Biochemistry and Biophysics Reports 43 (2025) 102069

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

Role of oxidative stress in prediabetes development

Aarthi Yesupatham , Radha Saraswathy *

Department of Biomedical Sciences, School of BioSciences and Technology, Vellore Institute of Technology, Vellore, Tamil Nadu, India

ARTICLE INFO

Keywords:
Oxidative stress
Insulin resistance
Beta cell dysfunction
Prediabetes
Hyperglycemia and risk factors

ABSTRACT

An imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense systems is known as oxidative stress, and it is a major factor in diseases like atherosclerosis, vascular inflammation, endothelial dysfunction, and others that are largely caused by elevated oxidative stress. Interestingly, oxidative stress has also been implicated in the progression of prediabetes to type 2 diabetes (T2DM). Prediabetes, characterized by increased blood glucose levels than the diabetes threshold, impacts a substantial portion of the global population. In India alone, the estimated prevalence of prediabetes by 2023 is approximately 15.3 %. Hyperglycaemia, a hallmark of prediabetes, can promote vascular dysfunction by increasing ROS formation and upregulating chronic inflammatory markers. Additionally, oxidative stress contributes to insulin resistance and impaired beta cell function. Various risk factors of oxidative stress are associated with prediabetes development. This review focuses on ROS's role in prediabetes pathogenesis and its risk factors increasing the effect of oxidative stress. Various ROS scavengers were used as oxidative stress indicators, and ROS scavenging has a deleterious impact on disease progression. Lack of study has reported on role of oxidative stress in prediabetes development and this will be the first review covers pathogenesis and impact of oxidative stress biomarker in prediabetes. This review comprises managing the risk factors of oxidative stress would pave the way for the management of prediabetes progression to T2DM.

1. Introduction

Prediabetes is a condition with a raised position of blood glucose, and below the threshold for the opinion of diabetes but linked to an elevated threat of diabetes development. According to the World Health Organization's(WHO) criteria, Impaired glucose tolerance (IGT) and impaired fasting glucose(IFG) are generally used to define prediabetes [4]. In 2021, the global statistics estimated the prevalence of prediabetes was 10.6% [73]. Based on a recent study, the overall frequency of prediabetes in India by 2023 was about 15.3% [2]. By 2030, it's reported to be over 472 million cases of prediabetes worldwide, with 70 of these cases progressing to diabetes [6]. Prediabetes is becoming more extensively honored as a significant metabolic condition that raises an existent threat of developing diabetes [3]. Prediabetes is caused by several threat factors, including high-calorie diets, smoking, alcohol consumption, hypertension, hyperlipidemia, and abdominal rotundity. It's suggested that individuals with prediabetes, following a healthy life and diet could minimize their threat of developing diabetes mellitus [7] (see Tables 1–3)

Inflammation and oxidative stress influence significantly to the development of metabolic comorbidities such hyperlipidemia, high blood pressure, and raised glucose intolerance, several of which lead to metabolic dysfunction [74]. Several comorbidities, including diabetes, hypertension, insulin resistance, and hyperlipidemia, are associated with rotundity, these conditions can raise the burden of oxidative stress, but most constantly, they rise together. An illustration of such a condition is a metabolic pattern, which is honored by insulin resistance, hypertension, and hyperlipidemia and is frequently seen in adult US citizens [10]. Insulin resistance has been linked to prediabetes, a condition that has a high threat of getting diabetes [5]. Prediabetics are known to have inflammation and oxidative stress, which makes them sensitive to dyslipidemia and cardiovascular problems [6]. Oxidative stress is triggered by a conflict between the natural system's ability to eliminate these reactive consequences and the production of oxygen-reactive species in cells. ROS acts as several physiological functions, including cell signaling, which generally arise as derivations of oxygen metabolism [9].

This oxidative stress, or unstable redox equilibrium, causes

* Corresponding author: Professor Higher academic grade, Department of Biomedical Sciences, School of Biosciences and Technology, Vellore Institute of Technology, Vellore, India.
E-mail address: radhasaraswathy@vit.ac.in (R. Saraswathy).

https://doi.org/10.1016/j.bbrep.2025.102069
Received 27 December 2024; Received in revised form 26 May 2025; Accepted 28 May 2025

differences in cell signaling that affect anility, programmed cell death, and the loss of vital cellular functions [10]. Oxidative stress, or an imbalance between the body's antioxidants and free radicals, can be significantly affected by environmental and lifestyle factors. Numerous diseases and conditions, including as aging, exercise, and cardiovascular and neurological disorders, as well as cancer, are recognized to be obstructed by oxidative stress [72]. Particularly, the impact of exercise on redox balance is highly complex and varies according to age, sex, and exercise intensity and duration.

Insulin resistance, a hallmark of prediabetes, significantly increases the threat of developing diabetes. Individuals with prediabetes retain elevated oxidative stress situations, emphasizing the need for effective operation strategies [12]. However, Epigenetic alterations, such as DNA methylation, histone modifications, and non-coding RNAs, have been linked to the regulation of gene expression in beta-cell function and insulin sensitivity. Understanding these epigenetic pathways could assist us comprehend more thoroughly how genetic and environmental factors interact to cause metabolic diseases [80]. Therapeutic advances have demonstrated promising outcomes in preventing and treating disease by targeting oxidative stress. Recent research have revealed unique insights into the molecular mechanisms linking oxidative stress with insulin resistance and beta-cell dysfunction, indicating possible treatment targets to prevent the progression from prediabetes to T2DM [81]. Understanding the interplay between several factors involved in oxidative stress and prediabetes is pivotal for precluding complaint progression at an early stage.

1.1. Pathophysiology

Prediabetes, a high-risk condition for developing diabetes, has been related to insulin resistance. A person with prediabetes has elevated levels of plasma glucose that are above normal but still below the threshold of clinical diabetes. Total body elimination of glucose drops in people with T2DM, with about 80 % of this impairment due to muscle insulin resistance. Numerous risk factors, including obesity, insulin resistance, inflammation, dyslipidemia, hypertension, and hereditary factors, have been related to the development of prediabetes. Insulin resistance and decreased beta-cell activity are often already evident in prediabetes [15].

Insulin is an essential hormone that manages blood sugar levels; prediabetes, diabetes, and its effects are all directly linked to insulin resistance (IR). A pathophysiological component associated with impaired glucose tolerance and insufficient β-cell compensation in response to increasing IR leads to diabetes mellitus [25]. Insulin resistance acts as a the best indicator for the early onset of T2DM development from prediabetic conditions. In the peripheral insulin-sensitive tissues, Glucose transporter 4 (GLUT-4) plays a vital role in transporting the glucose from bloodstream to tissues. Increased expression of GLUT-4 receptors in the plasma membrane increases the absorption from the

Table: 2
Antioxidant enzymes: Their roles in ROS scavenging and implications for prediabetes.

Enzyme	Role in ROS scavenging	Impact on prediabetes
Superoxide Dismutase (SOD)	Alters superoxide radicals into hydrogen peroxide and oxygen.	Decreased levels of SOD in prediabetes can lead to increased oxidative stress and beta-cell dysfunction.
Catalase	Breaksdown hydrogen peroxide into water and oxygen.	Reduced catalase activity could exacerbate oxidative stress, contributing to beta-cell damage.
Glutathione peroxidase (GPx)	Decreased hydrogen peroxide and lipid peroxides using glutathione.	Lower GPx levels in prediabetes could result in higher oxidative stress and impaired beta-cell function.
Peroxiredoxin (Prx)	Reduces peroxides and protects cells from oxidative damage.	Altered Prx activity in prediabetes can lead to increased oxidative stress and beta-cell dysfunction.
Paraoxonase (PON1)	Protects cells from oxidative damage by hydrolyzing organophosphates and reducing lipid peroxides.	Decreased PON1 activity in prediabetes can contribute to oxidative stress and beta-cell dysfunction.

Table 3
Role of oxidative stress and its impact on prediabetes development.

Factor	Role in Oxidative Stress	Impact on Prediabetes Development
Hyperglycemia	Increase ROS production	This leads to beta-cell dysfunction and insulin resistance
Mitochondrial dysfunction	Produces excessive ROS	Contributes to oxidative stress and cellular damage.
Inflammation	Upregulates ROS production	Promotes beta-cell dysfunction and insulin resistance
Antioxidant deficiency	Reduces the body's ability to neutralize ROS.	Increase susceptibility to oxidative stress and cellular damage.
Lifestyle factors	Poor diet, lack of exercise and obesity	Exacerbates oxidative stress and accelerates prediabetes progression.
Genetic predisposition	Influences antioxidant enzyme levels and ROS production	Affects an individual's susceptibility to oxidative stress and prediabetes development.

Table 1
The Role of Reactive Oxygen Species and biomarkers.

ROS Agents	Status (increase or decrease)	Sample type	Category	Key findings	Author & year of publication
Hydroxyl Radical	Increase	Serum	T2DM patients	Insulin modified by hydroxyl radicals shows damage of α-helix and advance in β content. An increased level of hydroxyl radical implies T2DM individuals having diabetic complications.	Talha et al.,2021 [66]
Superoxide Anion Radical	Decrease	Islets cells	Wistar rat	High level of glucose suppresses the mitochondrial superoxide development in pancreatic beta cells.	Marten et al., 2005 [67]
Hydrogen peroxide	Increase	Liver cells	Mice	Inducing hydrogen peroxide resulted in increased oxidative stress and cellular damage.	Heit et al., 2017 [68]
Singlet oxygen	Increase	Plasma	T2DM Mice	Tsumura Suzuki obese diabetes (TSOD) mice observed increased levels of singlet oxygen than the normal mice. Thus, excessive level of singlet oxygen species production resulted in the development of insulin resistance and T2DM.	Onyango et al., 2017 [91]
Hypochlorite	Increase	–		Hypochlorite contributes to oxidative stress by generating excessive ROS. This imbalance resulted in cellular damage	Saghir et al., 2023 [6]
Nitric oxide radical	Increase	–	Diabetes mellitus	NO has beneficial effects, excessive production can damages cells and tissues. This oxidative stress is a key factor in the development of insulin resistance and beta-cell dysfunction, both of which are central to prediabetes	Nikolaeva et al., 2023 [64]
Peroxynitrite	Increase	–	Diabetes mellitus	Peroxynitrite can impair endothelial function, which is the health of the inner lining of blood vessels, contributing to vascular complications associated with prediabetes	Ann et al., 2023 [65]

bloodstream. Studies have shown that GLUT transporters play an important role in identifying and treating metabolic disorders. Understanding the function of different GLUTs might result in better treatment strategies [75]. Eventually, increased insulin signaling led to a negative effect on GLUT-4 in the membrane. According to studies, the distribution of GLUT4 between the plasma membrane and the inside of human muscle cells is constantly changing. However, adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) regulates GLUT4 redistribution through controlling exocytosis and endocytosis, which is necessary for glucose uptake [76]. As a result, blood glucose levels stay high, and in reaction, the pancreas produces more insulin. This causes a positive feedback loop that increases intravascular insulin levels and desensitizes peripheral tissues to insulin [21]. Recent investigations have shown that the expression of GLUT4 translocation-related genes is altered in prediabetic conditions, highlighting the role of this transporter in glucose homeostasis [78].

Hyperinsulinemia, or elevated plasma insulin levels, is linked to prediabetes. This is the result of the pancreatic beta cells compensating for the target tissues' reduced sensitivity to insulin's metabolic actions; this is known as insulin resistance in prediabetes. Whereas, Hyperglycaemia is primarily caused by disruption of the liver's glucostatic function, as the liver produces the enzyme glucose 6-phosphatase, which regulates the glucose to enter the bloodstream. Insulin promotes the synthesis of glycogen while preventing the liver from producing glucose. Insulin secretion often increases and hepatic glucogenesis typically decreases when plasma glucose levels are high. Since glucagon promotes gluconeogenesis, it may be a factor in hyperglycemia. Insulin sensitivity declines impedes the uptake and storage of carbohydrates, and results in elevated blood glucose levels [27]. Research indicates that hepatic insulin resistance plays a crucial role in the development of prediabetes, with high levels of hepatic enzymes being strong predictors of prediabetes and diabetes risk [79].

Pathophysiology of beta cell failure is associated with multiple potential processes that influence the secretory rate of individual β-cells. Genetic, epigenetic, or environmental factors acting on developing pancreatic tissue both prenatally and postnatally and influencing the differentiation of β-cell, insulin production, and cell death could be the cause of such abnormalities. Moreover, β-cell failure is further aggravated by glucotoxicity, lipotoxicity, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, inflammation, and other factors, creating a vicious cycle [34]. In fat conditions, insulin resistance is manifested by dropped glucose uptake by the insulin-sensitive tissues, performed in patient hyperinsulinemia. As the beta cell becomes overburdened in prediabetes, it no longer secretes sufficient insulin, performing in disabled glycemia [37]. Recent studies has shown elevated glucose levels and lipids in the liver activate serine kinases, which phosphorylate and inactivate insulin signaling molecules [77]. Understanding the molecular mechanisms behind insulin resistance and beta-cell dysfunction in prediabetes is critical for designing effective treatment methods. Interventions that improve GLUT4 translocation, increase insulin sensitivity, and safeguard beta-cell function show promise for avoiding the transition from prediabetes to diabetes.

1.2. Lifestyle and environmental risk factors

Prediabetes' etiology is multifaceted, with lifestyle and environmental factors playing important roles. Understanding these components is essential to effective prevention and management [83]. The risk of prediabetes and diabetes rises with a rising body mass index (BMI), the most often employed measurement to identify obesity levels, even though studies revealed that persistent weight loss is being shown to prevent the onset of prediabetes and diabetes [84]. At present, around 41.6 % of adult males and 25.6 % of adult women are obese, with the greatest obesity rate of 46.7 % among those in their 30s have reported. Also, people in their 30s also having unhealthy eating habits, such as consuming too much fat, alcohol, and sodium, along with eating excessive fast foods and convenience meals [85].

Studies revealed that smoking is strongly linked to type 2 diabetes; both active and passive smoking increased the chance of developing type 2 diabetes, and those who smoke with type 2 diabetes had a higher risk of having microvascular complications or glucose regulation over nonsmokers [86]. Prediabetic individuals who smoke are at a considerable risk of having different problems, particularly chronic obstructive pulmonary disease (COPD) [87].

According to studies, oxidative stress and inflammation caused by smoking play critical roles in the pathophysiology of COPD. Also, smoking causes oxidative DNA damage, persistent inflammation, and decreased immunity, all of which contribute to lung cancer [88]. However, environmental and lifestyle factors can have a substantial impact on oxidative stress, which is an imbalance of the body's antioxidants and free radicals. Numerous diseases and ailments, such as aging, exercise, cardiovascular and neurological disorders, and cancer, have been linked to oxidative stress [72].

Furthermore, prediabetes prevention and management require a comprehensive approach that includes lifestyle changes, environmental interventions, and smoking cessation. By correcting these factors, we can lower the prevalence of prediabetes and improve health outcomes for vulnerable populations [89].

2. Free radicals

There are molecules called free radicals that have one or more unpaired electrons in their outer shell. These molecules are unstable, but they react more strongly than non-radical species. Redox reactions form free radicals by breaking a chemical bond between the electrons and cleaving one electron to give another [17]. Therefore, the unstable molecule loses its electron and turns into a free radical state, resulting in damage to the living cell [18]. Free radicals have two sources for production: endogenous and exogenous. Various factors involved in the production of free radicals include age, intense exercise, mental stress, inflammation, ischemia, infection, malignancy, and immune cell activation. Meanwhile, exogenous factors comprise exposure of environmental pollutants, such as heavy metals (Cd, Hg, Pb, Fe, and As), specific drugs (cyclosporine, tacrolimus, gentamycin, and bleomycin), chemical thinners, cooking (smoked meat, used oil, and fat), alcohol, cigarettes, and radiation [16]. Overproduction leads the body to generate oxidative stress, and this could be a major factor in the emergence of several degenerative and chronic conditions, including cancer, diabetes, autoimmune diseases, aging, cataracts, and cardiovascular, and neurological conditions. Consequently, free radicals cause harm to proteins, fats, and DNA and cause a variety of illnesses in people [17].

Via three diverse pathways, the PKC pathway, the aldose reductase pathway, and the AGE generation pathway, free radicals are essential to the development and progression of diabetes. Adequate aldose reductase activity converts glucose to sorbitol utilizing the continuous oxidation of sorbitol to fructose, which is dependent on nicotinamide adenine dinucleotide phosphate (NADPH). Chronic hyperglycemia in diabetes saturates this mechanism early on, leading to the polyol pathway being the primary pathway for the metabolism of more than 30 % of glucose [36].

2.1. Reactive oxygen species (ROS) and its mechanism

ROS are highly reactive molecules with unpaired electrons that can interact quickly with other chemical compounds to change their structure and function. Reactive oxygen species are classified, Hydroxyl radical (•OH), Superoxide radical anion ($O2^{\bullet -}$), Peroxyl radical (ROO•), Alkoxyl radical (RO•), hydrogen peroxide (H_2O_2), perhydroxyl radical (HOO•), Singlet oxygen ($^1O_2$) [11]. However, ROS production is a necessary part of normal metabolism, and maintaining normal physiology requires some level of ROS formation. The primary cause of the oxidative stress that is building up inside the cellular machinery is

reactive oxygen species [13]. Overproduction of ROS has a significant impact on cellular respiration by lowering the need for oxygen consumption, which leads to aberrant metabolism and disease conditions.

One essential cause of ROS from the oxidative process is in the mitochondria. The enzyme known as Superoxide dismutase (SOD) plays a crucial role in the dismutation reaction that occurs inside the mitochondria and in the extracellular matrix of each cell, where it transforms superoxide ions into hydrogen peroxide. These free radicals are recognized to be stabilized by peroxidase in the extracellular matrix and catalase in the peroxisome. They can transform hydrogen peroxide (H_2O_2) into molecules of oxygen and water. H_2O_2 breakdown is aided by both $NADP^+$ oxidation and glutathione (GSH) reduction [24].

Antioxidants maintain a highly complex balance between producing ROS and protecting from oxidative damage. This includes enzymatic (like superoxide dismutase, catalase, and glutathione peroxidase) and non-enzymatic (like dietary antioxidants, vitamins, and thiols) mechanisms. The oxidant-generating Enzymes cause proteins, lipids, and nucleic acids to oxidize irreversibly due to the impaired activity of the antioxidant level. This oxidative stress, or unbalanced redox equilibrium, causes alterations in cell signaling that result in senescence, programmed cell death, and the loss of vital cellular functions [10].

Increased ROS levels also activate several signal transduction pathways, including the MAPK pathway, and block the insulin signaling pathway. Naturally occurring byproducts from normal cellular metabolism comprise ROS, composed of free radicals and other highly reactive chemicals [19]. Afterward, additional oxidase enzymes, like cytochrome P450 enzymes in the smooth endoplasmic reticulum (SER) and xanthine oxidase (XOD) in the cytoplasm, can also produce β-cell $O2^{\cdot-}$ in different cell compartments. In a recent research investigation, intermittent high glucose eventually increased the XOD activity and $O2^{-}$ of the INS-1 β-cell line. Additional repercussions of this included reduced viability and an accumulation of cells in the growth phase during the cell cycle. It was discovered that substantial fluctuations in glucose concentration were more detrimental to β-cell function than consistently elevated levels [53].

In addition to directly promoting the production of $O2^{\cdot-}$ and other ROS, the activity of these enzymes can also aid in the bioactivation of harmful substances like nitrosamines, which are frequently derived from harmful sources like processed or smoked meats [14]. O_2, other reactive oxygen species, and nitrosamines are frequently produced by cytochrome P450 enzymes. Furthermore, they have been demonstrated to cause DNA damage in BRIN-BD11 β-cells and to be able to generate highly reactive nitrogen species (RNS) [54]. As a crucial rate-determining enzyme, glucokinase is necessary for a proper glycolytic flux as well as the production of a high ATP/ADP ratio, which is necessary on behalf of the release of insulin. It's interesting to note that 3-morpholiydnonimine and hydroxylamine, two NO donors, likewise encouraged insulin release in INS-1 cells. In INS-1 β-cells and rat islets, it was found that intracellular ·NO levels rise under glucose and Ca^{2+} influx, while scavenging of ·NO inhibited insulin production. Consequently, physiological signaling is influenced by low levels, whereas β-cell activity is negatively impacted by greater levels [55].

Furthermore, β-cells in the diabetic condition may be exposed to glucose overload long-term, which can result in increased Ca^{2+} oscillations, tricarboxylic acid cycle activity, and elevated glycolytic flux and glucose oxidation [52]. However, when this reduction is not complete and leaves behind a superoxide anion instead of water as the outcome, ROS is created. Conversely, when an electron eludes the ETC process, a single electron reduction of oxygen develops a superoxide anion. There are more sources of ROS generation than there are documented sources of mitochondria [51].

On the other hand, oxidative stress occurs after the body generates more of these, and its antioxidant defenses can sustain them [35]. Hyperglycaemia and excess production of ROS overwhelm the body's natural defenses against oxidative stress, which may result in cell damage and the onset of diabetes complications [39]. Vasoconstriction, endothelial dysfunction, and increased salt absorption are triggered by elevated ROS levels in the kidney [33].

An increase in blood glucose causes oxidative stress by generating an excess of free radicals through a range of metabolic processes. Several factors associated with diabetes are adversely affected by this oxidative stress, including reduced insulin sensitivity and beta-cell activity, which results in poor glucose regulation [36]. Oxidative stress has become considered a disease trigger and contributes significantly to the development of inflammation and fibrogenesis. Moreover, elevated blood glucose levels cause an increase in the production of ROS, which in turn causes an elevated prooxidant condition [40].

Meanwhile, the effect of oxidative stress delves into pathological aspects including male infertility. Researchers propose that oxidative stress primarily causes abnormal male infertility. It was discovered that the seminal plasma of 30 %–40 % of infertile males in the US exhibited elevated ROS levels. Both endogenous and external factors can produce ROS in human seminal plasma [47]. This is to be believed only because of excessive alcohol intake and smoking along with some environmental circumstances, including radioactive effects and toxins leading to increased levels of ROS in seminal plasma in males. In this instance, sperm harm may result from the incredibly high ROS levels in seminal plasma. Numerous studies link abnormally high amounts of ROS, IL-6, IL-8, and tumor necrosis factor to reduced sperm function [48]. Thus, alcohol intake could lead to an increased ROS level in seminal plasma, impairing the eminence of semen [49].

2.2. ROS and insulin resistance

Oxidative stress is considered an essential molecular mechanism in insulin resistance. The overproduction of ROS based on hyperglycemia can cause insulin resistance by disrupting insulin signaling [23]. The impairment of the insulin signaling mechanism and the acceleration of type 2 diabetes are caused by the stimulation of numerous signaling pathways, such as c-Jun N-terminal kinase (JNK), MAPK, and NF-κB, which are linked to the deprivation of IRS [24]. Studies revealed that damage to ROS species has a direct effect on the progress of various chronic conditions, comprising insulin resistance and type 2 diabetes mellitus [21].

ROS alters different phases of insulin receptor signal transduction, leading to a reduction in the expression of the GLUT-4 transporter in the cellular membrane and the development of insulin resistance in peripheral tissues. The most extensively investigated pathway is the NF-κB pathway, which is considered to be important for cellular responses that cause inflammation and apoptosis. The activation of additional pathways in response to the overproduction of ROS triggered by hyperglycemia is initiated by this signaling cascade [43].

Studies revealed that Stress-activated kinases have been postulated for enhancing the serine-phosphorylation of important mechanisms of the insulin signalling, such as IRS or IR, leading to IRS degradation and consequent interruption of the insulin-signaling pathway. In addition, the phosphorylation of the IRS increases its ability to interact with the insulin receptor and proteins that contain Src homology 2 (SH2) domains, including PI3K. These stress-induced pathways play a crucial role in ROS-induced IR because their activation is linked to altered insulin signaling [44]. A study found that high levels of reactive oxygen species (ROS) cause casein-kinase 2 (CK-2) to become active, which in turn causes retromer activation. This process activates the trans-Golgi network, facilitating the translocation of GLUT-4 to lysosomes rather than the plasma membrane. The issue of hyperglycemia and hyperinsulinemia in the tissues is exacerbated by this decline in GLUT-4 levels, which leads to the resistance of peripheral tissues to insulin [45].

Insulin resistance and systemic inflammation are caused by inflammatory substances produced by both macrophages and adipocytes. In adipocytes, some saturated free fatty acids (SFAs), laurate, myristate, and palmitate increase the expression of inflammatory genes. Nuclear factor κB (NF-κB) transactivation and the generation of ROS are linked

to these processes [56]. It has recently been proposed that the pathophysiology of obesity-associated is ultimately influenced by chronic ROS generation. ROS is physiologically essential to adipocyte differentiation. Insulin signaling regulates the short half-life of these physiological. Both genetically and diet-induced obese mice exhibit significantly elevated ROS levels within the visceral adipose tissue [57]. Studies revealed that there has been increasing evidence that antioxidants might decrease insulin resistance and restore insulin signaling in obese mice. To improve insulin sensitivity in genetic and diabetic mice, for instance, the antioxidant manganese tetrakis porphyrin and the cell-permeable small-peptide antioxidant SS31 (D-Arg-2′,6′-dimethyltyrosine-Lys-Phe-NH2) are administered without affecting body weight [58]. Studies have shown a strong relationship between increased levels of oxidative stress and insulin resistance [49].

2.3. ROS and beta cells

ROS are oxygen-derived reactive molecules and free radicals, with O^{2-} serving as the precursor for most forms. One of the main sources of ROS is the mitochondrial electron transport chain, where oxidative phosphorylation converts oxygen consumed into O^2 up to 4 %. Synthesis, storage, and release of insulin are carried out by pancreatic β cells [32]. Beta cells function as glucose sensors and these cells are essential for the release of insulin in response to glucose stimulation. Excessive production of ROS during hyperglycaemic or hyperlipidaemic conditions leads to β cell failure, which impairs the pancreatic islets to synthesize and release insulin [41]. High glucose metabolism in β-cells frequently produces ROS in the mitochondria, which impairs the function of the insulin secretory pathway. Therefore, ROS are often produced in mitochondria due to the high amount of glucose metabolism in β-cells [67].

Furthermore, the expression of antioxidant enzymes like SOD and Gpx/catalase in β-cells are roughly 30 % and 5 % of liver values respectively. β-cells are vulnerable to oxidative stress damage resulting from the poor secretion of antioxidant enzymes. Although excessive glucose exposure causes mitochondrial ROS production in β-cells, β-cells may have compromised insulin secretory action [28]. The harmful effects of ROS result in beta-cell failure and death, affecting the production and release of insulin. Insulin resistance is also a result of oxidative stress, which reduces insulin's ability to promote cells' uptake of glucose [36]. However, prolonged high glucose may result in intracellular oxidative stress because of increased glucose metabolism and mitochondrial reactive oxygen species generation, particularly in the pancreatic β-cell but also in several insulin-sensitive organs [50].

Glucose metabolism increases intracellular Ca^{2+} levels, which activates protein kinase C and NADPH oxidase (NOX) and produces O^{2-} [1]. Inhibiting NOX disrupts intracellular Ca^{2+} dynamics and GSIS, resulting in ROS production during GSIS. NOX2 does not influence β-cell function or glucose-induced oxidative damage. Peroxynitrite (ONOO −), a reactive species produced by O^{2-} and free radical nitric oxide (NO), damages β-cells in response to pro-inflammatory cytokines. However, cytokines do not activate β-cells to cause ONOO-. Thioredoxins and peroxiredoxins are overexpressed in the first line of defense against H_2O_2, and they are required for redox signaling. The most highly upregulated gene in human islets in response to glucose is thioredoxin-interacting protein (TXNIP). TXNIP binds to and inhibits thioredoxin, which modifies the cellular redox state and causes oxidative stress [29]. Owing to NOX's involvement in the functioning of immune cells and the newly discovered dual beneficial roles of NOX isoforms in β-cell function, pro-inflammatory cytokines (like IL-1β, TNF-α, and INF-γ) and glucose excess can cause NOX dysregulation in T1DM and T2DM, which can lead to cellular dysfunction and impaired insulin secretion [50]. Furthermore, β-cells in the diabetic condition may be exposed to glucose overload long-term, which can result in increased Ca^{2+} oscillations, tricarboxylic acid cycle activity, and elevated glycolytic flux and glucose oxidation [52].

2.4. ROS production and its effects on prediabetes development and diabetes complications

The onset of prediabetes and T2DM are influenced by many factors, including lifestyle habits, oxidative stress, and genetic predisposition that might affect their onset and progression (Fig. 1) Increased secretion of ROS in response to hyperglycemia (through the main mechanisms described above) damages many macromolecules in cells, leads to cell injury, and finally causes oxidative stress. Increased ROS and oxidative stress are related to deficiencies in insulin secretion and action, as well as β-cell dysfunction and the emergence of insulin resistance. T2DM and its complications are influenced by several risk factors, also suppression of antioxidant responses, and the elevation of oxidative stress [20].

3. Beta cells ROS scavenging

The regulation of β-cell function and glucose homeostasis appears to involve the interaction of ROS, antioxidants, and the adaptive antioxidant response. Antioxidants, which are classified into two types: enzymatic and nonenzymatic components, are required to minimize and/or neutralize the negative effects of reactive substances. The three basic enzymatic antioxidants—superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidases (GPx)—have been studied for the treatment of diseases and catabolic states caused by oxidative stress and/or damage [59]. Antioxidants protect β-cells from oxidative damage and malfunction, but can also suppress ROS signaling activated by glucose, reducing glucose-stimulated insulin production. Our bodies have a several defense systems against reactive oxygen species (ROS) and oxidative stress, including glutathione peroxidase, SOD, and catalase. However, the chronic inflammation associated with diabetes impairs these defense mechanisms, which accelerates the development of damage and the disease ultimately [36]. The antioxidants are listed below.

3.1. Superoxide dismutase

SOD, an important antioxidant enzyme, creates H_2O_2 and O_2 by dismutating the superoxide anion (O^{2-}). SOD is said to help with T2DM by reducing oxidative stress caused by hyperglycemia. In T2DM patients, a drop in SOD concentrations may increase sensitivity to oxidative stress [31]. SOD activity was decreased in prediabetes patients compared to normoglycemic patients [30]. In addition, studies have proven the antioxidant capabilities of chemically modified SOD in streptozotocin (STZ)-induced diabetic rats (such as carboxymethylcellulose-SOD and polymethyl vinyl ether-co-maleic anhydride-SOD).

3.2. Catalase

Catalase is an antioxidant enzyme that converts hydrogen peroxide into water and oxygen. This enzyme is found in all aerobic species and is thought to be the final step in detoxification, where SOD is initiated [60]. Furthermore, investigations conducted by Japanese, Swiss, and Hungarian individuals have shown that the catalase enzyme possesses peroxidase activity when it interacts with H^+ sources such as methanol, ethanol, formic acid, or phenol. CAT gene polymorphisms and some mutations can result in a catalase deficiency. Low H_2O_2 excretion due to CAT deficiency or mutation has been linked to oxidative stress, which can cause diseases like diabetes, hyperlipidemia, gangrene, atherosclerosis, and hypertension [61]. Decreased CAT levels make it difficult for pancreatic β-cells to protect against hazardous quantities of H_2O_2, especially when glucose is used to activate the cells [62].

Catalase deficiency raises the risk of T2DM and contributes to the failure of β-cell function by shielding them from ROS-induced damage [31]. Low CAT levels can hinder pancreatic β-cells' ability to guard against dangerous excess H_2O_2, particularly when glucose is used to activate the cells.

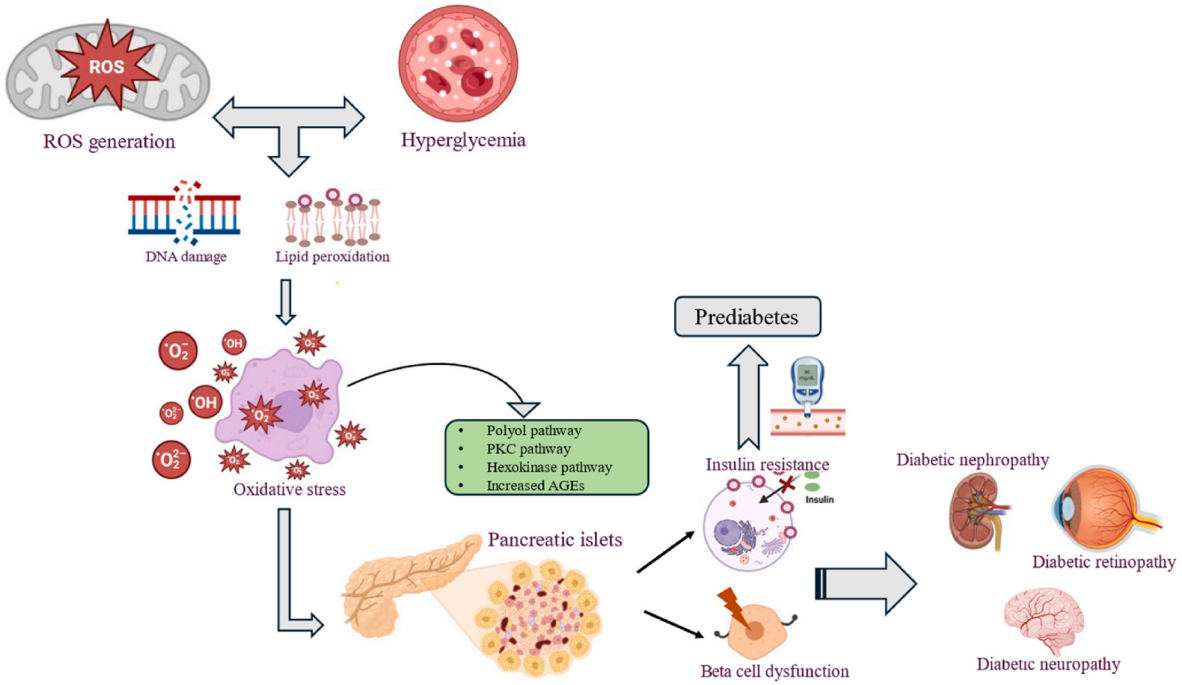

Fig. 1. ROS production and its effects on prediabetes development and diabetic complications.

3.3. Glutathione peroxides

Lipid and intracellular hydrogen peroxides are reduced by the selenium-dependent enzyme glutathione peroxidase 1 (GPX1) [63]. The enzymatic antioxidant defense system is largely supported by the glutathione peroxidase (GPx) family. GPx1, an isoform of the GPx family that is widely expressed, detoxifies toxic lipid peroxides by converting hydrogen peroxide to water and lipid alcohol [33].

The mitochondria of mammalian cells contain the majority of this antioxidant enzyme, while the cytoplasm contains trace amounts. To further protect the cell from various oxidative stresses, GPx detoxifies the cell from both organic and inorganic peroxides [38]. Wang and colleagues' study in China found a significant decrease in pancreatic β-cells, as well as hyperinsulinemia, mild hyperglycemia, and decreased ATP generation. In a different study, Gpx1−/−2 mice were given a high-calorie diet for 12 weeks and showed symptoms of chronic and systemic oxidative stress associated with hyperglycemia. Chronic oxidative stress from ROS led to decreased β-cell mass and insulin secretion, despite no variation in insulin sensitivity. This was linked to Pdx1 gene expression [64].

Clinical evidence has connected human GPX1 gene variants to an increased risk of diabetes onset and progression [38]. Subsequent research, including epidemiological studies, has found that high or low selenium intake is associated with an increased risk of diabetes [65].

3.4. Paraoxonase

Paraoxonase, often known as PON1, is a glycoprotein that has anti-inflammatory and antioxidant activity. Mostly produced in the liver and delivered into the bloodstream, it then attaches to high density lipoprotein (HDL) in the circulation. PON1's antioxidant characteristics may promote insulin secretion with high glucose levels by protecting against oxidative damage [40].

PON1 appears to have a cytoprotective impact on β cells, increasing their viability and insulin production. PON1 increases insulin synthesis in β cells, showing its crucial role in insulin production [42].

4. Oxidative stress and prediabetes

4.1. Influence of oxidative stress on insulin signalling

Prediabetes, the most significant predictor of T2DM, is described as impaired glucose tolerance or fasting glucose levels. It has also been associated with dyslipidemia, endothelial dysfunction, hypertension, and impaired fibrinolysis [42]. Obesity, advancing age, and inadequate nutrition are among the most prominent risk factors that contribute to an oxidative environment that may change insulin sensitivity by reducing insulin resistance or worsening glucose tolerance. Reactive oxygen species (ROS) have been found to disrupt insulin signaling, with dose- and time-dependent effects. Millimolar ROS concentrations play a physiological role in insulin signaling via a process involving NADPH oxidase. Increased ROS levels also activate various signal transduction pathways, including the MAPK pathway, while inhibiting the insulin signaling pathway [10].

Insulin stimulation causes a transient and low-dose exposure to ROS via an increase in H_2O_2 production. Insulin resistance has been linked to a variety of causes, with ROS being identified as a major contributor to its development. Studies have found that treating the mouse adipocyte cell line with hydrogen peroxide-ROS resulted in insulin resistance [22]. This exposure stimulates the insulin signaling cascade by inhibiting tyrosine phosphatase activity, resulting in increased basal tyrosine phosphorylation of the insulin receptor and its substrates. The most common symptom of poor insulin signaling is insulin resistance, which occurs when normal insulin levels are insufficient to permit muscle, fat, or liver cells to respond appropriately to insulin. Oxidative stress interferes with insulin signaling, leading to insulin resistance [26].

T2DM occurs when β-cells fail to adapt to decreasing insulin sensitivity caused by increasing insulin resistance. This impairs the pancreas, liver, bones, and brain's capacity to operate properly. According to studies, hepatic insulin resistance impairs glucose absorption and the insulin signaling pathway in persons with liver disease, reducing glycogenesis and raising blood sugar levels [40].

Increased ROS levels also activate various signal transduction pathways, including the MAPK pathway, while inhibiting the insulin signaling pathway. T2DM and associated consequences are principally

caused by the stimulation of multiple pro-inflammatory (TNF-α, NF-κB), pro-fibrotic (TGF-β) factors, macromolecular changes (typically lipids and proteins), mitochondrial dysfunction, and cellular injury by ROS [24].

4.2. Relationship between oxidative stress and prediabetes

However, ROS synthesis is an essential component of regular metabolism, and maintaining normal physiology necessitates some amount of ROS formation [10]. The body's overproduction of free radicals causes oxidative stress. This could play a significant role in the onset of a variety of degenerative and chronic ailments, such as cancer, diabetes, autoimmune diseases, aging, cataracts, and cardiovascular and neurological disorders. Obesity, insulin resistance, inflammation, dyslipidemia, hypertension, and genetic factors all contribute to the development of prediabetes. As a result, free radicals damage proteins, lipids, and DNA, causing a wide range of human disorders [17].

This stress caused numerous dysfunctions in pancreatic beta cells and may have affected sensitivity in the liver and adipose tissues. Thus, prediabetes is caused by the degradation of insulin secretion and fat [69]. A study in Iran found that prediabetes had a lower dietary total antioxidant capacity (DTAC) than the control group. Thus, it emphasizes the role of free radicals in oxidative stress in prediabetics [8].

Therefore, excessive free radical production might play a role in the pathogenesis of prediabetes. Another study from Saudi Arabia reported that individuals with prediabetes were associated with dyslipidemia, decreased total antioxidant capacity, and obesity. According to experimental research, oxidative stress impairs insulin signaling and lowers insulin production from beta cells in the pancreas, hastening the progression from insulin resistance to type 2 diabetes.

5. Progression rate of prediabetes to diabetes

Every year, between 10 % and 15 % of people with prediabetes develop diabetes; however, the conversion rate varies depending on the characteristics of the population and how prediabetes is defined. The prevalence of prediabetes, diabetes, and "any dysglycaemia" was found to be 22.2, 29.5, and 51.7 cases per 1000 person-years, in that order.

A total of 45.1 % of those with normal glucose tolerance transitioned to dysglycemia, with 19.4 % developing diabetes and 25.7 % becoming prediabetic. Additionally, 58.9 % of people with prediabetes eventually developed diabetes. Factors such as growing older, a family history of diabetes, 2-h plasma glucose, glycated hemoglobin (HbA1c), poor HDL cholesterol, and physical inactivity were all associated with a higher risk of dysglycemia [27].

A Danish population study indicated that patients with prediabetes had the highest risk for major adverse cardiovascular events and all-cause death. This underscores that prediabetes is linked to serious health implications in adults [46].

6. Proposed management strategies

Studies have revealed, a healthy lifestyle, sustainable dietary changes, physical activity, particularly regular exercise that promotes weight loss, and psychological support with medication can all help regulate pre-diabetes [82].

Motivational interviewing and individualized diet are critical components of patient involvement, while routine diagnostics, such as HbA1c testing and fasting plasma glucose, as well as the use of digital technologies, are required for monitoring and follow-up [90].

7. Conclusion

Prediabetes often results in insulin resistance and impaired beta-cell activity. Hyperglycaemia can promote vascular dysfunction by increasing the formation of ROS and upregulating indicators of chronic inflammation. Low antioxidant levels cause ROS levels to increase in prediabetes. This damages the body's lipids, proteins, carbohydrates, and DNA, affecting cellular structure and function. To delay the onset of diabetes and prevent diabetic complications, it is essential to effectively manage hyperglycemia and suppress the elevated levels of ROS. Our paper summarizes that excessive production of ROS affects the beta cell function leading to failure. There has been lack of studies which addresses the role of oxidative stress in prediabetes development. This review comprises the pathogenesis and impact of oxidative stress biomarker in prediabetes. Also, this review implies a complete understanding of oxidative stress plays an important role as one of prediabetes's underlying causes may pave the way for early prediabetes diagnosis and therapy, preventing its progression into type 2 diabetes mellitus.

CRediT authorship contribution statement

Aarthi Yesupatham: Writing – review & editing, Writing – original draft. **Radha Saraswathy:** Supervision.

Funding

None.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr.Radha Saraswathy reports article publishing charges was provided by Vellore Institute of Technology. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors acknowledge Vellore Institute of Technology, Vellore, Tamil Nadu, India. A. Y is grateful to VIT for providing a teaching cum research assistant (TRA) fellowship.

Data availability

The data that has been used is confidential.

References

[1] A. Konior, A. Schramm, M. Czesnikiewicz-Guzik, T.J. Guzik, NADPH oxidases in vascular pathology, Antioxidants Redox Signal. 20 (17) (2024) 2794–2814.
[2] R.M. Anjana, R. Unnikrishnan, M. Deepa, R. Pradeepa, N. Tandon, A.K. Das, S. Ghosh, Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17), Lancet Diabetes Endocrinol. (2023).
[3] U. Hostalek, Global epidemiology of prediabetes - present and future perspectives, Clinical diabetes and endocrinology 5 (2019) 5.
[4] M.R. Rooney, M. Fang, K. Ogurtsova, B. Ozkan, J.B. Echouffo-Tcheugui, E.J. Boyko, E. Selvin, Global prevalence of prediabetes, Diabetes Care 46 (7) (2023) 1388–1394.
[5] K. Luc, A. Schramm-Luc, T.J. Guzik, T.P. Mikolajczyk, Oxidative stress and inflammatory markers in prediabetes and diabetes, J. Physiol. Pharmacol. 70 (6) (2019).
[6] F.S. Saghir, F.S. Ibrahim, Z. Amom, L. Othman, The role of oxidative stress and inflammation in prediabetes: a review, Malaysian Journal of Medicine & Health Sciences 19 (4) (2023).
[7] E. Karimi-Nazari, A. Nadjarzadeh, R. Masoumi, A. Marzban, S.A. Mohajeri, N. Ramezani-Jolfaie, A. Salehi-Abargouei, Effect of saffron (Crocus sativus L.) on lipid profile, glycemic indices and antioxidant status among overweight/obese prediabetic individuals: a double-blinded, randomized controlled trial, Clinical nutrition ESPEN 34 (2019) 130–136.
[8] G. Sotoudeh, M. Abshirini, F. Bagheri, F. Siassi, F. Koohdani, Z. Aslany, Higher dietary total antioxidant capacity is inversely related to prediabetes: a case-control study, Nutrition (Burbank, Los Angel. Cty., Calif.) 46 (2018) 20–25.

[9] G. Pizzino, N. Irrera, M. Cucinotta, G. Pallio, F. Mannino, V. Arcoraci, A. Bitto, Oxidative stress: harms and benefits for human health, Oxid. Med. Cell. Longev. (2017).
[10] F. Holguin, A. Fitzpatrick, Obesity, asthma, and oxidative stress, J. Appl. Physiol. 108 (3) (2010) 754–759.
[11] S. Tangvarasittichai, Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus, World J. Diabetes 6 (3) (2015) 456–480.
[12] E.J. Henriksen, M.K. Diamond-Stanic, E.M. Marchionne, Oxidative stress and the etiology of insulin resistance and type 2 diabetes, Free Radic. Biol. Med. 51 (5) (2011) 993–999.
[13] J. Checa, J.M. Aran, Reactive oxygen species: drivers of physiological and pathological processes, J. Inflamm. Res. (2020) 1057–1073.
[14] B.M. Sahoo, B.K. Banik, P. Borah, A. Jain, Reactive oxygen species (ROS): key components in cancer therapies, Anti Cancer Agents Med. Chem. 22 (2) (2020) 215–222.
[15] A.G. Tabák, C. Herder, W. Rathmann, E.J. Brunner, M. Kivimäki, Prediabetes: a high-risk state for diabetes development, Lancet (London, England) 379 (9833) (2012) 2279–2290.
[16] G. Pizzino, N. Irrera, M. Cucinotta, G. Pallio, F. Mannino, V. Arcoraci, F. Squadrito, D. Altavilla, A. Bitto, Oxidative stress: harms and benefits for human health, Oxid. Med. Cell. Longev. (2017) 8416763.
[17] L.A. Pham-Huy, H. He, C. Pham-Huy, Free radicals, antioxidants in disease and health, International journal of biomedical science: IJBS 4 (2) (2008) 89.
[18] A. Phaniendra, D.B. Jestadi, L. Periyasamy, Free radicals: properties, sources, targets, and their implication in various diseases, Indian J. Clin. Biochem. 30 (2015) 11–26.
[19] K.V. Chaitanya, A.A.K. Pathan, S.S. Mazumdar, G.P. Chakravarthi, N. Parine, V. Bobbarala, Role of oxidative stress in human health: an overview, J. Pharm. Res. 3 (6) (2010) 1330–1333.
[20] S. Tangvarasittichai, Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus, World J. Diabetes 6 (3) (2015) 456.
[21] S. Hurrle, W.H. Hsu, The etiology of oxidative stress in insulin resistance, Biomed. J. 40 (5) (2017) 257–262.
[22] A. Rudich, A. Tirosh, R. Potashnik, R. Hemi, H. Kanety, N. Bashan, Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes, Diabetes 47 (10) (1998) 1562–1569.
[23] N. Wang, Y. Wu, J. Bian, X. Qian, H. Lin, H. Sun, X. Zhang, Current development of ROS-modulating agents as novel antitumor therapy, Curr. Cancer Drug Targets 17 (2) (2017) 122–136.
[24] J.S. Bhatti, A. Sehrawat, J. Mishra, I.S. Sidhu, U. Navik, N. Khullar, P.H. Reddy, Oxidative stress in the pathophysiology of type 2 diabetes and related complications: current therapeutics strategies and future perspectives, Free Radic. Biol. Med. 184 (2022) 114–134.
[25] X. Zhao, X. An, C. Yang, W. Sun, H. Ji, F. Lian, The crucial role and mechanism of insulin resistance in metabolic disease, Front. Endocrinol. 14 (2023) 1149239.
[26] J.L. Rains, S.K. Jain, Oxidative stress, insulin signaling, and diabetes, Free Radic. Biol. Med. 50 (5) (2011) 567–575.
[27] J.S.S. Kacker, N. Saboo, J. Sorout, Prediabetes: pathogenesis and adverse outcomes, Int. J. Med. Res. Prof. 4 (2018) 1–6.
[28] M. Tiedge, S. Lortz, J. Drinkgern, S. Lenzen, Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells, Diabetes 46 (11) (1997) 1733–1742.
[29] W.L. Suarez-Pinzon, C. Szabó, A. Rabinovitch, Development of autoimmune diabetes in NOD mice is associated with the formation of peroxynitrite in pancreatic islet β-cells, Diabetes 46 (5) (1997) 907–911.
[30] M. Madi, S. Babu, S. Kumari, S. Shetty, S. Achalli, A. Madiyal, M. Bhat, Status of serum and salivary levels of superoxide dismutase in type 2 diabetes mellitus with oral manifestations: a case control study, Ethiopian journal of health sciences 26 (6) (2016) 523–532.
[31] N. Promyos, P.P. Phienluphon, N. Wechjakwen, J. Lainampetch, P. Prangthip, K. Kwanbunjan, Inverse correlation of superoxide dismutase and catalase with type 2 diabetes among rural thais, Nutrients 15 (9) (2023) 2071.
[32] J. Pi, Q. Zhang, M.E. Andersen, Reactive oxygen species and antioxidants in pancreatic β-cell function—yin and yang, in: I. Laher (Ed.), Systems Biology of Free Radicals and Antioxidants, 2014, pp. 3319–3337.
[33] M.G.A. Ansari, S. Sabico, M. Clerici, M.N.K. Khattak, K. Wani, S. Al-Musharaf, O. E. Amer, M.S. Alokail, N.M. Al-Daghri, Vitamin D supplementation is associated with increased glutathione peroxidase-1 levels in arab adults with prediabetes, Antioxidants 9 (2) (2020) 118.
[34] A. Serbis, V. Giapros, K. Tsamis, F. Balomenou, A. Galli-Tsinopoulou, E. Siomou, Beta cell dysfunction in youth-and adult-onset type 2 diabetes: an extensive narrative review with a special focus on the role of nutrients, Nutrients 15 (9) (2023) 2217.
[35] H.J. Forman, H. Zhang, Targeting oxidative stress in disease: promise and limitations of antioxidant therapy, Nat. Rev. Drug Discov. 20 (9) (2021) 689–709.
[36] A. Caturano, M. D'Angelo, A. Mormone, V. Russo, M.P. Mollica, T. Salvatore, F. C. Sasso, Oxidative stress in type 2 diabetes: impacts from pathogenesis to lifestyle modifications, Curr. Issues Mol. Biol. 45 (8) (2023) 6651–6666.
[37] V.A. Salunkhe, R. Veluthakal, S.E. Kahn, D.C. Thurmond, Novel approaches to restore beta cell function in prediabetes and type 2 diabetes, Diabetologia (Berl.) 61 (2018) 1895–1901.
[38] J.Q. Huang, J.C. Zhou, Y.Y. Wu, F.Z. Ren, X.G. Lei, Role of glutathione peroxidase 1 in glucose and lipid metabolism-related diseases, Free Radic. Biol. Med. 127 (2018) 108–115.
[39] J. Dworzański, M. Strycharz-Dudziak, E. Kliszczewska, M. Kiełczykowska, A. Dworzańska, B. Drop, M. Polz-Dacewicz, Glutathione peroxidase (GPx) and superoxide dismutase (SOD) activity in patients with diabetes mellitus type 2 infected with Epstein-Barr virus, PLoS One 15 (3) (2020) e0230374.
[40] M.J. Meneses, R. Silvestre, I. Sousa-Lima, M.P. Macedo, Paraoxonase-1 as a regulator of glucose and lipid homeostasis: impact on the onset and progression of metabolic disorders, Int. J. Mol. Sci. 20 (16) (2019) 4049.
[41] R. Laybutt, W. Hasenkamp, A. Groff, S. Grey, J.C. Jonas, H. Kaneto, G. Weir, Beta-cell adaptation to hyperglycemia, Diabetes 50 (suppl_1) (2010) S180.
[42] M. Koren-Gluzer, M. Aviram, E. Meilin, T. Hayek, The antioxidant HDL-associated paraoxonase-1 (PON1) attenuates diabetes development and stimulates β-cell insulin release, Atherosclerosis 219 (2) (2011) 510–518.
[43] J.L. Evans, I.D. Goldfine, B.A. Maddux, G.M. Grodsky, Are oxidative stress–activated signaling pathways mediators of insulin resistance and β-cell dysfunction? Diabetes 52 (1) (2003) 1–8.
[44] B. Draznin, Molecular mechanisms of insulin resistance: serine phosphorylation of insulin receptor substrate-1 and increased expression of p85α: the two sides of a coin, Diabetes 55 (8) (2006) 2392–2397.
[45] J. Ma, Y. Nakagawa, I. Kojima, H. Shibata, Prolonged insulin stimulation down-regulates GLUT4 through oxidative stress-mediated retromer inhibition by a protein kinase CK2-dependent mechanism in 3T3-L1 adipocytes, J. Biol. Chem. 289 (1) (2014) 133–142.
[46] B.U. Nwosu, The progression of prediabetes to type 2 diabetes in children and adolescents in the United States: current challenges and solutions, Endocrine (Basingstoke) 3 (3) (2022) 545–551.
[47] S.K. Bardaweel, M. Gul, M. Alzweiri, A. Ishaqat, H.A. Alsalamat, R.M. Bashatwah, Reactive oxygen species: the dual role in physiological and pathological conditions of the human body, The Eurasian journal of medicine 50 (3) (2018) 193.
[48] P. Gharagozloo, R.J. Aitken, The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy, Hum. Reprod. 26 (7) (2011) 1628–1640.
[49] A. Agarwal, S.A. Prabakaran, Mechanism, Measurement, and Prevention of Oxidative Stress in Male Reproductive Physiology, 2005.
[50] P. Newsholme, V.F. Cruzat, K.N. Keane, R. Carlessi, Jr P.I. H. de Bittencourt, Molecular mechanisms of ROS production and oxidative stress in diabetes, Biochem. J. 473 (24) (2016) 4527–4550.
[51] S. Bhattacharya, Reactive oxygen species and cellular defense system, Free radicals in human health and disease (2015) 17–29.
[52] P.A. Gerber, G.A. Rutter, The role of oxidative stress and hypoxia in pancreatic beta-cell dysfunction in diabetes mellitus, Antioxidants Redox Signal. 26 (10) (2017) 501–518.
[53] Z. Zhang, J. Li, L. Yang, R. Chen, R. Yang, H. Zhang, H. Chen, The cytotoxic role of intermittent high glucose on apoptosis and cell viability in pancreatic beta cells, J. Diabetes Res. (1) (2014) 712781.
[54] D.J.L. Murdock, Y.A. Barnett, C.R. Barnett, DNA damage and cytotoxicity in pancreatic β-cells expressing human CYP2E1, Biochem. Pharmacol. 68 (3) (2004) 523–530.
[55] S.R. Smukler, L. Tang, M.B. Wheeler, A.M.F. Salapatek, Exogenous nitric oxide and endogenous glucose-stimulated β-cell nitric oxide augment insulin release, Diabetes 51 (12) (2002) 3450–3460.
[56] C.Y. Han, Roles of reactive oxygen species on insulin resistance in adipose tissue, Diabetes & metabolism journal 40 (4) (2016) 272–279.
[57] S. Furukawa, T. Fujita, M. Shimabukuro, M. Iwaki, Y. Yamada, Y. Nakajima, I. Shimomura, Increased oxidative stress in obesity and its impact on metabolic syndrome, J. Clin. Investig. 114 (12) (2017) 1752–1761.
[58] K.A. Edgel, T.S. McMillen, H. Wei, N. Pamir, B.A. Houston, M.T. Caldwell, R. C. LeBoeuf, Obesity and weight loss result in increased adipose tissue ABCG1 expression in db/db mice, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1821 (3) (2012) 425–434.
[59] C. Affourtit, Mitochondrial involvement in skeletal muscle insulin resistance: a case of imbalanced bioenergetics, Biochim. Biophys. Acta Bioenerg. 1857 (10) (2016) 1678–1693.
[60] R. Radi, J.F. Turrens, L.Y. Chang, K.M. Bush, J.D. Crapo, B.A. Freeman, Detection of catalase in rat heart mitochondria, J. Biol. Chem. 266 (32) (1991) 22028–22034.
[61] L. Góth, A new type of inherited catalase deficiencies: its characterization and comparison to the Japanese and Swiss type of acatalasemia, Blood Cell Mol. Dis. 27 (2) (2001) 512–517.
[62] L. Goth, J.W. Eaton, Hereditary catalase deficiencies and increased risk of diabetes, The Lancet 356 (9244) (2000) 1820–1821.
[63] T.L. Merry, M. Tran, M. Stathopoulos, F. Wiede, B.C. Fam, G.T. Dodd, T. Tiganis, High-fat-fed obese glutathione peroxidase 1-deficient mice exhibit defective insulin secretion but protection from hepatic steatosis and liver damage, Antioxidants Redox Signal. 20 (14) (2014) 2114–2129.
[64] Nikolaeva, M., & Johnstone, M. Nitric oxide, its role in diabetes mellitus and methods to improve endothelial function. In *Diabetes And Cardiovascular Disease* 2023, (pp. 159-200). Cham: Springer International Publishing.
[65] Y. An, B.T. Xu, S.R. Wan, X.M. Ma, Y. Long, Y. Xu, Z.Z. Jiang, The role of oxidative stress in diabetes mellitus-induced vascular endothelial dysfunction, Cardiovasc. Diabetol. 22 (1) (2023) 237.
[66] M. Talha, A.R. Mir, S. Habib, M. Abidi, M.S. Warsi, S. Islam, Hydroxyl radical induced structural perturbations make insulin highly immunogenic and generate an auto-immune response in type 2 diabetes mellitus, Spectrochim. Acta Mol. Biomol. Spectrosc. 255 (2021) 119640.
[67] G.A. Martens, Y. Cai, S. Hinke, G. Stangé, M. Van de Casteele, D. Pipeleers, Glucose suppresses superoxide generation in metabolically responsive pancreatic β cells, J. Biol. Chem. 280 (21) (2005) 20389–20396.

[68] C. Heit, S. Marshall, S. Singh, X. Yu, G. Charkoftaki, H. Zhao, D.J. Orlicky, K. S. Fritz, D.C. Thompson, V. Vasiliou, Catalase deletion promotes prediabetic phenotype in mice, Free Radic. Biol. Med. 103 (2017) 48–56.
[69] M. Priyatharshini, P. Muraliswaran, P. Kanagavalli, G. Radhika, The effect of oxidative stress and inflammatory status in pre-diabetic subjects, IOSR J. Dent. Med. Sci. 16 (12) (2017) 91–95.
[72] M. Valko, D. Leibfritz, J. Moncol, M.T. Cronin, M. Mazur, J. Telser, Free radicals and antioxidants in normal physiological functions and human disease, Int. J. Biochem. Cell Biol. 39 (1) (2007) 44–84.
[73] T.B. Vuong, T.M. Tran, N.Q. Tran, High prevalence of prediabetes and type 2 diabetes, and identification of associated factors, in high-risk adults in Vietnam: a cross-sectional study, Diabetes Epidemiology and Management 17 (2025) 100239.
[74] S.K. Masenga, L.S. Kabwe, M. Chakulya, A. Kirabo, Mechanisms of oxidative stress in metabolic syndrome, Int. J. Mol. Sci. 24 (9) (2023) 7898, https://doi.org/10.3390/ijms24097898.
[75] A. Ismail, M. Tanasova, Importance of GLUT transporters in disease diagnosis and treatment, Int. J. Mol. Sci. 23 (15) (2022) 8698.
[76] A. Ray, J. Wen, L. Yammine, J. Culver, I.S. Parida, J. Garren, T.E. McGraw, Regulated dynamic subcellular GLUT4 localization revealed by proximal proteome mapping in human muscle cells, J. Cell Sci. 136 (23) (2023).
[77] P. Chandrasekaran, R. Weiskirchen, Cellular and molecular mechanisms of insulin resistance, Current Tissue Microenvironment Reports (2024) 1–12.
[78] T. Kristensen, M. Fredholm, S. Cirera, Expression study of GLUT4 translocation-related genes in a porcine pre-diabetic model, Mamm. Genome 26 (2015) 650–657.
[79] E. Faramarzi, S. Mehrtabar, R. Molani-Gol, S. Dastgiri, The relationship between hepatic enzymes, prediabetes, and diabetes in the Azar cohort population, BMC Endocr. Disord. 25 (1) (2025) 41.
[80] I.V. Bure, M.V. Nemtsova, E.B. Kuznetsova, Histone modifications and non-coding RNAs: mutual epigenetic regulation and role in pathogenesis, Int. J. Mol. Sci. 23 (10) (2022) 5801.
[81] N. Eguchi, N.D. Vaziri, D.C. Dafoe, H. Ichii, The role of oxidative stress in pancreatic β cell dysfunction in diabetes, Int. J. Mol. Sci. 22 (4) (2021) 1509.
[82] D. Mohajan, H.K. Mohajan, Prevention and management strategies of pre-diabetes, Frontiers in Management Science 2 (5) (2023) 32–36.
[83] H. Kolb, S. Martin, Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes, BMC Med. 15 (2017) 1–11.
[84] American Diabetes Association, 5. Lifestyle management: standards of medical care in diabetes—2019, Diabetes Care 42 (Supplement_1) (2019) S46–S60.
[85] K.S. Park, S.Y. Hwang, Lifestyle-related predictors affecting prediabetes and diabetes in 20-30-year-old young Korean adults, Epidemiology and health 42 (2020).
[86] A. Pan, Y. Wang, M. Talaei, F.B. Hu, T. Wu, Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis, Lancet Diabetes Endocrinol. 3 (12) (2015) 958–967.
[87] T.A. Addissouky, I.E.T. El Sayed, M.M. Ali, Y. Wang, A. El Baz, N. Elarabany, A. A. Khalil, Oxidative stress and inflammation: elucidating mechanisms of smoking-attributable pathology for therapeutic targeting, Bull. Natl. Res. Cent. 48 (1) (2024) 16.
[88] R. Sun, D. Méndez, K.E. Warner, Association of electronic cigarette use by US adolescents with subsequent persistent cigarette smoking, JAMA Netw. Open 6 (3) (2023) e234885.
[89] N.A. ElSayed, R.G. McCoy, G. Aleppo, K. Balapattabi, E.A. Beverly, K. Briggs Early, S. Polsky, 3. Prevention or delay of diabetes and associated comorbidities: standards of care in diabetes—2025, Diabetes Care 48 (2025).
[90] American Diabetes Association, Introduction: standards of medical care in diabetes—2022, Diabetes Care 45 (Supplement_1) (2022) S1–S2.
[91] A.N. Onyango, The Contribution of Singlet Oxygen to Insulin Resistance, Oxidative medicine and cellular longevity 2017 (2017) 8765972. https://doi.org/10.1155/2017/8765972.