.

Free radicals and antioxidants

Reactive oxygen species (ROS) and reactive nitrogen species (RNS), primarily derived from nitric oxide (NO), represent the most significant class of radical molecules produced in biological systems [14]. These radicals arise as byproducts of standard cellular metabolism and can have both positive and negative effects on tissues, depending on their concentrations. Free radicals are defined as molecules or fragments that possess one or more unpaired electrons, which contribute to their high reactivity. ROS are generated during reduction-oxidation (redox) reactions that convert oxygen into water [15]. The endothelium, a crucial layer of cells lining blood vessels, plays a vital role in maintaining vascular integrity and homeostasis. This metabolically active layer responds to various biomechanical and biochemical stimuli, with emerging research highlighting the significance of redox signaling in mediating these responses [16].

Reactive oxygen species (ROS) generated in endothelial cells primarily originate from several sources, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, xanthine oxidases, cyclooxygenases (COXs), mitochondria, and, under specific conditions, endothelial nitric oxide synthases (NOS). When stimulated by angiotensin II, NADPH oxidase activity is heightened in both endothelial and smooth muscle cells, indicating that an activated renin-angiotensin system whether local or systemic can

lead to increased superoxide anion production and subsequent dysfunction. Xanthine oxidase also contributes to ROS generation by catalyzing the conversion of hypoxanthine to xanthine and uric acid. This enzyme exists in two forms that differ mainly by their preferred oxidizing substrates; the dehydrogenase form typically uses NAD+ but can also transfer electrons to molecular oxygen [17-20]. Mitochondria are recognized as a significant source of ROS within cells, and elevated mitochondrial ROS levels are implicated in various pathological conditions, including type 2 diabetes. Recent findings have identified a new pathway for regulating mitochondrial ROS involving the p66Shc protein, which is encoded by the ShcA gene and exists in three isoforms of approximately 46, 52, and 66 kDa in mammals [21]. Studies suggest that p66Shc plays a crucial role in managing intracellular redox balance and oxidative stress. Elevated levels of p66Shc may inhibit the expression of ROS-scavenging enzymes by interfering with FOXO transcription factors, leading to decreased antioxidant enzyme expression. In its inactive form, p66ShcA is bound by peroxiredoxin 1 (Prx1). Under stress conditions, p66ShcA dissociates from Prx1 and undergoes serine phosphorylation by PKC-β [22]. The phosphorylated p66ShcA then associates with Pin1 isomerase and translocates into the inter-mitochondrial space (IMS), where it oxidizes cytochrome c and reduces oxygen to produce mitochondrial ROS. The p66(Shc) gene has been identified as a novel gerontogene influencing health across the lifespan, particularly in relation to western lifestyle factors like hypercaloric diets and aging [23-26]. High glucose levels have been shown to promote excessive mitochondrial ROS production, with p66ShcA regulating apoptotic responses to oxidative stress. The involvement of p66Shc in insulin resistance has also been explored; it appears to contribute to insulin desensitization in adipocytes due to nutrient excess. However, definitive evidence demonstrating increased superoxide production in diabetic organs remains limited. Recent studies indicate that diabetic kidneys exhibit reduced superoxide levels and mitochondrial biogenesis, suggesting that a general decrease in mitochondrial superoxide production may result from a shift of carbons and electrons away from mitochondria into the cytosol [27].The clinical relevance of p66Shc in diabetes is highlighted by findings that its gene expression is elevated in mononuclear cells from patients with type 2 diabetes and correlates with plasma levels of 8-isoprostane, a marker of oxidative stress . Ultimately, recent research positions p66Shc as a vital mediator of prolonged vascular hyperglycemic stress in diabetes, offering molecular insights into the progression of vascular complications associated with the condition despite optimal glycemic management [28,29].

Mitochondrial superoxide production is thought to play a crucial role in signaling and is essential for normal physiological communication within cells. However, under pathological conditions or treatments such as anthracyclins, heightened oxidative stress in the mitochondria due to disrupted oxidative metabolism may lead to increased lipid peroxidation and damage to cellular membranes and DNA. This can trigger a series of signaling events that worsen the disease's severity. The processes of mitochondrial fusion and fission significantly affect ROS production [30]. Beyond their role in the electron transport chain, mitochondria also produce hydrogen peroxide (H2O2) through monoamine oxidase (MAO), which is attached to their outer membrane. MAO metabolizes endogenous amines and serves as a major source of H2O2, contributing to oxidative stress in cardiovascular diseases, including diabetes. Mitochondria are

well-recognized for producing considerable amounts of hydrogen peroxide (H2O2). Although H2O2 does not possess unpaired electrons and is not classified as a radical species in the strict sense, its production under normal physiological conditions is estimated to represent about 2% of the total oxygen consumed by the organism. The principal reactive nitrogen species (RNS) is nitric oxide (- NO), which is produced by endothelial nitric oxide synthase (eNOS) and serves as a critical gaseous mediator influencing endothelial function [31]. - NO is known for its powerful vasodilatory, anti-inflammatory, and anti-thrombotic effects. Under normal conditions, eNOS synthesizes - NO in the presence of its substrate L-arginine and co-factors like tetrahydrobiopterin (BH4). However, when there is insufficient BH4 relative to nitric oxide synthase (NOS), the enzyme becomes "uncoupled," leading to the production of superoxide instead of - NO. Furthermore, the synthesis of - NO can be inhibited by guanidino-substituted analogues of L-arginine, such as asymmetric dimethylarginine (ADMA), which naturally occurs in plasma and various tissues. Studies indicate that plasma ADMA levels in humans and rats typically range from 0.3 to 0.5 mmol/L [32]. Elevated ADMA levels have been observed in individuals with type 1 or type 2 diabetes, suggesting a link between increased ADMA production and the onset of obesity and diabetes. Additionally, arginine methylation has implications for cardiovascular and metabolic diseases, with heightened ADMA levels potentially arising from early oxidative stress development. Elevated serum ADMA is recognized as an early indicator of vascular dysfunction and insulin resistance in type 2 diabetes [33]. The free radical - NO has a very short half-life of only a few seconds in aqueous environments. It readily reacts with molecular oxygen and ROS, forming various oxidation products, including RNS. A well-studied reaction involves - NO interacting with superoxide (O2- -), which occurs at nearly diffusion-limited rates to produce peroxynitrite (ONOO−). This compound is a strong oxidizer that can generate hydroxyl radicals (- OH) and nitrogen dioxide (- NO2) upon protonation. Other reactive radicals can also originate from various endogenous molecules, such as carbon monoxide (CO) and nitrogen dioxide [34,35]. To counteract the effects of free radicals from multiple sources, organisms have developed defense mechanisms involving antioxidant agents. Antioxidants are substances that significantly delay or inhibit oxidation reactions when present in low concentrations compared to oxidizable substrates.

Defense mechanisms against oxidative stress caused by free radicals can be categorized into three main types: (a) preventive mechanisms, (b) repair mechanisms, and (c) antioxidant defenses [36]. The enzymatic components of antioxidant defenses include superoxide dismutases (SOD), glutathione peroxidases (GPx), catalases (CAT), and other enzymes such as peroxiredoxins (Prx), metallothioneins (MTs), and thioredoxins. Non-enzymatic antioxidants consist of vitamins like ascorbic acid (Vitamin C) and tocopherol (Vitamin E), as well as other compounds such as glutathione (GSH), folic acid, lipoic acid, and thiols. Additionally, indirect antioxidants can include agents that chelate redox-active metals or pharmacological drugs [37-39]. The presence of metal ions in the body is crucial; however, an imbalance—either an excess or deficiency—can disrupt protein functions, hinder proper protein folding, or, in the case of iron or copper, lead to increased oxidative stress. This involvement of metal ions in conditions like diabetes has made them a focus for therapeutic strategies. For instance, iron can catalyze the formation of harmful free radicals, and excess iron is typically sequestered by ferritin to prevent

toxicity. When levels of ceruloplasmin are low, which requires copper for its ferroxidase activity, the transfer of iron to transferrin may be compromised, leading to iron accumulation in tissues—a phenomenon observed in both copper-deficient animals and humans lacking functional ceruloplasmin [40]. Zinc regulation is also important, with metallothioneins playing a significant role in its intracellular distribution. Recent studies have highlighted zinc's influence on redox states, enzyme activities, gene expression, and energy metabolism. Metallothioneins may help protect organs from high glucose-induced ROS and subsequent inflammation associated with diabetic conditions [41-43].

Under normal circumstances, there exists a balance between the production of reactive oxygen species (ROS) and the activity of antioxidant defense mechanisms within cells. Oxidative stress is typically characterized by an imbalance where pro-oxidants exceed antioxidants. This imbalance is also implicated in the aging process, which is influenced by disrupted thiol-redox circuits that can lead to abnormal cell signaling and compromised redox control. In the bloodstream, oxidative stress can be assessed by measuring the redox state of plasma glutathione, specifically the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG). As research into subcellular redox organization progresses, there is potential for developing targeted antioxidants that can restore redox signaling and aid in disease prevention [44]. Lipids are particularly susceptible to oxidation due to the high content of polyunsaturated fatty acids in cell membranes and the presence of oxygen at millimolar concentrations within lipid bilayers. Unsaturated phospholipids, glycolipids, and cholesterol are key targets for oxidative damage, which can lead to lipid peroxidation—a degenerative process that disrupts the structure and function of cellular components. Lipid hydroperoxides (LOOHs), which are formed from unsaturated lipids, serve as significant intermediates in peroxidative reactions initiated by reactive species like hydroxyl radicals, peroxyl radicals, singlet oxygen, and peroxynitrite [45]. Specifically, cardiolipin, an unsaturated phospholipid found in the inner mitochondrial membrane, tends to decrease in concentration during periods of prominent lipid peroxidation, as observed in conditions such as aging and diabetes. Increased oxidative stress linked to lipid peroxidation in endothelial cells may significantly contribute to complications arising from hyperglycemia in diabetes. Endothelial dysfunction is marked by heightened pro-oxidant activity and an imbalance in mediator production and release [46]. The pathogenesis of diabetes involves a convergence of metabolic factors, oxidative stress, and inflammation that promotes monocyte adhesion to endothelial cells. Aging is associated with heightened oxidative stress levels, and both type 1 and type 2 diabetic patients exhibit increased oxidative stress indices in their plasma. Furthermore, individuals with diabetes show diminished nitric oxide-dependent vasodilation [47]. In conclusion, when oxidative stress occurs, free radicals that remain non-neutralized can inflict damage on all major cellular macromolecules—nucleic acids, lipids, and proteins. The oxidation of lipids can alter membrane structure and fluidity, adversely affecting cellular processes and overall function.

Oxidative stress targeted molecular pathways in T2DM pathogenesis

In type 2 diabetes mellitus (T2DM), prolonged exposure to elevated glucose and free fatty acid levels plays a significant role in beta cell dysfunction. These beta cells are particularly vulnerable to oxidative stress due to their limited antioxidant defenses [48]. The resulting oxidative stress can damage mitochondria, leading to a marked reduction in insulin secretion and potentially contributing to insulin resistance. Under normal physiological conditions, cellular metabolic processes, such as glucose oxidation, produce superoxide anions (O2-). The body's antioxidant defense system typically manages these radicals within a certain threshold [49]. However, during hyperglycemic states, the production of O2- increases, overwhelming the body's antioxidant capacity and resulting in oxidative stress that damages various biomolecules, including DNA. When DNA is damaged, it activates poly-ADP-ribose polymerase-1 (PARP-1), an enzyme involved in DNA repair [50]. PARP-1 acts as a potent inhibitor of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in the glycolysis pathway, leading to an accumulation of glycolytic intermediates such as glyceraldehyde 3-phosphate, fructose-6-phosphate, and glucose-6-phosphate [51]. This accumulation promotes additional pro-oxidant pathways, including those mediated by protein kinase C and the formation of advanced glycation end products through hexosamine and polyol pathways.

Insulin resistance (IR) and oxidative stress

In skeletal muscle and adipose tissue, insulin enhances glucose uptake by initiating a complex series of signaling events. When insulin binds to its receptor, it triggers the tyrosine phosphorylation of various protein substrates, which subsequently activates phosphoinositide 3-kinase (PI3K). This process is linked to the translocation of GLUT4 from intracellular compartments to the plasma membrane, facilitating glucose transport into the cells. Insulin resistance (IR) is characterized by an insufficient response from insulin-target tissues, including skeletal muscle, liver, and adipose tissue, to the physiological effects of circulating insulin. The primary consequences of IR include reduced insulin-stimulated glucose uptake in skeletal muscle, impaired inhibition of hepatic glucose production in the liver, and diminished insulin's ability to suppress lipolysis in adipose tissue. This discussion focuses on how nutrient availability and obesity influence inflammatory pathways in relation to oxidative stress across three key areas: 1) the pancreas, 2) adipose and skeletal tissues, and 3) the liver.

Pancreas, insulin resistance and oxidative stress:

In type 2 diabetes mellitus (T2DM), the chronic presence of elevated glucose and free fatty acids significantly contributes to beta cell dysfunction. These beta cells are particularly susceptible to oxidative stress due to their relatively low levels of antioxidant enzymes, such as catalase and glutathione peroxidase [52]. As a result, oxidative stress can damage mitochondria, leading to reduced insulin secretion and potentially causing insulin resistance. Under normal conditions, metabolic processes like glucose oxidation generate superoxide anion radicals (O2-), which the body's antioxidant defense system can manage to some extent. However, in hyperglycemic conditions, the production of O2- increases, overwhelming the antioxidant capacity and resulting in oxidative stress that harms various biomolecules,

including DNA [53]. The presence of oxidative stress markers, such as 8-hydroxy-2-deoxyguanosine (8-OHdG) and 4-hydroxy-2,3-nonenal (4-HNE), is elevated in islets under diabetic conditions. Prolonged exposure to high glucose levels reduces insulin gene expression and secretion; however, this decline can be mitigated by antioxidants like probucol, glutathione peroxidase, N-acetyl L-cysteine (NAC), or vitamins C and E. The activation of the c-Jun N-terminal kinase (JNK) pathway is linked to decreased insulin gene expression caused by oxidative stress [54]. Inhibiting the JNK pathway can protect cells from oxidative damage. This pathway's activation likely results in reduced activity of pancreatic transcription factors PDX-1 and Mafa, which are crucial for insulin gene transcription in the diabetic state. Notably, overexpressing Mafa in the liver alongside PDX-1 significantly improves glucose tolerance [55].

Beta-cell dysfunction in type 2 diabetes mellitus (T2DM) arises from chronic exposure to high levels of glucose and free fatty acids (FFA), or a combination of both. Sustained high glucose concentrations lead to increased oxidation of glucose in the tricarboxylic acid (TCA) cycle, resulting in higher production of reactive oxygen species (ROS). In insulin resistance (IR) syndrome, there is an elevated influx of FFAs from adipose tissue into arterial endothelial cells, which may enhance mitochondrial FFA oxidation [56]. In vitro studies show that elevated FFA levels have numerous negative effects on mitochondrial function, including disrupting oxidative phosphorylation and increasing ROS generation. Prolonged exposure to FFAs in vitro also suppresses insulin mRNA levels and synthesis, with distinct impacts observed from saturated and monounsaturated fatty acids on beta-cell turnover and functionality [57].

The Etiology of insulin resistance (IR) is multifaceted, with the endoplasmic reticulum (ER) playing a significant role [58]. The ER is the main organelle responsible for the proper folding, maturation, and transport of proteins. It also acts as a dynamic reservoir for calcium, regulating intracellular calcium levels. When there is an accumulation of improperly folded or unfolded proteins within the ER, it leads to a state known as ER stress, which activates an adaptive response called the unfolded protein response (UPR). There is a close connection between protein folding in the ER and the production of reactive oxygen species (ROS), highlighting the interplay between calcium signaling and oxidative stress [59].

Trace elements such as selenium and zinc may serve as antioxidants. Zinc is essential for insulin secretion because it forms co-crystals with insulin in exocytotic vesicles. Upon insulin release into the bloodstream, which has a higher pH, zinc is also released and has been shown to inhibit alpha cell secretion [60-62]. Although zinc is redox-inert and not an antioxidant in the strictest sense, it offers various indirect antioxidant effects. Specifically, zinc enhances the cell's antioxidant capacity by competing with metals like copper and iron that can catalyze harmful reactions, such as the Fenton reaction. Furthermore, low zinc levels can make insulin more susceptible to structural changes, suggesting that zinc plays a protective role against oxidative damage [63,64]. In conditions characterized by chronic hyperglycemia and hyperlipidemia—common in type 2 diabetes—there is an increase in reactive oxygen species (ROS) and electrophiles that lead to beta-cell dysfunction and glucose toxicity. Additionally, oxidative stress activates the transient receptor potential (TRP) channel superfamily, which facilitates calcium influx into beta cells [65].

Adipose and skeletal tissue, insulin resistance and oxidative stress:

Adipose tissue is composed of various cell types, including adipocytes, immune cells (such as macrophages and lymphocytes), preadipocytes, and endothelial cells. Adipocytes secrete adipokines like leptin and adiponectin, which enhance insulin sensitivity, while also releasing proteins such as resistin and retinol-binding protein 4 (RBP4) that can reduce insulin sensitivity [65]. Additionally, adipokines such as adiponectin and adipocyte fatty acid-binding protein (A-FABP) serve as prognostic biomarkers for cardiovascular disease and may represent promising therapeutic targets for treatment [66].

Obesity, characterized by an increase in body fat mass, results from a prolonged positive energy balance over months or years [67]. Cells have intrinsic pathways that can quickly detect changes in energy balance or nutrient availability. Chronic activation of pro-inflammatory pathways within insulin-sensitive tissues can lead to insulin resistance (IR) associated with obesity. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and C-reactive protein (CRP) have been observed in individuals with IR and diabetes. Various peptides, including pro-inflammatory cytokines, chemokines, and hormones, can act in both endocrine and paracrine manners within adipose tissue [68,69]. Specifically, TNF-α and IL-6 are known to disrupt insulin signaling in insulin-sensitive tissues, thereby increasing IR.

Oxidative stress and insulin resistance (IR) are closely interconnected processes. As previously noted, the gene p66ShcA plays a significant role in regulating the apoptotic responses to oxidative stress and is a key mediator of IR. Research has shown that p66Shc is involved in insulin signaling, particularly in promoting fat accumulation induced by insulin [70]. While p66Shc contributes to the generation of reactive oxygen species (ROS) and heightens cellular oxidative stress in various pathological conditions, it may also function as an adaptor molecule that aids in forming supramolecular complexes essential for the propagation of insulin signaling.

Oxidative stress and insulin resistance (IR) are closely interconnected processes. One of the effects of oxidative stress is the activation of various serine kinase cascades, which are involved in the insulin signaling pathway, including the insulin receptor (IR) and insulin receptor substrate (IRS) proteins [71-73]. Research has indicated that hydrogen peroxide (H2O2) can inhibit insulin-stimulated glucose transport. The activation of pathways such as NF-κB, p38 MAPK, and JNK/SAPK is sensitive to oxidative stress and is associated with impaired insulin action, indicating their involvement in oxidative stress-induced IR. Furthermore, adiponectin, a protein secreted by adipocytes, has been shown to have potent insulin-sensitizing effects and can inhibit NF-κB activation. When adipocytes are exposed to oxidative stress, there is a decrease in anti-inflammatory adiponectin levels and an increase in pro-inflammatory adipocytokines [74]. The protective effects of adiponectin against cellular damage are partly due to its antioxidative and nitrosative properties; it reduces oxidative/nitrosative stress by inhibiting the expression of NADPH oxidase and inducible nitric oxide synthase (iNOS). The connection between oxidative stress and IR appears to be multifaceted, with evidence suggesting that the local renin-angiotensin-aldosterone system (RAAS) may also mediate oxidative stress in adipocytes [75]. In summary, inflammation in

adipose tissue is marked by changes in immune cell populations that lead to altered adipo/cytokine profiles, ultimately inducing IR in skeletal muscle and the liver.

Liver, insulin resistance and oxidative stress

After a meal, the intestine becomes the primary source of glucose, which increases glucose availability to the pancreas and stimulates insulin secretion. In individuals with insulin resistance (IR), there is an impairment in the insulin-mediated suppression of hepatic glucose production. As a result, these individuals initially maintain normal blood sugar levels through excessive insulin production by the pancreas. However, prolonged hypersecretion can eventually lead to pancreatic beta cell dysfunction [76]. In the liver, macrophages play a crucial role in maintaining metabolic homeostasis. These immune cells respond to metabolic signals and produce various pro-inflammatory and anti-inflammatory mediators that help regulate metabolism [77]. While it is clear that metabolic stressors such as fatty acids, ceramides, and oxidized low-density lipoprotein (oxLDL) can trigger macrophage inflammation, the specific mechanisms by which these pro-inflammatory pathways contribute to metabolic diseases, particularly in the context of IR, are not fully understood. Resident macrophages in organs like the liver adapt to their local environments and display diverse functional and morphological characteristics [78]. They have the capacity to engulf and metabolize lipids, linking lipid metabolism with inflammation. Increased lipid accumulation in the liver is considered a contributing factor to the development of IR. This accumulation is associated with heightened free fatty acid (FFA) flux, leading to an excess of fatty acid intermediates such as ceramide [79]. These lipid intermediates can activate intracellular serine kinases, which may inhibit insulin signaling. The synthesis of ceramide is largely dependent on the availability of long-chain saturated fatty acids, which are involved in the initial rate-limiting step of de novo ceramide production. Ceramide has been shown to activate enzymes that generate reactive oxygen species (ROS), including NADPH oxidase, xanthine oxidase, and nitric oxide synthase. Additionally, ceramide interacts with the mitochondrial electron transport chain, contributing to ROS generation. Early studies indicated that ceramide could inhibit insulin's activation of upstream signaling pathways. Manipulating enzymes responsible for sphingolipid synthesis or degradation in animal models has demonstrated significant effects on IR and alleviated lipotoxic responses linked to obesity. Ceramides are recognized for their role in promoting IR, and it has been suggested that other lipid intermediates may also influence insulin sensitivity. Ceramide is now viewed as a critical metabolite that can alter cellular metabolism and induce apoptosis [80]. One major mechanism by which ceramide affects cellular metabolism is through its strong inhibition of Akt, a serine/threonine kinase essential for linking insulin and other growth factors to nutrient transporter expression and function. Consequently, targeting ceramide synthesis or enhancing its degradation may offer new therapeutic strategies for managing diabetes.

Antioxidant strategies to control oxidative stress in diabetes

The intricate relationship between increased oxidative stress and inflammation in conditions like type 2 diabetes complicates the determination of their temporal sequence. In diabetic patients, heightened oxidative stress correlates with a reduction in cellular antioxidant defenses. Various strategies have been

explored to mitigate oxidative stress-related cellular changes in diabetes through antioxidant supplementation [81]. The justification for utilizing certain vitamins and compounds in the prevention and management of diabetes largely stems from experimental and epidemiological studies. Dietary components, including long-chain omega-3 fatty acids, antioxidants, and pharmacological agents, have the potential to influence the risk of inflammatory conditions [82]. These substances operate through multiple mechanisms, such as reducing the production of inflammatory mediators by affecting cell signaling pathways and gene expression.

Clinical Trial of Antioxidant Therapy in Patients with Diabetes

Inflammation is closely linked to elevated levels of glycated haemoglobin (HbA1c), which serves as a reliable indicator of chronic hyperglycemia. Setting a treatment goal for HbA1c below 6% in high-risk diabetic patients has been shown to reduce the incidence of nonfatal myocardial infarctions over five years, as demonstrated by the ACCORD Study Group. A new approach to treating type 2 diabetes mellitus (T2DM) with antioxidants that also possess anti-inflammatory properties is emerging as a promising therapeutic strategy. Evidence from various studies suggests that compounds like ginger, resveratrol, and rutin flavonoid can lower HbA1c levels, blood glucose levels, and the homeostatic model assessment of insulin resistance (HOMA-IR), which is an indicator of long-term glycemic control. Additionally, allium sativum, olea europaea oil, and astaxanthin have been found to reduce LDL and total serum cholesterol levels. Mudan granules have demonstrated neuroprotective effects in diabetic patients, suggesting a potential synergy between these antioxidants and anti-inflammatory agents like resveratrol and rutin flavonoid when combined with mudan granules. Notably, ginger has been shown to increase nitric oxide (NO) production, while resveratrol and rutin flavonoid can reduce levels of C-reactive protein (CRP) and interleukin-6 (IL-6), respectively [83]. Therefore, antioxidants may offer effective treatment options for managing cytokine storms associated with diabetes. The advancement of these compounds from preclinical research to human studies indicates their potential efficacy. The data presented highlight the clinical relevance of antioxidants with anti-inflammatory properties in T2DM management. However, further research is necessary to assess their effectiveness against complications related to T2DM, such as hyperlipidemia, pro-inflammatory mediators, and insulin resistance. It is also essential to identify diabetic patients at various stages of the disease to ensure that the anti-inflammatory and antidiabetic effects of these compounds are clearly observable.

Conclusions and Future Implications

The intricate connection between increased oxidative stress and inflammation in conditions such as type 2 diabetes mellitus (T2DM) complicates the understanding of their temporal relationship. In diabetic individuals, elevated oxidative stress is often associated with diminished antioxidant defenses at the cellular level. Numerous studies have explored the potential of antioxidant supplementation to mitigate oxidative stress-related cellular changes in diabetes. The rationale for using specific vitamins and other compounds in diabetes prevention and management is primarily based on findings from experimental and epidemiological research [84]. Various dietary components, including long-chain omega-3 fatty acids,

antioxidants, and pharmacological agents, may help modulate the risk of inflammatory conditions. These compounds can act through multiple mechanisms, such as reducing the production of inflammatory mediators by influencing cell signaling pathways and gene expression. Inflammation is closely linked to elevated levels of glycated haemoglobin (HbA1c), a marker of chronic hyperglycemia. Setting treatment goals for HbA1c below 6% in high-risk diabetic patients has been shown to reduce the incidence of nonfatal myocardial infarctions, as observed in the ACCORD Study Group. A new approach that focuses on treating patients with antioxidants that have anti-inflammatory properties is emerging as a promising strategy for managing T2DM. Evidence suggests that compounds like ginger, resveratrol, and rutin flavonoid can lower HbA1c levels, blood glucose levels, and homeostatic model assessment of insulin resistance (HOMA-IR), while substances such as allium sativum, olea europaea oil, and astaxanthin can reduce LDL and total serum cholesterol [85]. Mudan granules have demonstrated neuroprotective effects in diabetic patients, indicating a potential synergy with antioxidants like resveratrol and rutin flavonoid. Notably, ginger has been shown to increase nitric oxide (NO) production, while resveratrol and rutin flavonoid reduce levels of C-reactive protein (CRP) and interleukin-6 (IL-6), respectively. As such, antioxidants may provide effective treatment options for managing cytokine storms associated with diabetes. The transition of these compounds from preclinical research to human trials underscores their potential effectiveness. While the clinical utility of antioxidants with anti-inflammatory effects in T2DM is evident, further research is needed to evaluate their efficacy against complications related to diabetes, such as hyperlipidemia, pro-inflammatory mediators, and insulin resistance. It is also crucial to identify diabetic patients at various stages of the disease to ensure that the anti-inflammatory and antidiabetic effects of these compounds are clearly observable. As the prevalence of diabetes is expected to rise over the next decade, it is increasingly important for research to focus on developing new anti-inflammatory drugs with improved efficacy and safety profiles, as well as antioxidants that can act as "safety switches" by neutralizing free radicals to prevent unwanted inflammatory responses.

Reference

1. Porte D Jr. Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications. Diabetes Metab Res Rev 2001; 17:181-8.
2. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003; 46:3-19.
3. Rehman A, Nourooz-Zadeh J, Moller W, Tritschler H, Pereira P, Halliwell B. Increased oxidative damage to all DNA bases in patients with type II diabetes mellitus. FEBS Lett 1999;448: 120-2.
4. Sakuraba H, Mizukami H, Yagihashi N, Wada R, Hanyu C, Yagihashi S. Reduced beta-cell mass and expression of oxida tive stress-related DNA damage in the islet of Japanese type II diabetic patients. Diabetologia 2002;45:85-96.
5. Mohamed AK, Bierhaus A, Schiekofer S, Tritschler H, Ziegler R, Nawroth PP. The role of oxidative stress and NF-kappaB activation in late diabetic complications. Biofactors 1999;10:157 67.
6. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hy pothesis of type 2 diabetes. Endocr Rev 2002;23:599-622.

7. Grankvist K, Marklund SL, Taljedal IB. CuZn-superoxide dis mutase, Mn-superoxide dismutase, catalase and glutathione peroxidase in pancreatic islets and other tissues in the mouse. Biochem J 1981;199:393-8.
8. Lenzen S, Drinkgern J, Tiedge M. Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. Free Radic Biol Med 1996;20:463-6.
9. Kaneto H, Kajimoto Y, Miyagawa J, Matsuoka T, Fujitani Y, Umayahara Y, Hanafusa T, Matsuzawa Y, Yamasaki Y, Hori M. Beneficial effects of antioxidants in diabetes: possible protec tion of pancreatic beta-cells against glucose toxicity. Diabetes 1999; 48:2398-406.
10. Kubisch HM, Wang J, Bray TM, Phillips JP. Targeted overexpression of Cu/Zn superoxide dismutase protects pancreatic beta-cells against oxidative stress. Diabetes 1997; 46:1563-6.
11. Pi J, Bai Y, Zhang Q, Wong V, Floering LM, Daniel K, Reece JM, Deeney JT, Andersen ME, Corkey BE, Collins S. Reactive oxygen species as a signal in glucose-stimulated insulin secretion. Diabetes 2007; 56:1783-91.
12. Affourtit C, Jastroch M, Brand MD. Uncoupling protein-2 at tenuates glucose-stimulated insulin secretion in INS-1E insulinoma cells by lowering mitochondrial reactive oxygen species. Free Radic Biol Med 2011; 50:609-16.
13. Saadeh M, Ferrante TC, Kane A, Shirihai O, Corkey BE, Dee ney JT. Reactive oxygen species stimulate insulin secretion in rat pancreatic islets: studies using mono-oleoyl-glycerol. PLoS One 2012;7:e30200.
14. B. Halliwell, J.M. Gutteridge, The definition and measurement of antioxidants in biological systems, Free Radic Biol Med, 18 (1995) 125-126.
15. C. Vergely, V. Maupoil, G. Clermont, A. Bril, L. Rochette, Identification and quantification of free radicals during myocardial ischemia and reperfusion using electron paramagnetic resonance spectroscopy, Arch Biochem Biophys, 420 (2003) 209-216.
16. A.C. Montezano, R.M. Touyz, Reactive oxygen species and endothelial function--role of nitric oxide synthase uncoupling and Nox family nicotinamide adenine dinucleotide phosphate oxidases, Basic & clinical pharmacology & toxicology, 110 (2012) 87-94.
17. A. Oudot, C. Martin, D. Busseuil, C. Vergely, L. Demaison, L. Rochette, NADPH oxidases are in part responsible for increased cardiovascular superoxide production during aging, Free Radic Biol Med, 40 (2006) 2214-2222.
18. C. Richard, B. Lauzier, S. Delemasure, S. Talbot, S. Ghibu, B. Collin, J. Senecal, F. Menetrier, C. Vergely, R. Couture, L. Rochette, Effects of angiotensin-1 converting enzyme inhibition on oxidative stress and bradykinin receptor expression during doxorubicin-induced cardiomyopathy in rats, J Cardiovasc Pharmacol, 52 (2008) 278-285.
19. S. Nemoto, T. Finkel, Redox regulation of forkhead proteins through a p66shc-dependent signaling pathway, Science, 295 (2002) 2450-2452.
20. E. Migliaccio, M. Giorgio, P.G. Pelicci, Apoptosis and aging: role of p66Shc redox protein, Antioxidants & redox signaling, 8 (2006) 600-608.
21. K. Su, D. Bourdette, M. Forte, Mitochondrial dysfunction and neurodegeneration in multiple sclerosis, Frontiers in physiology, 4 (2013) 169.
22. A. Berry, F. Cirulli, The p66(Shc) gene paves the way for healthspan: evolutionary and mechanistic perspectives, Neuroscience and biobehavioral reviews, 37 (2013) 790-802.
23. P. Pinton, R. Rizzuto, p66Shc, oxidative stress and aging: importing a lifespan determinant into mitochondria, Cell Cycle, 7 (2008) 304-308.
24. S.C. Ranieri, S. Fusco, E. Panieri, V. Labate, M. Mele, V. Tesori, A.M. Ferrara, G. Maulucci, M. De Spirito, G.E. Martorana, T. Galeotti, G. Pani, Mammalian life-span determinant p66shcA mediates obesity-induced insulin resistance, Proceedings of the National Academy of Sciences of the United States of America, 107 (2010) 13420-13425.
25. L.L. Dugan, Y.H. You, S.S. Ali, M. Diamond-Stanic, S. Miyamoto, A.E. DeCleves, A. Andreyev, T. Quach, S. Ly, G. Shekhtman, W. Nguyen, A. Chepetan, T.P. Le, L. Wang, M. Xu, K.P. Paik, A. Fogo, B. Viollet, A. Murphy, F. Brosius, R.K. Naviaux, K. Sharma, AMPK dysregulation promotes diabetes related reduction of superoxide and mitochondrial function, The Journal of clinical investigation, 123 (2013) 4888-4899.

26. E. Pagnin, G. Fadini, R. de Toni, A. Tiengo, L. Calo, A. Avogaro, Diabetes induces p66shc gene expression in human peripheral blood mononuclear cells: relationship to oxidative stress, The Journal of clinical endocrinology and metabolism, 90 (2005) 1130-1136.
27. F. Paneni, P. Mocharla, A. Akhmedov, S. Costantino, E. Osto, M. Volpe, T.F. Luscher, F. Cosentino, Gene silencing of the mitochondrial adaptor p66(Shc) suppresses vascular hyperglycemic memory in diabetes, Circulation research, 111 (2012) 278-289.
28. S.F. Nunes, I.V. Figueiredo, J.S. Pereira, E.T. de Lemos, F. Reis, F. Teixeira, M.M. Caramona, Monoamine oxidase and semicarbazide-sensitive amine oxidase kinetic analysis in mesenteric arteries of patients with type 2 diabetes, Physiol Res, 60 (2011) 309-315.
29. Z. Xia, P.M. Vanhoutte, Nitric oxide and protection against cardiac ischemia, Curr Pharm Des, 17 (2011) 1774-1782.
30. M. Feletou, R. Kohler, P.M. Vanhoutte, Nitric oxide: orchestrator of endothelium-dependent responses, Annals of medicine, 44 (2012) 694-716.
31. C. Korandji, M. Zeller, J.C. Guilland, C. Vergely, P. Sicard, L. Duvillard, P. Gambert, D. Moreau, Y. Cottin, L. Rochette, Asymmetric dimethylarginine (ADMA) and hyperhomocysteinemia in patients with acute myocardial infarction, Clin Biochem, 40 (2007) 66-72.
32. L. Tarnow, P. Hovind, T. Teerlink, C.D. Stehouwer, H.H. Parving, Elevated plasma asymmetric dimethylarginine as a marker of cardiovascular morbidity in early diabetic nephropathy in type 1 diabetes, Diabetes Care, 27 (2004) 765-769.
33. J.H. Lee, G.H. Park, Y.K. Lee, J.H. Park, Changes in the arginine methylation of organ proteins during the development of diabetes mellitus, Diabetes research and clinical practice, 94 (2011) 111 118.
34. C. Korandji, M. Zeller, J.C. Guilland, B. Collin, B. Lauzier, P. Sicard, L. Duvillard, F. Goirand, D. Moreau, Y. Cottin, L. Rochette, C. Vergely, Time course of asymmetric dimethylarginine (ADMA) and oxidative stress in fructose-hypertensive rats: a model related to metabolic syndrome, Atherosclerosis, 214 (2011) 310-315.
35. S. Abhary, N. Kasmeridis, K.P. Burdon, A. Kuot, M.J. Whiting, W.P. Yew, N. Petrovsky, J.E. Craig, Diabetic retinopathy is associated with elevated serum asymmetric and symmetric dimethylarginines, Diabetes Care, 32 (2009) 2084-2086.
36. L. Rochette, C. Vergely, [Hydrogen sulfide (H2S), an endogenous gas with odor of rotten eggs might be a cardiovascular function regulator], Ann Cardiol Angeiol (Paris), 57 (2008) 136-138.
37. L. Rochette, C. Vergely, Forgotten radicals in biology, International Journal of Biomedical Sciences, 4 (2008) 255-259.
38. L. Rochette, Y. Cottin, M. Zeller, C. Vergely, Carbon monoxide: mechanisms of action and potential clinical implications, Pharmacol Ther, 137 (2013) 133-152.
39. L. Rochette, E. Tatou, V. Maupoil, M. Zeller, Y. Cottin, S. Jazayeri, R. Brenot, C. Girard, M. David, C. Vergely, Atrial and vascular oxidative stress in patients with heart failure, Cell Physiol Biochem, 27 (2011) 497-502.
40. J.Y. Uriu-Adams, C.L. Keen, Copper, oxidative stress, and human health, Molecular aspects of medicine, 26 (2005) 268-298.
41. B. Ruttkay-Nedecky, L. Nejdl, J. Gumulec, O. Zitka, M. Masarik, T. Eckschlager, M. Stiborova, V. Adam, R. Kizek, The role of metallothionein in oxidative stress, International journal of molecular sciences, 14 (2013) 6044-6066.
42. H. Tachibana, D. Ogawa, N. Sogawa, M. Asanuma, I. Miyazaki, N. Terami, T. Hatanaka, C.S. Horiguchi, A. Nakatsuka, J. Eguchi, J. Wada, H. Yamada, K. Takei, H. Makino, Metallothionein deficiency exacerbates diabetic nephropathy in streptozotocin-induced diabetic mice, Am J Physiol Renal Physiol, 306 (2014) F105-115.
43. C. Martin, H. Dubouchaud, L. Mosoni, J.M. Chardigny, A. Oudot, E. Fontaine, C. Vergely, C. Keriel, L. Rochette, X. Leverve, L. Demaison, Abnormalities of mitochondrial functioning can partly explain the metabolic disorders encountered in sarcopenic gastrocnemius, Aging Cell, 6 (2007) 165-177.
44. D.P. Jones, Redefining oxidative stress, Antioxid Redox Signal, 8 (2006) 1865-1879.

45. D.P. Jones, Y.M. Go, Redox compartmentalization and cellular stress, Diabetes Obes Metab, 12 Suppl 2 (2010) 116-125.
46. J.R. Roede, Y.M. Go, D.P. Jones, Redox equivalents and mitochondrial bioenergetics, Methods Mol Biol, 810 (2012) 249-280.
47. C. Courderot-Masuyer, J.J. Lahet, B. Verges, J.M. Brun, L. Rochette, Ascorbyl free radical release in diabetic patients, Cell Mol Biol (Noisy-le-grand), 46 (2000) 1397-1401.
48. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 2010; 4: 118-126.
49. Nita M, Grzybowski A. The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults. Oxid Med Cell Longev 2016; 2016: 3164734.
50. Du X, Matsumura T, Edelstein D, Rossetti L, Zsengellér Z, Szabó C, Brownlee M. Inhibition of GAPDH activity by poly(ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. J Clin Invest 2003; 112: 1049-1057.
51. Mendonca HR, Carpi-Santos R, da Costa Calaza K, Blanco Martinez AM. Neuroinflammation and oxidative stress act in concert to promote neurodegeneration in the diabetic retina and optic nerve: galectin-3 participation. Neural Regen Res 2020; 15: 625-635.
52. S. Gorogawa, Y. Kajimoto, Y. Umayahara, H. Kaneto, H. Watada, A. Kuroda, D. Kawamori, T. Yasuda, M. Matsuhisa, Y. Yamasaki, M. Hori, Probucol preserves pancreatic beta-cell function through reduction of oxidative stress in type 2 diabetes, Diabetes research and clinical practice, 57 (2002) 1-10.
53. Y. Tanaka, P.O. Tran, J. Harmon, R.P. Robertson, A role for glutathione peroxidase in protecting pancreatic beta cells against oxidative stress in a model of glucose toxicity, Proc Natl Acad Sci U S A, 99 (2002) 12363-12368.
54. H. Kaneto, Y. Kajimoto, J. Miyagawa, T. Matsuoka, Y. Fujitani, Y. Umayahara, T. Hanafusa, Y. Matsuzawa, Y. Yamasaki, M. Hori, Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity, Diabetes, 48 (1999) 2398-2406.
55. J.L. Evans, I.D. Goldfine, B.A. Maddux, G.M. Grodsky, Are oxidative stress-activated signaling pathways mediators of insulin resistance and beta-cell dysfunction?, Diabetes, 52 (2003) 1-8.
56. H. Kaneto, G. Xu, N. Fujii, S. Kim, S. Bonner-Weir, G.C. Weir, Involvement of c-Jun N-terminal kinase in oxidative stress-mediated suppression of insulin gene expression, J Biol Chem, 277 (2002) 30010-30018.
57. H. Kaneto, T.A. Matsuoka, Y. Nakatani, T. Miyatsuka, M. Matsuhisa, M. Hori, Y. Yamasaki, A crucial role of MafA as a novel therapeutic target for diabetes, J Biol Chem, 280 (2005) 15047-15052.
58. V. Poitout, R.P. Robertson, Minireview: Secondary beta-cell failure in type 2 diabetes--a convergence of glucotoxicity and lipotoxicity, Endocrinology, 143 (2002) 339-342.
59. K. Maedler, G.A. Spinas, D. Dyntar, W. Moritz, N. Kaiser, M.Y. Donath, Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function, Diabetes, 50 (2001) 69-76.
60. C. Piperi, C. Adamopoulos, G. Dalagiorgou, E. Diamanti-Kandarakis, A.G. Papavassiliou, Crosstalk between advanced glycation and endoplasmic reticulum stress: emerging therapeutic targeting for metabolic diseases, J Clin Endocrinol Metab, 97 (2012) 2231-2242.
61. A. Gorlach, P. Klappa, T. Kietzmann, The endoplasmic reticulum: folding, calcium homeostasis, signaling, and redox control, Antioxid Redox Signal, 8 (2006) 1391-1418.
62. C. Perrin-Sarrado, O. Bouchot, C. Vergely, L. Rochette, Release of secondary free radicals during post-ischaemic reperfusion is not influenced by extracellular calcium levels in isolated rat hearts, Mol Cell Biochem, 297 (2007) 199-207.
63. R.P. Robertson, H. Zhou, M. Slucca, A role for zinc in pancreatic islet beta-cell cross-talk with the alpha-cell during hypoglycaemia, Diabetes Obes Metab, 13 Suppl 1 (2011) 106-111.
64. B. Colsoul, R. Vennekens, B. Nilius, Transient receptor potential cation channels in pancreatic beta cells, Reviews of physiology, biochemistry and pharmacology, 161 (2011) 87-110.

65. M.S. Jamaluddin, S.M. Weakley, Q. Yao, C. Chen, Resistin: functional roles and therapeutic considerations for cardiovascular disease, Br J Pharmacol, 165 (2012) 622-632.
66. P.M. Perez, R. Moore-Carrasco, D.R. Gonzalez, E.Q. Fuentes, I.G. Palomo, Gene expression of adipose tissue, endothelial cells and platelets in subjects with metabolic syndrome (Review), Molecular medicine reports, 5 (2012) 1135-1140.
67. P. Wang, E. Mariman, J. Renes, J. Keijer, The secretory function of adipocytes in the physiology of white adipose tissue, Journal of cellular physiology, 216 (2008) 3-13.
68. N.S. Kalupahana, N. Moustaid-Moussa, K.J. Claycombe, Immunity as a link between obesity and insulin resistance, Molecular aspects of medicine, 33 (2012) 26-34.
69. S.C. Ranieri, S. Fusco, G. Pani, p66(ShcA): linking mammalian longevity with obesity-induced insulin resistance, Vitamins and hormones, 91 (2013) 219-241.
70. J.L. Evans, I.D. Goldfine, B.A. Maddux, G.M. Grodsky, Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes, Endocrine reviews, 23 (2002) 599-622.
71. J.L. Evans, B.A. Maddux, I.D. Goldfine, The molecular basis for oxidative stress-induced insulin resistance, Antioxid Redox Signal, 7 (2005) 1040-1052.
72. A.F. Soares, M. Guichardant, D. Cozzone, N. Bernoud-Hubac, N. Bouzaidi-Tiali, M. Lagarde, A. Geloen, Effects of oxidative stress on adiponectin secretion and lactate production in 3T3-L1 adipocytes, Free Radic Biol Med, 38 (2005) 882-889.
73. L. Tao, E. Gao, X. Jiao, Y. Yuan, S. Li, T.A. Christopher, B.L. Lopez, W. Koch, L. Chan, B.J. Goldstein, X.L. Ma, Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress, Circulation, 115 (2007) 1408-1416.
74. P.W. Peake, Y. Shen, A. Walther, J.A. Charlesworth, Adiponectin binds C1q and activates the classical pathway of complement, Biochem Biophys Res Commun, 367 (2008) 560-565.
75. A. Nguyen Dinh Cat, R.M. Touyz, A new look at the renin-angiotensin system--focusing on the vascular system, Peptides, 32 (2011) 2141-2150.
76. M. Stumvoll, B.J. Goldstein, T.W. van Haeften, Type 2 diabetes: principles of pathogenesis and therapy, Lancet, 365 (2005) 1333-1346.
77. X. Li, K.A. Becker, Y. Zhang, Ceramide in redox signaling and cardiovascular diseases, Cell Physiol Biochem, 26 (2010) 41-48.
78. S.A. Summers, Ceramides in insulin resistance and lipotoxicity, Progress in lipid research, 45 (2006) 42-72.
79. S. Lecour, E. Van der Merwe, L.H. Opie, M.N. Sack, Ceramide attenuates hypoxic cell death via reactive oxygen species signaling, J Cardiovasc Pharmacol, 47 (2006) 158-163.
80. J.A. Chavez, S.A. Summers, A ceramide-centric view of insulin resistance, Cell Metab, 15 (2012) 585-594.
81. H. Kaneto, N. Katakami, D. Kawamori, T. Miyatsuka, K. Sakamoto, T.A. Matsuoka, M. Matsuhisa, Y. Yamasaki, Involvement of oxidative stress in the pathogenesis of diabetes, Antioxid Redox Signal, 9 (2007) 355-366.
82. H. Otani, Oxidative stress as pathogenesis of cardiovascular risk associated with metabolic syndrome, Antioxid Redox Signal, 15 (2011) 1911-1926.
83. M. Rocha, N. Apostolova, J.R. Herance, S. Rovira-Llopis, A. Hernandez-Mijares, V.M. Victor, Perspectives and potential applications of mitochondria-targeted antioxidants in cardiometabolic diseases and type 2 diabetes, Medicinal research reviews, 34 (2014) 160-189.
84. Q. Liu, L. Sun, Y. Tan, G. Wang, X. Lin, L. Cai, Role of iron deficiency and overload in the pathogenesis of diabetes and diabetic complications, Current medicinal chemistry, 16 (2009) 113 129.
85. S.H. Han, Y.H. Kim, I. Mook-Jung, RAGE: the beneficial and deleterious effects by diverse mechanisms of actions, Molecules and cells, 31 (2011) 91-97.