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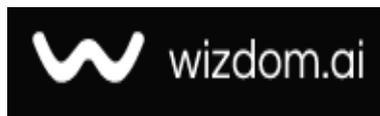
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The Role of Oxidative Stress in the Pathophysiology and Progression of Type 2 Diabetes Mellitus: Molecular Mechanisms and Therapeutic Perspectives: A Narrative Review

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Abstract

General Background: Type 2 diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia, insulin resistance, and progressive β -cell dysfunction, with increasing global prevalence and associated complications. **Specific Background:** Oxidative stress, defined as an imbalance between reactive oxygen species production and antioxidant defenses, has been increasingly recognized as a central factor in metabolic dysregulation and disease progression. **Knowledge Gap:** Despite extensive research, uncertainties remain regarding the precise molecular pathways linking oxidative imbalance to insulin resistance, β -cell dysfunction, and diabetic complications, as well as the translational value of antioxidant-based therapies. **Aims:** This narrative review aims to synthesize current evidence on the role of oxidative stress in the pathophysiology of type 2 diabetes mellitus and to elucidate key molecular mechanisms and therapeutic approaches. **Results:** Findings indicate that chronic hyperglycemia promotes excessive reactive oxygen species generation through mitochondrial dysfunction, polyol and hexosamine pathways, advanced glycation end-products formation, and endoplasmic reticulum stress, leading to impaired insulin signaling, β -cell apoptosis, inflammation, and vascular complications. **Novelty:** The study integrates molecular, cellular, and clinical perspectives into a comprehensive framework linking oxidative stress with metabolic dysfunction and disease progression. **Implications:** Improved understanding of oxidative stress mechanisms may support the development of targeted therapeutic strategies, including antioxidant interventions and lifestyle modifications, for better management and prevention of type 2 diabetes mellitus.

Highlights:

- Chronic Hyperglycemia Drives Reactive Oxygen Species Through Multiple Biochemical Pathways
- Mitochondrial Dysfunction and Endoplasmic Reticulum Stress Contribute to Metabolic Imbalance
- Therapeutic Approaches Include Antioxidants, Pharmacological Agents, and Lifestyle Strategies

Keywords: Type 2 Diabetes Mellitus, Oxidative Stress, Reactive Oxygen Species, Insulin Resistance, Antioxidant Therapy.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is an increasingly prevalent metabolic disorder associated with significant morbidity, mortality, and economic burden. T2DM is driven primarily by obesity, characterized by both insulin resistance (IR) and pancreatic β -cell dysfunction, and is related to the development of macro- and microvascular complications. In the last two decades, metabolic disease has emerged as a major risk factor for the development of T2DM; the disease process is proposed to commence decades before a T2DM diagnosis. Accumulating evidence supports a link between oxidative stress and T2DM incidence [1,2]. Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (ROS) and an organism's ability to reduce and eliminate these reactive products without damage. In preclinical models of T2DM, multiple metabolic and inflammatory pathways linking oxidative stress to β -cell dysfunction and IR have been identified, such as a decrease in insulin receptor substrate 2 (IRS2) and insulin receptor substrate 1 (IRS1) levels, endoplasmic reticulum (ER) stress-associated unfolded protein response (UPR) activation, and generation of advanced glycation end-products (AGEs). Importantly, oxidative stress is also implicated in the pathophysiology of T2DM complications, including retinopathy, neuropathy, nephropathy, and cardiovascular disease. Strategies targeting oxidative stress, including the use of antioxidant molecules, are being explored in the context of T2DM [3],[4].

Methodology

The methodology used for this narrative review is a systematic search of scientific literature to detail the contribution of oxidative stress to the pathophysiology and the development of type 1 diabetes mellitus (T2DM). To investigate the association among reactive oxygen species (ROS), metabolic dysfunction, and diabetic complications, a systematic review of all relevant peer-reviewed studies including experimental, clinical, and mechanistic studies published through October 2023 was conducted. This review aims at elucidating essential molecular pathways in generating oxidative stress, including mitochondrial abnormalities, activation of the polyol and hexosamine pathways, AGEs, and endoplasmic reticulum stress. Discussion These pathways were critically reviewed to understand the contribution of oxidative imbalance to insulin resistance, β -cell dysfunction and chronic inflammation. The methodology also includes the reciprocation of cellular signaling pathways including both NLRP3 inflammasome activation and disrupted insulin signaling cascades which can outline an in-depth mechanistic description of disease progression. The paper also amalgamates data on oxidative stress biomarkers and antioxidant defense systems, which encompass both NADPH- and FADH₂-dependent enzymatic and nonenzymatic mechanisms, to evaluate their utility in the assessment of disease diagnosis and progression. We also reviewed the therapeutic approaches targeting oxidative stress that have been investigated including antioxidant supplementation, pharmacological approaches, and lifestyle modifications and we compared this data with its reported efficacy. This approach integrates data from multiple domains and provides a systems framework that relates molecular pathways with clinical outcomes and can provide a global view of oxidative stress as a pathophysiological mechanism and a therapeutic target in T2DM.

2. Oxidative Stress: Concepts, Measurement, and Relevance to Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is a debilitating chronic disease that has reached epidemic proportions throughout the world. In addition to being classified as an epidemic by the World Health Organization, T2DM also ranks as the fifth leading cause of death according to the Global Burden of Disease Study [5]. Rising global T2DM prevalence could elevate the overall human morbidity and mortality profile beyond the projections presented by the Global Burden of Disease study. Both the pathophysiology and progression associated with T2DM, combined with its deleterious systemic complications, adds to the general human disease and suffering burden worldwide [6],[7]. Reactive oxygen species (ROS) are elevated in T2DM, as are both systemic and intra-organ oxidative stress biomarkers in humans and experimental models. Persistent exposure to pro-oxidative stimuli in T2DM results in elevation and propagation of oxidative stress impairment in non-target cells by tissue and organs already affected by the disease [8],[9]. Oxidative stress significantly exacerbates all the major pathophysiology pathways governing T2DM progression, including the secretory functions of β -cells in the pancreas, insulin response in liver and muscle cells, mitochondrial dysfunction and endoplasmic reticulum stresses in all major target organs, and propagation of pro-inflammatory macrophage immune responses [10],[11]. Despite an immense global attention to T2DM over the last two decades, major knowledge gaps and several misperceptions around its progression pathways, including oxidative stress pathways and propagation, still represent significant bottlenecks preventing successful disease slowing and reversal globally [12],[13].

3. Molecular Mechanisms Linking Oxidative Stress to Type 2 Diabetes

Oxidative stress is a critical factor in type 2 diabetes pathogenesis and progression. In diabetic and prediabetic animal models and human populations, excessively elevated levels of reactive oxygen species (ROS), coupled with diminished levels of endogenous antioxidant defenses, have been detected in a broad range of tissues. Compelling evidence associates excessive ROS generation with the onset of impaired gluoregulatory mechanisms, including defective insulin secretion, reduced peripheral insulin responsiveness, and hepatocellular insulin resistance [14],[15].

Mitochondrial dysfunction emerges as a central player in diabetes-associated oxidative stress. Greater ROS production during fatty acid oxidation and glucose oxidation has been identified as the leading driver of mitochondrial respiratory chain hyperactivity. The tendency of the post-prandial glucose excursion to rise and the inability to suppress insulin-resistant

hepatic glucose production among prediabetic and diabetic subjects empower the acceleration of fatty acid oxidation and glucose oxidation, further fueling mitochondrial overactivity and ensuing β -cell and hepatic oxidative stress [16],[17].

Notably, under both aerobic and anaerobic conditions elevated glucose concentrations evoke mitochondrial activation of the hexosamine biosynthetic pathway and the polyol pathway. In parallel, elevated fatty acid concentrations enhance the contribution of mitochondrial fatty acid oxidation to pyruvate oxidation. These augmented pathways elevate further NADH inputs to the mitochondrial respiratory chain, intensifying mitochondrial hyperactivity and ROS production. Of note, there is mounting evidence that glucose and fatty acid supply may represent metabolic amplifiers of different origin in the genesis of oxidative stress in diabetes [18].

In addition to mitochondrial dysfunction, the collapse of the adaptive and cytoprotective capabilities of the endoplasmic reticulum (ER) is emerging as another key contributor to oxidative stress. In prediabetic and diabetic conditions, elevated glucose and fatty acid concentrations elevate cytoplasmic burdens of misfolded proteins, thereby leading to ER stress and instigating the unfolded protein response (UPR). Pancreatic β -cells and hepatocytes in such metabolic situations become unable to down-regulate UPR signaling, and excessive UPR activity triggers systemic inflammation and further ROS production [19].

Finally, low-grade inflammatory conditions, amplified by oxidative stress, are positively correlated with the incidence of type 2 diabetes, and there is close interplay between oxidative stress and inflammation. Persistent metabolic stresses, such as excessive nutrient surplus, lead to the constant activation of the NLRP3 inflammasome. NLRP3 overactivation fosters the release of pro-inflammatory cytokines, engendering a vicious cycle of inflammation. Excessive secretion of interleukin 1 β down-regulates the insulin gene by inhibiting the transcription factor PDX1 in pancreatic β -cells and stimulates the evolution of liver insulin resistance [18],[19].

3.1. Insulin Secretion and β -Cell Vulnerability

The increase in insulin secretion following a meal plays a crucial role in maintaining glucose homeostasis. This process begins with glucose-induced stimulation of the pancreatic β -cells. After glucose uptake into the β -cell, glucose enters glycolysis in the cytosol and thereafter in the mitochondria where the citric acid cycle produces reduced equivalents (NADH, FADH₂) that drive the synthesis of ATP via mitochondrial oxidative phosphorylation in the inner mitochondrial membrane [20],[21]. The β -cell requires a glucose concentration of at least 5 mM to secrete insulin. At this threshold, the glucose-stimulated increase in the ATP/ADP ratio leads to closure of the ATP-sensitive potassium channels (KATP channels) in the plasma membrane, resulting in membrane depolarization and subsequent opening of voltage-gated calcium channels. Increased intracellular calcium Ca²⁺ triggers exocytosis of insulin-containing secretory granules [22].

The prolonged exposure to high glucose has an adverse effect on the β -cells. Oxidative stress induced by glucose is one of the pathogenic mechanisms contributing to the impaired glucose-stimulated insulin secretion and, ultimately, to β -cell death. Reactive oxygen species (ROS), mainly derived from mitochondrial metabolism of excess nutrients, negatively regulate many bioenergetic and secretory functions [23],[24].

3.2. Insulin Signaling and Peripheral Insulin Resistance

Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance in skeletal muscle and fat tissue, increased liver gluconeogenesis, abnormal incretin secretion, and impaired regulation of food intake and energy expenditure [25]. Hyperglycemia arises from a combination of peripheral insulin resistance and declining insulin secretory capacity, often linked to insufficient β cell mass. Impaired glucose-stimulated insulin secretion may be a primary cause or a consequence of deregulated metabolism. Metabolic disorders, including redox imbalance, impaired insulin signaling, and mitochondrial dysfunction, contribute to T2DM development. Progressive oxidative stress damages proteins, lipids, DNA, and impairs redox signaling, insulin signaling, autophagy, and mitochondrial quality control, ultimately leading to β cell dysfunction. Lipotoxicity from excess fatty acids and glucotoxicity from high blood glucose also contribute to β cell damage. Mitochondrial dysfunction, including decreased oxidative phosphorylation, is a key factor in insulin resistance and diabetes progression [26],[27].

Insulin signaling involves a complex pathway that regulates glucose uptake in peripheral tissues mainly through GLUT4. In response to insulin, cells increase GLUT4 expression on the plasma membrane, enhancing glucose uptake. However, high levels of insulin signaling can decrease GLUT4 presence, leading to elevated blood glucose and increased insulin secretion. This positive feedback loop results in insulin desensitization and downregulation of GLUT4, contributing to insulin resistance. Oxidative stress and reactive oxygen species are also linked to the development of insulin resistance, with ROS damaging cells and playing a role in chronic disease progression, including T2DM [28],[29].

3.3. Mitochondrial Dysfunction and Reactive Oxygen Species Production

Characteristically, hyperglycaemia is accompanied by an imbalance between production of reactive oxygen species and antioxidant protection, leading to oxidative stress, a condition that plays a key role in the pathogenesis of T2D and its complications [30]. Under normal physiological conditions, the mitochondria constitute the major source of oxidative metabolic energy and the main source of intracellular reactive oxygen species (ROS) in all organisms [31]. Nevertheless, the accumulation of cytotoxic substances such as free fatty acids and the induction of excessive ROS production demand a change of configuration that converts the microtubular transport system toward organelle-organelle contacts, such as

mitochondria-endoplasmic reticulum and mitochondria-nucleus contacts, which latter can block the harmful formation of free fatty acids and ROS among others. In T2D, mitochondrial dysfunction, including an altered activity of antioxidant enzymes (notably manganese superoxide dismutase) associated with the elevation of oxidative stress determined by the alteration of complex I of the electron transport chain, is a well-organised event during the progression of disease [32].

3.4. Endoplasmic Reticulum Stress and UPR Activation

The endoplasmic reticulum (ER) is responsible for folding and processing of the vast majority of secretory and membrane proteins produced by insulin-producing pancreatic β -cells. Various stimuli, including obesity and hyperglycemia, can overwhelm the cellular capacity to carry out these processes, leading to ER stress. The ER stress response comprises three branches, referred to as the unfolded protein response (UPR), which is a cytoprotective response and attempt to restore normal ER homeostasis [33],[34]. However, excessive or prolonged stress may ultimately lead to cell death [33]. The accumulation of misfolded proteins stimulates translational repression via inositol-requiring enzyme 1 α (IRE1 α) and cytoplasmic activation of CCAAT/enhancer-binding protein homologous protein (CHOP) via protein kinase RNA-like endoplasmic reticulum kinase (PERK). IRE1 α also triggers activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), linking metabolism and inflammation to the pathogenesis of metabolic diseases [35]. The chronic activation of ER stress observed in islet cells of human donors with type 2 diabetes and in multiple genetic models of diabetes has therefore implicated this response in pancreatic β -cell dysfunction in diabetes [36],[37].

3.5. Inflammation, Oxidative Stress, and NLRP3 Inflammasome

Prolonged hyperglycemia and alterations in insulin action or secretion can result in type 2 diabetes, also known as non-insulin-dependent diabetes or adult-onset diabetes. Insulin resistance (impaired ability of insulin-sensitive tissues to increase glucose uptake and lipid storage) and/or β -cell dysfunction (decline in the capacity of pancreatic β -cells to secrete insulin in response to glucose and other stimuli) can take place, leading to disturbed glucose homeostasis. Subsequent development of microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (atherosclerosis) complications is common. Diabetes is a chronic disease characterized by excessive accumulation of advanced glycation end-products (AGEs) and low-grade inflammation, which plays an important role in pathogenetic processes. Accumulating scientific evidence indicates a pivotal role for β -cell oxidative stress in type 2 diabetes and related cardiovascular complications, reinforced by studies on SIRT2, SIRT3 and the anti-aging polyphenol resveratrol. The NLRP3 inflammasome appears central to the link between inflammation and oxidative stress under hyperglycemic conditions [38,39]. NLRP3 is activated by diverse ligand classes, including glucose stress, and complexes with ASC and procaspase-1 to form a stable signaling platform that triggers proteolytic maturation of pro-IL-1 β and pro-IL-18 into the active cytokines. Thus, the NLRP3-inflammasome represents a pivot for the interface between innate immunity and metabolism: a prime therapeutic target to restore metabolic homeostasis while modulating inflammation [40,41].

3.6. Advanced Glycation End-Products and Receptor-MAGE Pathways

Advanced glycation end-products (AGEs) are produced through non-enzymatic reactions between reducing sugars and proteins, lipids, and nucleic acids, leading to structural damage and functional impairment of these molecules. During normal conditions, AGE formation is moderate but accelerates under hyperglycemia, contributing to diabetic complications [42]. AGEs can modify both long-lived and short-lived proteins, especially in diabetic patients with impaired renal clearance. They cause irreversible damage by forming crosslinks within and between proteins, resulting in decreased protein function, resistance to degradation, and increased reactive oxygen species [43]. Interaction of AGEs with cell surface receptors activates signaling pathways that promote inflammation and oxidative stress, linking their accumulation to the progression of diabetes and its complications [44,45]. Diabetic vascular complications, such as cardiovascular disease, stroke, and microangiopathy, lead to high morbidity and mortality in long-term diabetes. Extensive formation of AGEs contributes to vascular injuries. AGE-induced cellular dysfunction involves receptor-dependent mechanisms, notably through the receptor for AGE (RAGE), which mediates inflammatory signals and tissue damage. RAGE is a pattern-recognition receptor and pro-inflammatory molecule. Strategies targeting RAGE and its ligands are important for preventing and treating diabetic vascular complications. AGE are formed through non-enzymatic reactions between reducing sugars and proteins, resulting in complex, irreversible derivatives. Reactive dicarbonyls like methylglyoxal, glyoxal, and 3-deoxyglucosone, produced in glycolysis and other metabolic pathways, rapidly interact with proteins to produce AGE [46,47].

4. Oxidative Stress in the Complications of Type 2 Diabetes

Within type 2 diabetes (T2D), micro- and macrovascular complications are associated with increased oxidative stress (OS) and involve several interconnected mechanisms [5]. Persistent hyperglycemia leads to OS via multiple pathways, including enhanced formation of advanced glycation end products (AGEs) [47]. Continuous stimulation of the polyol pathway increases intracellular sorbitol and fructose concentrations, inducing OS and endothelial dysfunction. Furthermore, excess mitochondrial superoxide contributes to OS in pancreatic β -cells and peripheral tissues, while low-grade inflammation activates the NLRP3-inflammasome-mediated pathway, amplifying the production of pro-inflammatory cytokines, including interleukin-1 β (IL-1 β) [48]. Glucose and lipid loads lead to β -cell death and reduced insulin secretion, favouring T2D progression. Five principal complications of T2D are highlighted: retinopathy, nephropathy, neuropathy, atherosclerosis, and cardiovascular diseases [49,50].

4.1. Microvascular Complications

Hyperglycemia associated with type 2 diabetes is a major risk factor for microvascular and macrovascular complications and is considered a key link between oxidative stress and diabetic complications. ROS produced during hyperglycemia have been reported to contribute directly to the development of diabetic nephropathy, retinopathy, and neuropathy [51,52]. In a diabetic animal model, caspase-3 is shown to be activated with mitochondrial damage and superoxide generation. Mitochondrial damage leads to the activation of downstream mitochondria-dependent apoptotic pathway involving the release of cytochrome c, activation of caspase-3 and poly ADP ribose polymerase cleavage [53]. In response to pathological stimuli such as hyperglycemia and hypoxia, the retinal Müller glial cells undergo adaptive alterations to maintain retinal homeostasis for neuronal cells. However when cellular dysfunction progresses, Müller cell oxidative stress becomes central to diabetes-induced retinal neuronal death [54,55]

4.2. Macrovascular Complications and Atherosclerosis

Type 2 diabetes is associated with macrovascular complications, particularly atherosclerosis, which affects both large and medium-sized arteries [5]. Diabetic atherosclerosis can occur in the aorta, coronary, cerebral, renal, and peripheral arteries, and it is one of the leading causes of morbidity and mortality in patients with the disease [56]. Epidemiological studies indicate that individuals with type 2 diabetes have a two- to threefold greater risk of ischaemic heart disease, and around 70% of patients die from cardiovascular-related complications [56,57]. Atherosclerosis is a multifactorial disease characterized by endothelial dysfunction, arterial lipid deposition, and inflammatory responses, and it is enhanced by hyperglycaemia, oxidative stress, and inflammation in the diabetic patient [58].

4.3. Neuropathy, Nephropathy, and Retinopathy

The chronic hyperglycemia characterizing diabetes causes various complications, contributing to a worsening of life quality and increasing morbidity and mortality. The glucotoxic effects, which occur via various molecular mechanisms contributing to the pathogenetic cascade of diabetic complications, are strongly influenced by oxidative stress. In considering diabetic complications, the scenarios regarding the most prevalent microvascular complications and some important macrovascular events are worth mentioning. In particular, neuropathy, nephropathy and retinopathy, corresponding to the triad called “the 3N’s of diabetes,” are the most common microvascular complications [61]. These complications are reported to present an estimation of up to 90% of diabetic patients. Furthermore, there is a strong association between the duration of these complications and the onset of cardiovascular disease [59,60].

5. Therapeutic Perspectives Targeting Oxidative Stress

Cumulative evidence has fostered interest in antioxidant therapies, yet clinical efficacy remains uncertain [61]. Several preclinical studies support antioxidant supplementation for diabetes and related complications. Nevertheless, human trials exhibit contradictory results, limiting the translatability of findings. Antioxidants exert heterogeneous effects depending on structural characteristics and cellular targets, potentially confounding interpretation. Furthermore, association between oxidative stress and disease outcomes does not necessarily imply causality, as oxidative modification of biomolecules may occur subsequent to other pathophysiological processes [62,63]. Strategies targeting hyperglycaemia remain acceptable, albeit reduction exceeds physiological concentrations promoting oxidative stress. Overdependence on oxidation- and glycation-scavenging approaches to mitigate vascular damage assumes deleterious properties of oxidative and glycation stresses in the absence of unequivocal mechanistic evidence [64,65].

5.1. Antioxidant Strategies: Evidence from Preclinical and Clinical Studies

Diabetes mellitus is a global health threat associated with high morbidity and mortality attributed to major vascular complications including cardiopathy, nephropathy, and retinopathy. The importance of oxidative stress in the pathophysiology of diabetes was extensively documented several decades ago [6]. Overproduction of reactive oxygen species (ROS) arises from multiple pathways, and the resulting imbalance between pro-oxidants and antioxidant defenses triggers glucolipotoxicity, insulin resistance, and inflammation [5]. Hyperglycemia also promotes cellular damage and complications including atherosclerosis, neuropathy, and retinopathy [66,67].

Pro-oxidative mechanisms associated with type 2 diabetes (T2D) are potential pharmacological targets for the prevention of T2D and its associated complications, yet large-scale clinical trials evaluating antioxidant therapies for diabetes have generated negative results. Accumulation of evidence points to the integral role of hyperglycemia as the initiating event of the diabetes pathophysiological cascade and clearly establishes glycosylated hemoglobin (HbA1c) as the leading surrogate endpoint. The autonomous identification of T2D prior to or soon after the onset of metabolic disorders therefore is paramount to reduce glucose levels back to non-diabetic thresholds and prevent irreversible progression [68,69].

Several studies offer pre-clinical evidence for the potential of multiple natural and synthetic antioxidants to attenuate the hyperglycemia-induced oxidative stress associated with T2D. However, on review of clinical studies of agents with antioxidant effects but not primarily aimed at oxidative balance, no conclusive benefit for broader arterial or organ protection emerges [69]. Additional large-phase, longer-duration clinical trials are necessary to evaluate the efficacy of antioxidant agents or salubrious dietary mixtures on T2D, cardiovascular risk, and early-onset vascular injury [70].

5.2. Lifestyle Interventions and Oxidative Balance

Lifestyle modifications exert favorable metabolic effects in type 2 diabetes mellitus (T2DM), contributing to the achievement of targeted glycemic levels, systemic oxidative balance, and overall improved health status 5. Epidemiological studies indicate a consistent model of enhanced glycemic control, diminished oxidative stress, and slowed progression of T2DM in subjects practicing regular physical activity and consuming a diet abundant in fruits and vegetables. Several clinical trials confirm that dietary and exercise modifications lower oxidative stress. These therapeutic effects are attributed to decreased elevation of blood glucose levels, enhanced glucose metabolism, augmented antioxidant capability, improved glycemic control, and reduced systemic inflammation. Effective measures for restoring redox balance through lifestyle changes comprise regular physical exercise, weight reduction, and a vegetarian dietary pattern [71,72].

5.3. Pharmacological Agents Modulating Redox Homeostasis

Pharmacological and dietary strategies to modulate the redox state and improve oxidative stress in adipose tissue, skeletal muscle, the brain, and other insulin-sensitive tissues have beneficial effects in models of T2DM. Metformin, a first-line T2DM therapy, provides glucose-lowering benefits not only by lowering hepatic glucose production but also by impacting redox status. In liver and skeletal muscle, metformin enhances glycerol kinase activity in the degradation of glycerol-3-phosphate into glycerol, leading to the restoration of NRF2 levels [73]. Metformin activation of AMPK, which regulates several redox-sensitive pathways, diminishes free fatty acid-induced oxidative stress and apoptosis in skeletal myoblasts 73. Metformin impacts several redox-sensitive aspects of insulin action. In adipocytes, metformin-induced AMPK improves insulin action on the glucose transporter GLUT4, and human studies indicate that metformin restores postprandial GLUT4 translocation to the sarcolemma of skeletal muscle [74]. Metformin also enhances glucose-dependent insulin-mediated Akt signaling in response to both intramuscular and systemic delivery of short-acting insulin. Metformin treatment of high-fat-fed mice restores redox and inflammatory homeostasis and insulin action in white adipose tissue, leading to a delay in the onset of hyperglycemia. Six to eight weeks of metformin therapy improves insulin action in skeletal muscle and reduces plasma non-esterified fatty acids in T2DM patients [75,76].

5.4. Novel and Emerging Therapeutic Approaches

Type 2 diabetes is among the most prevalent chronic diseases worldwide and is a well-known risk factor for numerous complications. Hence, despite the improving access to antidiabetic medications, new treatment approaches are constantly being investigated in order to identify better targets and deal with the rising incidence of diabetes. Diabetes arises from a complex interplay of factors related to obesity and an unhealthy environment, including changes at the genetic, epigenetic, microbiota, and metabolite levels. The deficiency of insulin secretion and insulin sensitivity impairment and their underlying mechanisms are established and extensively studied [77,78]. The compensatory secretion of insulin from pancreatic β -cells is crucial for maintaining euglycemia. Type 2 diabetes occurs when insulin resistance advances to an extent that it severely impairs the glucose homeostasis.

Experiments in animals and humans have demonstrated that the secretion of insulin in the pancreas is tightly regulated by the oscillation of intracellular calcium that is controlled by thousands of proteins. Mitochondria regulate the intracellular concentration of calcium and are of high importance in regulating many metabolic processes of β -cells, including insulin secretion and their vulnerability. The β -cell mass gradually declines following the onset of diabetes and remains the best predictor of type 2 diabetes progression. The mass of β -cells is maintained by a constant balance between proliferation, differentiation, and apoptosis in adulthood. Type 2 diabetes affects all three processes. Identification of therapeutic approach for mass preservation of β -cells remains a top priority for diabetes researchers 61. Extensive research has revealed active involvement of microRNAs in all these three processes in different species and hence targeting of microRNAs is promising approach to target therapy for prevention of diabetes [79,80].

6. Future Directions and Research Gaps

Numerous aspects warrant further investigation, from the oxidative stress mechanisms underpinning the pathogenesis of type 2 diabetes (T2D) to identifying reliable dosage biomarkers for early detection and risk stratification of diabetes and its associated cardiovascular and microvascular complications. Elucidation of the role of microRNAs in the regulation of oxidative stress and pancreatic β -cell function, together with the possible adverse effects of therapeutic modulation, transient action, and safety concerns associated with chronic treatment, could facilitate the rational design of targeted miRNA-based interventions capable of revolutionising T2D management . Another important avenue for further research considers the connections between age-related deregulation of redox homeostasis and comorbid conditions in T2D. Addressing this interplay could lead to a more integrated approach to the management of the disease and its complications. Finally, greater understanding of the mechanisms by which oxidative stress contributes to the development and progression of diabetic complications, together with the expansion of screening methodologies for their detection, remains of paramount importance [80].

7. Conclusion

The existing scientific literature illustrates that oxidative stress is involved in both the pathophysiology and progression of T2DM and its associated micro- and macrovascular complications, as well as in its extra-pancreatic comorbidities. Assessment of oxidative stress may serve as both a predictive and diagnostic factor for T2DM and derive from elevated levels of AGEs. These AGEs elicit deleterious effects via interaction with RAGE and binding to macrophage Gal-lectin, prompting further ROS production. The key hydrophilic or lipophilic antioxidants or compounds with antioxidant mechanism

demonstrated neutralization of various ROS and lowered diabetes progression. In patients already with one or a few diabetic complications, the levels of oxidative stress were evidently increased. Supplying antioxidant or non-antioxidant compounds may halt the progression of diabetic complications. All available evidence supports the inclusion of agents targeting oxidative stress and/or AGEs into the armamentarium of therapeutics for T2DM. Several strategies focusing on counteracting oxidative stress in T2DM and its complications, however, have failed to cope with the problem. Various preclinical and clinical investigations have been elucidated on the linkage between oxidative stress and T2DM and its associated complications. Moreover, lifestyle intervention including dietary approach and physical activity is suggested to underscore the importance of pursuance of healthy lifestyle for the delay and prevention of T2DM onset.

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