Review Article

Oxidative stress and diabetes mellitus: Unravelling the intricate connection -A comprehensive review

ABSTRACT

Background: Diabetes mellitus (DM) is often associated with oxidative stress (OS), which is defined as an imbalance between the body's antioxidant defense systems and the generation of reactive oxygen species (ROS). OS serves as a crucial factor in the intricate relationship between DM and cellular dysfunction, influencing the generation of ROS and subsequent DM complications such as retinopathy, cardiomyopathy, neuropathy, nephropathy, encephalopathy, and peripheral arteriopathy. **Objective:**This comprehensive review aims to elucidate the complex interplay between OS and DM, providing a thorough understanding of the underlying mechanisms and highlighting emerging therapeutic interventions for the management of OS-related complications in DM. It also explores novel antioxidant-based therapies aiming at specific OS markers and developing personalized interventions, which represents a promising avenue for enhancing treatment efficacy in DM. **Method:**The search was conducted on scientific databases and web portals such as PubMed, ScienceDirect, Web of Science, Embase, Google Scholar, EBSCO, DOAJ, *etc*. **Conclusion:**In conclusion, OS and DM are related through a dynamic and intricate interaction involving genetic, molecular, and environmental variables. Interdisciplinary approaches hold the potential to uncover novel biomarkers for early detection, prognosis, and oriented therapeutic interventions, thereby revolutionizing the clinical management of DM-related complications. With research continuing to advance and customized treatments being more widely incorporated into clinical practice, there is hope that the impact of OS-related DM complications will be significantly mitigated in the future. Despite notable progress, certain unexplored facets necessitate deeper investigations into the precise mechanisms through which OS exacerbates the progression of DM.

Keywords: Oxidative stress, Diabetes mellitus, Reactive oxygen species, Insulin resistance, Diabetic complications.

1. INTRODUCTION

A physiological state known as oxidative stress (OS) is defined by an imbalance between the body's ability to neutralize reactive oxygen species (ROS) and the amount of ROS it produces. ROS are very reactive substances that can damage deoxyribonucleic acid (DNA), proteins, and lipids. Examples of these molecules are superoxide radicals, hydrogen peroxide, and hydroxyl radicals[1]. Under normal conditions, the body possesses an advanced defense mechanism that includes enzymes, antioxidants, and other substances to offset the damaging effects of ROS. On the other hand, OS develops when the body's ability to combat ROS is outmatched by their creation. This condition can cause tissue damage and cellular dysfunction and contribute to the onset and advancement of a number of diseases, including DM[2] (Figure 1).

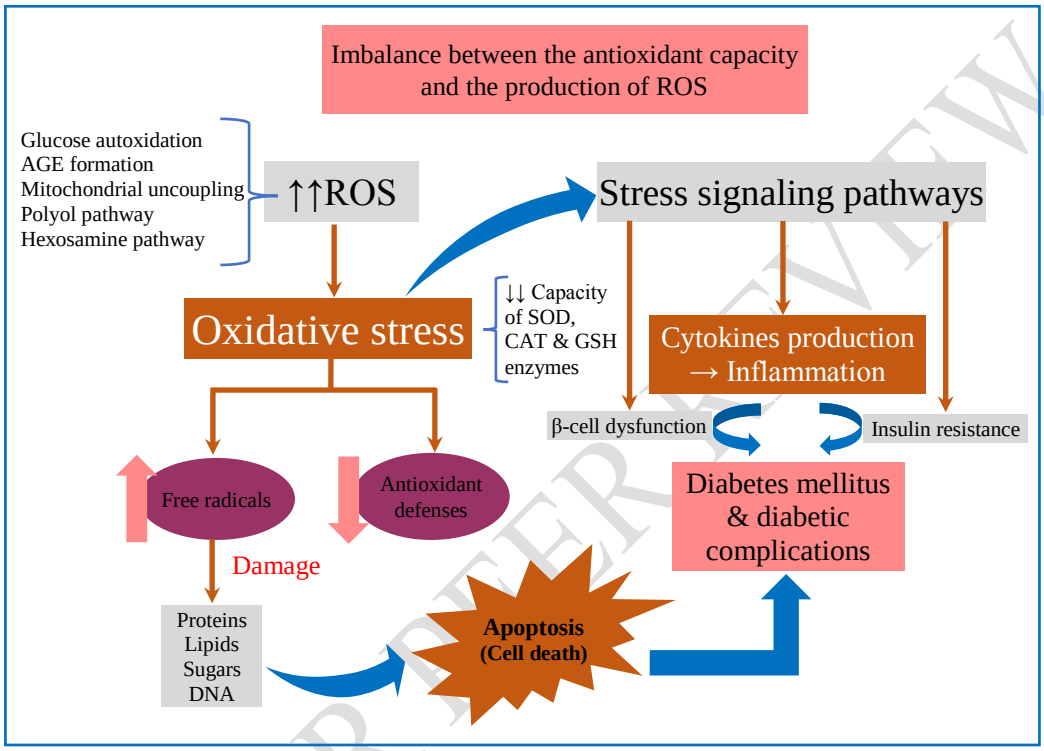

Fig. 1. Relationship between OS and DM:A physiological state known as OS is defined by an imbalance between the body's generation of ROS and its capacity to counteract them with antioxidants. This condition can lead to cellular malfunction and tissue damage, which can initiate and worsen a variety of diseases, including diabetes mellitus and its complications.

Within the context of DM, OS is a major player in the disease's aetiology. It has a strong connection to the emergence of DM issues, beta-cell malfunction, and insulin resistance. In order to develop oriented treatment strategies to reduce the consequences of OS, it is imperative to understand how OS affects the progression and complications of DM[3,4]. We attempted to clarify the intricate relationship between OS and DM in this comprehensive review, offering a clear grasp of the underlying mechanisms and highlighting recently developed therapeutic approaches for the treatment of complications in DM related to OS.

2. THE ROLE OF OS IN DM DEVELOPMENT

DM develops primarily as a result of oxidative damage. ROS are produced in excess due to several mechanisms, such as mitochondrial malfunction and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity[5]. Consequently, lipid peroxidation (LPO), protein modification, and DNA damage cause cellular destruction. Important components in the pathophysiology of DM, insulin resistance, and decreased beta-cell activity are caused by these processes[6]. To create oriented therapy solutions, it is imperative to comprehend these complex systems.

2.1 Mechanisms of OSgeneration

A complicated web of biological processes that result in the body producing too many ROS is what causes OS[7]. Several mechanisms contribute to the generation of OS in the context of DM (Figure 2).DM-related OS is caused by a variety of factors. ROS generation is increased by mitochondrial malfunction, and oxidative damage is intensified by advanced glycation end products (AGEs). Increased ROS levels are caused by elevated NADPH oxidase activity, and the oxidative load is increased by activating the polyol pathway. Importantly, disturbances in the balance of metal ions and inflammatory pathways work together to cause damage to cells and advance issues associated with DM[7,8]. Generally termed the "powerhouses" of the cell, mitochondria are essential for oxidative phosphorylation, the process that produces energy in cells. But they also contribute significantly to ROS production. High blood sugar in diabetics can cause mitochondrial malfunction, which raises the generation of ROS[9]. AGEs can develop as a result of elevated blood glucose levels, arising from the chemical process between carbohydrates and proteins. These molecules cause direct tissue damage and induce the formation of ROS, contributing to OS[10]. NADPH oxidase, an enzyme complex producing superoxide radicals, sees elevated activity in DM, leading to increased ROS synthesis, especially impactful in vascular tissues due to its role in endothelial dysfunction[11]. The polyol pathway, an additional glucose metabolism mechanism, results in sorbitol and fructose accumulation in DM, exacerbating OS by utilizing NADPH, necessary for antioxidant production[12]. In DM, chronic inflammation characterizes the activation of cyclooxygenase and lipoxygenase, contributing to ROS formation through inflammatory pathways[13]. Transition metals like iron and copper, imbalanced in DM, catalyze processes like Fenton and Haber-Weiss, further generating damaging radicals[14].

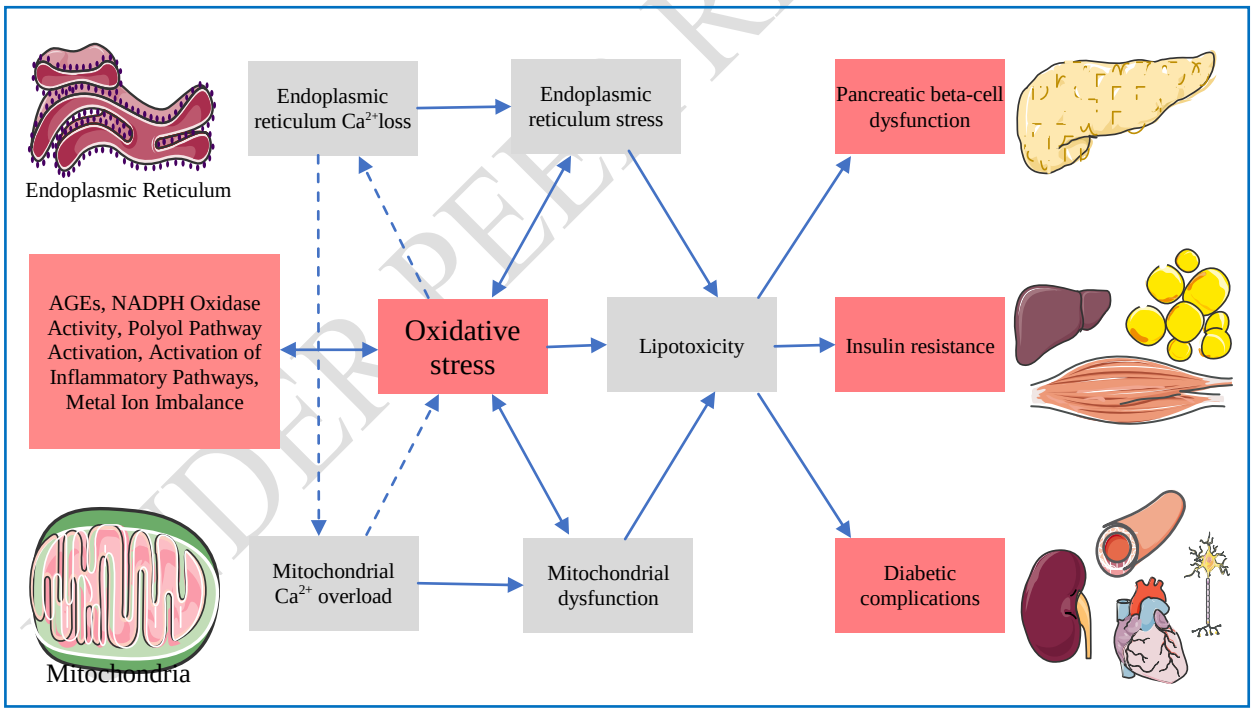

Fig. 2.The suggested mechanism through which OS is produced in relation to diabetic complications: Endoplasmic reticulum stress-induced lipotoxicity and mitochondrial dysfunction are factors that lead to insulin resistance in target tissues, pancreatic β-cell failure, and diabetic consequences.Adopted and modified from Luong *et al.*(2017)[7]**.**

2.2 Cellular damage and dysfunction

The pathophysiology of DM and its consequences is aided by OS, which has deleterious effects on cellular structures and activities. Cell membrane integrity is compromised by LPO. Protein mutation influences the structure and function of the protein, affecting vital biological functions. Mutations and genomic destabilization can result from damage to DNA.

ROS formation is made worse by mitochondrial malfunction, which impairs energy production. Protein folding and cellular equilibrium are interfered with by endoplasmic reticulum (ER) stress. Cellular discomfort is exacerbated by misregulated signaling pathways. DM problems arise from a lack of cellular balance brought on by the cumulative effect[15,16].LPO, induced by ROS, produces lipid peroxides and other hazardous byproducts that can damage cell membrane integrity, potentially compromising cell viability and leading to cell death[17]. Protein amino acids reacting with ROS generate AGEs, nitrotyrosine, and protein carbonyls, causing altered proteins to lose typical structure and functionality, leading to cellular dysfunction[18]. DNA strands suffer direct impact from ROS or secondary reactive species, resulting in degradation, crosslinks, alterations, and strand breakage, potentially causing mutations and genomic destabilization if not properly repaired[19,20]. Mitochondria, major ROS producers, are highly susceptible to oxidative damage, which hampers oxidative phosphorylation and energy synthesis, exacerbating cell malfunction[21]. OS compromising ER function leads to protein misfolding, triggering the unfolded protein response, associated with insulin resistance and dysfunctional beta cells[22]. OS affects cellular signaling pathways involving apoptosis, inflammation, and cellular survival, exacerbating cellular damage and dysfunction[23]. The disruption of cellular homeostasis by cumulative degradation and dysfunction results in altered ion gradients, impaired cellular metabolism, and disturbances in intracellular communication[24].

3. OS BIOMARKERS IN DM

Keeping an eye on biomarkers of OS in DM offers vital information about how the condition advances. An increased oxidative load is indicated by elevated ROS and reactive nitrogen species (RNS). Cellular membrane damage can be physically detected by LPO products[25]. Assessing antioxidant enzyme activity unveils the system's capacity to counteract OS. These biomarkers collectively offer a comprehensive assessment of OS levels, aiding in the development of targeted therapeutic interventions for individuals with DM.

3.1 ROS and RNS linked products

Significant roles are played by highly reactive substances known as ROS and RNS in OS and its consequences for DM[25]. ROS encompass various radicals such as superoxide radicals generated in the mitochondrial electron transport chain during cellular respiration, and by enzymes like NADPH oxidase, xanthine oxidase, and cytochrome P450[26]. Hydrogen peroxide (H_2O_2), though less reactive than superoxide, still poses significant cell harm, produced enzymatically or via superoxide dismutation[27]. Hydroxyl radicals ($^{\bullet}OH$) are produced via the Fenton and Haber-Weiss reactions, which involve transition metals like iron and copper, and are the most aggressive and damaging ROS[28]. RNS include nitric oxide (NO), crucial for signaling and vasodilation but can combine with superoxide under OS, forming peroxynitrite ($ONOO^-$)[29], a potent oxidant causing inflammation and cellular damage[30].As previously stated, this particular enzyme complex plays a significant role in the formation of superoxide. It is activated in OS circumstances and participates in multiple cellular functions[31]. The two most important isoforms of nitric oxide synthase (NOS) in relation to DM are endothelial NOS (eNOS) and inducible NOS (iNOS). They generate NO, which may be part of pathways that are harmful or beneficial[32,33]. The Mitochondrial electron transport chain (METC), especially during malfunction, becomes a substantial ROS source via superoxide production from oxidative phosphorylation electron leakage. Inflammatory cells like neutrophils and macrophages produce ROS as part of the immune response, intensifying DM-related inflammation and tissue damage.METC is a major ROS source, especially when there is mitochondrial malfunction. Superoxide can be produced when oxidative phosphorylation involves electron leakage[34].ROS can be produced by inflammatory cells as a component of the immune response, including neutrophils and macrophages. This exacerbates DM-related inflammation and tissue damage[35].

3.2 LPOproducts

One important mechanism by which OS damages cellular structures is LPO. It involves the oxidative breakdown of lipids, especially polyunsaturated fatty acids, which produces a number of hazardous byproducts. LPO products are a major cause of tissue damage and

cellular dysfunction in the context of DM[36]. One of the most widely recognized and extensively researched byproducts of LPO is malondialdehyde (MDA). It is produced when polyunsaturated fatty acids break down and is a trustworthy indicator of OS. Elevated peroxidation of lipids and oxidative deterioration are indicated by elevated MDA levels[37].Another extremely reactive aldehyde produced during LPO is 4-hydroxy-2-nonenal (4-HNE). It can interact with proteins, DNA, and different cellular constituents to generate adducts that impede function and change the structure of the cell. 4-HNE has been linked to a number of degenerative diseases, such as DM[38].Isoprostanes (IsoPs) are substances that resemble prostaglandins and are created when arachidonic acid undergoes non-enzymatic peroxidation. They function as trustworthy indicators of OS and LPO in biological tissues. DM patients have higher-than-normal quantities of IsoPs in their bodies[39].LPO produces the highly reactive and deadly chemical acrolein. It has the ability to react with DNA and proteins, causing damage to DNA and malfunctioning of cells. DM and other disorders linked to OS have been linked to elevated levels of acrolein[40].Lipid hydroperoxides are the early phases of the oxidative destruction of lipids and are intermediate products of LPO. They have the ability to interact further with other parts of the cell, intensifying the harmful consequences of OS[41].The oxidized counterparts of cholesterol are called oxysterols. They are created when interactions with ROS occur, and they can negatively impact cell membranes by changing their permeability and fluidity[42].

3.3 Antioxidant enzymes

The body's defense against OS depends on antioxidant enzymes because they neutralize ROS and prevent them from damaging cells. Changes in these enzymes' activity can have a major effect on the equilibrium between antioxidant defense mechanisms and OS in the context of DM[6]. Superoxide dismutase (SOD) is in charge of converting superoxide radicals into less dangerous compounds like oxygen (O_2) and H_2O_2. SOD comes in a variety of isoforms, including extracellular SOD (Ec-SOD), mitochondrial SOD (Mn-SOD), and cytosolic SOD (Cyt-SOD). They are dispersed throughout different cellular compartments to focus on particular sources of superoxide generation[27].One enzyme that helps break down H_2O_2 into water (H_2O) and O_2 is called catalase, and it is present in peroxisomes. Particularly in areas with high metabolic activity, it acts as an essential defense against the detrimental effects of accumulating H_2O_2[43].Reduced glutathione (GSH) is used as a cofactor by glutathione peroxidase (GPx) enzymes to lower lipid hydroperoxides and H_2O_2. This process changes GSH into its oxidized form glutathione-disulfide (GSSG), which is then regenerable by other enzymes, such as glutathione reductase. GPx enzymes play a critical role in limiting the buildup of hazardous peroxides[44].The thioredoxin framework, which is made up of the essential enzyme thioredoxin reductase, is responsible for preserving the redox balance of cells. It does this by facilitating the reduction of oxidized thioredoxin, which allows it to participate in antioxidant defense mechanisms[45].Hemeoxygenase-1 (HO-1) is an essential component of cellular defense against OS, despite not being a traditional antioxidant enzyme. It breaks down heme to release iron, carbon monoxide, and biliverdin. These metabolites exhibit strong cytoprotective and antioxidant properties[46].One important peroxidase family that is involved in neutralizing peroxides, such as H_2O_2, is called peroxiredoxin. They are extensively dispersed throughout different cellular compartments and are essential elements of the antioxidant defense mechanism[47].

4. OS AND INSULIN RESISTANCE

Insulin resistance is significantly influenced by OS. By preventing the insulin receptor substrate (IRS) from being phosphorylated, which is essential for subsequent signaling processes, it interferes with insulin signaling pathways. It also obstructs insulin-sensitive tissues' ability to absorb glucose, worsening hyperglycemia. All of these complex consequences of OS play a part in the emergence and advancement of insulin resistance, a feature of type 2 DM (T2DM). Comprehending these nuances is essential for focused treatments in the management of DM[48].Once insulin binds to the alpha sections, a number of substrate proteins are phosphorylated, with the IRS proteins proving to be the most significant. This results in the phosphorylation of the beta sections. Phosphorylated IRS proteins are initiated at tyrosine residues and can subsequently initiate two significant signaling cascades. Involved in both gene expression and cell proliferation, the first pathway

produces mitogen-activated protein kinase (MAPK).The second is the insulin metabolic pathway, which is controlled by the phosphatidylinositol-3 kinase (PI3K) pathway. Pyruvate dehydrogenase kinase (PDK) is activated when phosphatidyl inositol 3,4,5 trisphosphate (PIP3) is produced as a result of PI3K's phosphorylation of phosphatidyl inositol 4,5 bisphosphate (PIP2). PDK phosphorylates and activates Protein Kinase-B (PKB; often referred to as AKT), which causes the translocation of the glucose transporter 4 (GLUT4) to the cell membrane, which results in a subsequent glucose influx[49](Figure 3).

4.1 Impact on insulin signaling pathways

One of the main characteristics of T2DM is insulin resistance, which is characterized by a decrease in the cellular reactivity to the insulin signal. Insulin resistance is made worse by OS, which has a significant impact on the insulin signaling pathways. Insulin typically binds to its receptor and sets off a cascade of phosphorylation events that lead to the activation of signaling molecules downstream. These early phosphorylation activities are susceptible to disruption by OS, which hinders the activation of later signaling pathway components[50]. Insulin receptor signals are transmitted to downstream effectors through the critical intermediates, IRS proteins, in the insulin signaling cascade. Insulin signaling is inhibited when serine phosphorylation of IRS proteins occurs due to OS. This occurs because the IRS proteins are unable to bind to the insulin receptor. AKT, often referred to as PKB, is activated by the essential enzyme PI3K in the insulin signaling cascade. For most of the metabolic effects of insulin, AKT is an essential mediator. Reduction of AKT activation and decreased glucose absorption can result from PI3K inhibition caused by OS[51,52].

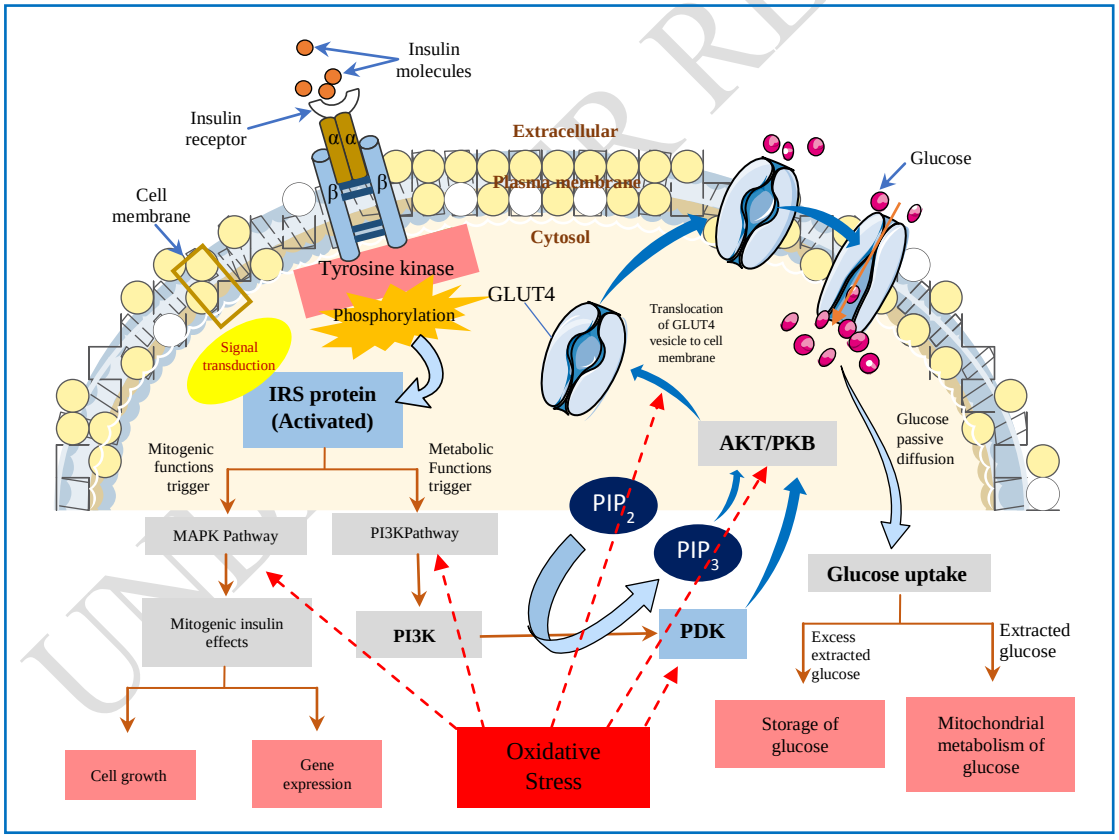

Fig.3.Insulin signaling pathways affected by OS:Tyrosine residues are the site of phosphorylation, and after that, phosphorylated IRS proteins can activate two important signaling pathways. First pathway leads to MAPK, being involved in cell growth and gene expression. The second is the PI3K pathway, that is in charge of insulin's metabolic function. OS disrupts both insulin signaling pathways by impeding tyrosine phosphorylation of the IRS, crucial for downstream signaling events. Additionally, it interferes with glucose uptake in insulin-sensitive tissues, further exacerbating hyperglycemia.

Muscle and adipose tissue in particular are insulin-sensitive cells, and GLUT4 is in charge of promoting glucose transport into these cells. The normal translocation of GLUT4 to the cell

membrane is disrupted by OS, which lowers glucose absorption and increases the risk of hyperglycemia. Activation of specific PKC isoforms can result from elevated OS levels. By encouraging the phosphorylation of IRS proteins in an inhibitory manner and interfering with downstream signaling events, this can obstruct insulin signaling[53].Chronic inflammation is a key component of insulin resistance and is closely associated with oxidative damage. Insulin signaling pathways can be directly disrupted by inflammatory cytokines and messenger molecules that are triggered by OS. Diacylglycerol (DAG), one lipid intermediary that can accumulate as a result of OS-induced mitochondrial malfunction, can activate PKC theta and disrupt insulin signaling[53,54].

4.2 Disruption of glucose uptake

Interfering with glucose uptake into insulin-sensitive cells is one of the main ways that OS leads to insulin resistance in DM. The two main sites of insulin-mediated glucose uptake, skeletal muscle and adipose tissue, are the primary targets of this disturbance. The major glucose transporter in muscle and adipose tissue that facilitates insulin-stimulated glucose absorption is called GLUT4[55]. Normally, insulin causes GLUT4 to move from intracellular vesicles to the cell membrane, which opens the door for glucose to enter the cell. This translocation pathway is hampered by OS, which lowers GLUT4's availability at the cell surface. OS disrupts essential elements of the insulin signaling cascade, as was previously mentioned. This disturbance directly impacts the proteins involved in vesicle trafficking and GLUT4 translocation, in addition to reducing AKT activation and impairing downstream effector phosphorylation[55,56].

Lipid intermediates like DAG and ceramides can build up as a result of mitochondrial malfunction brought on by OS. These lipid compounds cause insulin resistance by interfering with insulin signaling pathways. They may also cause the activation of protein kinase C isoforms, which further suppresses the effects of insulin. Chronic inflammation is linked to elevated levels of OS and is a major contributor to insulin resistance. Adipose tissue releases adipokines and inflammatory cytokines that can obstruct insulin signaling and impair the absorption of glucose[57].ER stress, which is defined by the build-up of misfolded proteins in the ER, can be brought on by OS. GLUT4 translocation can be decreased, and insulin signaling is hampered by ER stress. The synthesis of ATP can be hindered by damage to mitochondria caused by OS. Insulin resistance may worsen as a result of the decreased energy available for the transport and metabolism of glucose. Insulin sensitivity and glucose metabolism are significantly influenced by adipose tissue. Dysfunctional adipocytes, which release adipokines and cytokines that obstruct insulin signaling and glucose absorption, can be brought on by OS[58].

5. COMPLICATIONS OF DM MEDIATED BY OS

One major factor in problems with DM is OS. It is the underlying cause of cardiomyopathy, altering the heart's structure and function. Deficits in sensation and motor function result from oxidative damage to nerve cells, which causes neuropathy. Increased OS causes renal tissue damage in nephropathy. Cerebral OS causes encephalopathy, which affects cognitive function. The oxidative damage to blood vessels that results in peripheral vascular disease impairs blood flow. In conclusion, retinopathy presents as oxidative damage to the retina, endangering one's vision[59]. It is essential to comprehend these complexities in order to mitigate issues related to DM (Figure 4).

5.1 Cardiomyopathy

DM significantly increases the risk of cardiovascular problems, which are mostly brought on by OS. Stress reduces the availability of NO, which prevents arterial dilatation and inhibits endothelial function. OS-induced LDL oxidation speeds up the course of atherosclerosis, which is characterized by the accumulation of arterial plaque. This process promotes inflammation, the recruitment of monocytes, and the production of foam cells. Increased vascular resistance, decreased vasodilation, and renin-angiotensin-aldosterone system (RAAS) activation are the main causes of hypertension, which is frequent in people with DM[60,61].The heart is prone to oxidative damage, which can result in remodelling and

fibrosis, as well as impaired contractility and relaxation. The activation of platelets increases the risk of thrombosis. ROS-induced vascular inflammation attracts leukocytes, worsening the condition. Oxidative nerve damage causes autonomic neuropathy, a frequent DM consequence that impairs heart rate regulation. This increases the risk of arrhythmia and causes irregular heart rate variability. Additionally, OS reduces coronary flow reserve, which makes it more difficult for the heart to get enough blood while under stress or exercising. These results highlight the critical role that OS plays in DM-related cardiomyopathy and its associated consequences[61].

5.2 Neuropathy

OS plays a major role in the development of diabetic neuropathy, a condition marked by nerve damage. Particularly vulnerable to OS-induced mitochondrial dysfunction, which impairs synaptic function and energy production, are nerve cells. An accumulation of dangerous oxidative molecules brought on by overzealous antioxidant defenses directly damages cellular components and impairs neuronal function[62,63]. Furthermore, endothelial dysfunction brought on by OS exacerbates nerve injury by reducing blood flow. The development of neuropathy is significantly influenced by OS-induced inflammation, which is exacerbated by immune cells and inflammatory mediators.High blood sugar causes AGEs to develop, which worsen nerve function even further. Neural signal transmission is disrupted by OS-induced structural changes such as demyelination and axonal degeneration, leading to impairments in motor and sensory functions. Inequalities in neurotrophic factors, which are essential for the survival of nerve cells, exacerbate nerve injury. Furthermore, neuropathic pain—a prevalent sign of diabetic neuropathy—is exacerbated by OS, which alters pain perception pathways. Pain sensitization is caused by changes in neurotransmitters and increased inflammation[62].

5.3 Nephropathy

OS has a major role in diabetic nephropathy, a condition marked by kidney damage and decreased function. Under these conditions, pro-oxidant and antioxidant components in the glomeruli are out of balance, which causes oxidative damage and poor filtration. The progression of nephropathy and structural alterations are associated with activation of the fibrotic pathway and inflammatory responses[64]. Moreover, RAAS activation brought on by OS increases blood pressure and exacerbates renal impairment. The damage caused by OS impairs the function of podocytes, which are essential for filtration.Glomerular enlargement and the onset of nephropathy are caused by mesangial cell dysfunction. Damage to intracellular signaling networks results in malfunctioning cells and compromised repair systems. The AGEs produced by elevated glucose levels worsen inflammation and oxidative damage. Damaged components accumulate, and kidney damage gets worse as a result of OS's disruption of autophagy. Nephropathy is made worse by microvascular injury, which reduces oxygen and blood supply to the kidneys. These complex processes highlight how important OS is to diabetic nephropathy[65].

5.4 Retinopathy

OS is a major factor in diabetic retinopathy, which is defined by retinal blood vessel destruction and possible visual loss. Microvascular injury and fluid leaking into surrounding tissue are caused by this stress, which impairs endothelial cell function. High blood sugar causes AGEs to accumulate in the retinal tissues, which furthers the retinopathy's progression by causing OS, inflammation, and cellular damage[66]. Retinal edema is a result of blood and fluid leaking from damaged blood-retinal barriers, which increases vascular permeability. Damage to the retina is exacerbated by OS, which triggers inflammatory reactions that draw immune cells and release cytokines that promote inflammation. It is possible for ischemia to cause neovascularization; however, the retinopathy may worsen since these new arteries are frequently brittle and can burst.Contributing to visual impairment are retinal ganglion cell dysfunction and apoptosis, which are essential for the transmission of visual signals. Because OS causes an increase in vascular endothelial development factor, this may exacerbate damage by encouraging the creation of new blood vessels. Further

damage to retinal tissue results from OS's disruption of the regulation of retinal blood flow, which exacerbates ischemia-reperfusion injury. These results highlight how important OS is to the onset and course of diabetic retinopathy[67].

5.5 Encephalopathy

OS is intimately associated with encephalopathy, a disorder characterized by malfunction of the brain, especially in circumstances such as DM. The brain is more vulnerable to oxidative injury when glucose levels are high and antioxidant defenses are weakened. Because of their lipid-rich makeup and high metabolic activity, neurons are especially susceptible to the effects of ROS and RNS. This oxidative assault compromises cellular homeostasis, which results in decreased energy production, mitochondrial malfunction, and an ongoing cycle of ROS formation[68]. Furthermore, inflammation brought on by OS plays a major role in the onset and development of encephalopathy.Neuroinflammation is sparked by the upregulation of inflammatory mediators, including chemokines and cytokines, which exacerbates damage to neurons. OS can also weaken the blood-brain barrier, which is an important protective interface, and can let potentially hazardous compounds into the brain environment, which can lead to encephalopathy. Acknowledging the complex interactions between OS and encephalopathy is essential to designing focused treatment approaches to reduce brain dysfunction in both DM and other neurological conditions with increased oxidative load[68,69].

5.6 Peripheralarteriopathy

OS and peripheralarteriopathy are closely related, especially in the case of lower limb wounds. Long-term high glucose levels and weakened antioxidant defenses in diseases like DM foster an atmosphere that encourages oxidative damage to the peripheral vasculature. ROS and RNS have a particularly negative effect on endothelial cells, which are essential for vascular function. This oxidative attack compromises vasodilation, creates atherosclerotic plaque, and interferes with endothelial function[70]. Furthermore, inflammation brought on by OS plays a major role in the advancement of peripheralarteriopathy. Inflammatory mediators worsen endothelial dysfunction and encourage a milieu that is pro-inflammatory and favours atherogenesis. Additionally, soft muscle tissues in the vessel walls are directly impacted by OS, which promotes their growth and narrows the vessels. Furthermore, LPO brought on by OS intensifies the development of atherosclerotic plaque. Understanding the critical role that OS plays in the aetiology of peripheralarteriopathy is essential for creating focused treatment plans to reduce vascular consequences, particularly in patients with diseases like DM that have an elevated oxidative load[71].

6. ANTIOXIDANT DEFENSE SYSTEM

Protection against oxidative damage is provided by antioxidant defense systems in cells. Protecting the body from damaging ROS are endogenous antioxidants, such as SOD. Fruits and vegetables, which are rich in dietary antioxidants, help to protect the body from OS by restocking the antioxidant reservoir in the body [2] (Table 1).

6.1 Endogenous antioxidants

The body spontaneously produces endogenous antioxidants, which are vital for preserving redox balance and counteracting damaging ROS. The defense of tissues and cells against oxidative damage depends on these antioxidants [72]. Superoxide radicals are transformed into less dangerous molecules like H_2O_2 and O_2 by the catalyst action of SOD, a major endogenous antioxidant enzyme. SOD is found in multiple forms in different parts of the cell. These forms include extracellular SOD (Ec-SOD), mitochondrial SOD (Mn-SOD), and cytosolic SOD (Cyt-SOD)[26]. The essential enzyme catalase also functions in cellular peroxisomes. It helps to break down H_2O_2 into O_2 and H_2O, avoiding the buildup of this potentially dangerous molecule [43]. The GPx enzymes are a class of selenium-dependent enzymes that decrease H_2O_2 and lipid hydroperoxides by using GSH as a cofactor. This enzymatic process shields cells from oxidative harm [44]. This enzyme is necessary for the recycling and regeneration of GSH from GSSG, which is the oxidized form of this amino acid.

This recycling mechanism helps glutathione keep on acting as an effective cellular antioxidant [73]. Thioredoxin, thioredoxin reductase, and NADPH make up the thioredoxin system. It is essential for preserving the redox equilibrium within cells. By catalyzing the reduction of oxidized thioredoxin, thioredoxin reductase enables thioredoxin to take part in antioxidant defense mechanisms [74]. These proteins play a role in controlling the amount of iron that cells contain. They aid in preventing the production of hazardous ROS via Fenton reactions, which might end up in oxidative damage, by sequestering iron [75]. Heme, which is created when red blood cells break down, is broken down into bilirubin. It functions as a strong natural antioxidant that has the ability to counteract free radicals [76]. The natural result of purine metabolism is uric acid. Uric acid possesses antioxidant qualities and can aid in the neutralization of specific ROS forms, regardless of its link to gout [77].

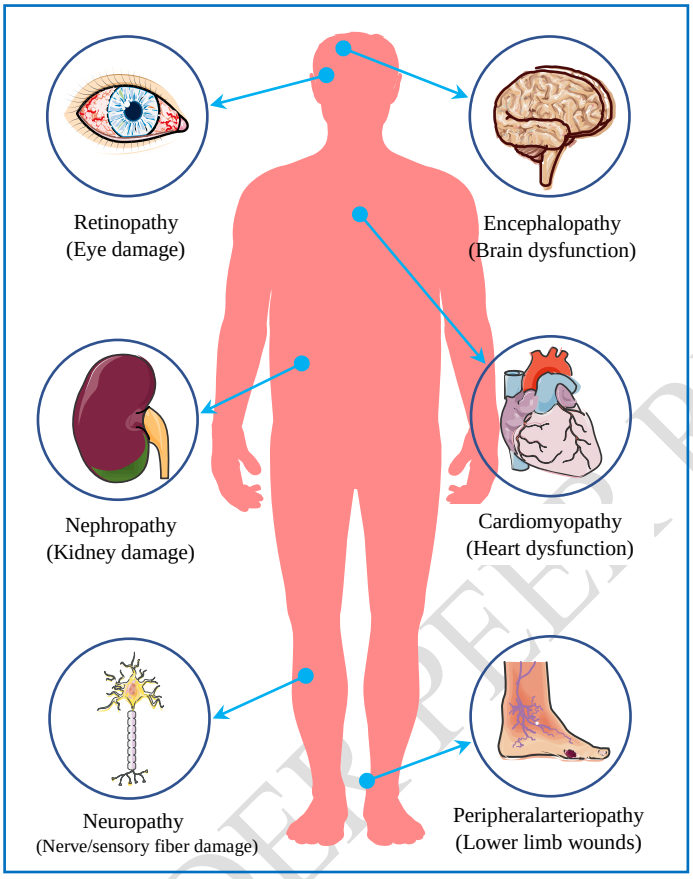

Fig.4. Diabetic complications caused by OS:OS underlies retinopathy, causing oxidative injury to the retina, threatening vision. Cardiomyopathy manifests as structural and functional changes in the heart. Neuropathy arises from oxidative damage to nerve cells, leading to sensory and motor deficits. Nephropathy involves renal tissue injury due to increased oxidative load. Encephalopathy results from cerebral OS, impacting cognitive function. Peripheralarteriopathyarises from oxidative damage to blood vessels, compromising circulation.

6.2 Dietary antioxidants

Dietary antioxidants are substances present in a wide range of foods that, by scavenging dangerous ROS and free radicals, can aid in shielding cells from oxidative damage. A person's general health and well-being can be enhanced by consuming a range of foods high in these antioxidants [78]. As a strong water-soluble antioxidant, vitamin C (ascorbic acid) can be found in citrus fruits (lemons, oranges), berries (strawberries, kiwi), leafy greens (kale, spinach), and bell peppers. It replenishes vitamin E, scavenges free radicals, and boosts immunity [79]. Rich sources of vitamin E (tocopherols and tocotrienols) include nuts (almonds, hazelnuts), seeds (pumpkin, sunflower), spinach, and vegetable oils (safflower, sunflower). This lipid-soluble antioxidant shields cell membranes from LPO [80]. Generally, orange fruits and vegetables, including carrots, sweet potatoes, and mangoes, are rich in beta-carotene, a precursor of vitamin A. It is an effective antioxidant that supports cell damage prevention [81].

Whole grains, chicken, fish (tuna, halibut), Brazil nuts, and fowl are good sources of selenium, a trace mineral. It is an important part of selenoproteins (SEP_S), which are necessary for antioxidant defense and include glutathione peroxidases [82]. Plant chemicals known as flavonoids are a varied class that feature antioxidant capabilities. Foods such as citrus fruits, onions, apples, tea, and berries (strawberries, blueberries) contain flavonoids. There are several health advantages, and flavonoids assist in scavenging free radicals [83]. Foods high in polyphenols include red wine, berries, grapes, dark chocolate, and green tea. They support general health since they have strong anti-inflammatory and antioxidant effects [84]. Lycopene, a red pigment, is abundant in watermelon, pink grapefruit, and tomatoes. It is a potent antioxidant that is well-known for helping to lower the risk of a number of chronic ailments, including heart disease and several types of cancer [85]. Fish, whole grains, and organ meats are good sources of coenzyme Q10 (ubiquinone). It is an essential part of the mitochondria's electron transport chain and functions as an antioxidant to shield cells from oxidative damage [86]. Meat, shellfish, nuts, and seeds are among the foods that contain zinc, a trace mineral. It is a crucial part of the enzymes that defend against free radicals and repair DNA [87]. Anthocyanins are pigments that can be found in purple, blue, and red fruits and vegetables, such as grapes, eggplants, and berries. They give these meals their vivid colours and have potent antioxidant qualities [88].

Table1. Types of antioxidants in defense system:(a) endogenous antioxidants which are produced within the body and neutralize harmful ROS, and (b) dietary antioxidants which bolster its ability to counteract OS[89]**.**

Types of antioxidants in defense system	
Endogenous Antioxidants	**Dietary Antioxidants**
Superoxide dismutase	Vitamin C & E
Catalase	Zinc
Glutathione peroxidase	Beta-carotene
Glutathione reductase	Selenium
Thioredoxin system	Flavonoids
Ferritin and heme oxygenase	Polyphenols
Bilirubin	Lycopene
Uric acid	CoenzymeQ10

7. THERAPEUTIC INTERVENTIONS

Numerous treatment options, including antioxidant supplements, lifestyle adjustments, and pharmaceutical therapies, have been investigated in the quest to mitigate OS in DM.

7.1 Antioxidant supplementation

In order to strengthen the body's natural defenses against OS, antioxidant supplementation refers to the use of exogenous antioxidants through food, supplements, or pharmaceuticals. Coenzyme Q10, beta-carotene, selenium, vitamins C and E, and other nutrients are common antioxidant supplements. These supplements come in a number of formats, including liquid extracts, pills, and capsules. Supplementing with antioxidants may help lessen oxidative damage and lower the chance of developing some chronic illnesses linked to high OS levels[90]. Conditions including age-related macular degeneration, some malignancies, and cardiovascular disease fall under this category. Researchers are still studying the efficacy of antioxidant supplements. While several studies point to possible dangers or no discernible effects at all in some populations, others indicate potential advantages. It's crucial to speak with a healthcare professional before beginning any antioxidant supplementation program because taking too much of some antioxidants can have negative consequences[91].

7.2 Lifestyle modifications

The management of OS and the mitigation of related problems are greatly aided by changes in lifestyle. Antioxidants and vital nutrients can be obtained by eating a balanced diet full of whole grains, fruits, vegetables, and lean meats. It also promotes general health by reducing OS. Active living can help lower OS and improve general well-being. Its benefits include improved cardiovascular health and strengthened antioxidant defense mechanisms. Both OS and chronic stress are related[92]. Its effects can be lessened by putting stress-reduction strategies like deep breathing exercises, mindfulness training, and meditation into practice. The two main causes of OS are smoking and binge drinking. The amount of OS that the body experiences can be greatly decreased by giving up smoking and consuming alcohol in moderation. The body's natural healing processes, which include those involving OS, depend on getting enough good sleep. To promote general health, try to get between seven and nine hours of sleep each night[92,93].

7.3 Pharmaceutical approaches

Medications or other treatments created specially to address OS and its related problems are used in pharmaceutical techniques. Certain pharmaceuticals either increase the body's natural antioxidant defenses or function as direct antioxidants. These include alpha-lipoic acid, N-acetylcysteine (NAC), and specific metal chelators. OS and inflammation are strongly connected. Medications that reduce inflammation, such as anti-inflammatory medicines or nonsteroidal anti-inflammatory drugs (NSAIDs), may be able to lessen the effects of OS.It is necessary to use pharmaceutical therapies designed to target the underlying pathology, depending on the particular OS-related consequence (such as cardiovascular disease or neurodegenerative illnesses). Pharmaceutical strategies must be customized based on each patient's unique medical history, risk factors, and treatment response. Finding the right pharmaceutical interventions requires consulting with a healthcare professional[94].

8. EMERGING RESEARCH AND FUTURE DIRECTIONS

To better understand the intricate connection between OS and DM and to develop targeted, individualized approaches for managing and treating OS-related complications linked to the disease, researchers are focusing on the following areas:

8.1 Novel therapies targeting OS

Novel treatment approaches are being intensively investigated in the quickly developing field of OS research. This involves the investigation of novel antioxidant chemicals that exhibit enhanced bioavailability and specificity in addressing particular forms of ROS, or OS, in discrete cellular divisions. Additionally, efforts are being directed toward creating treatments that target OS and mitochondrial malfunction directly, with possible drugs that protect and improve mitochondrial DNA[95]. To further boost the therapeutic efficiency of antioxidants, research is being done on how well nanoparticles and nanocarriers can carry antioxidants to

specific cellular compartments or tissues, enhance their bioavailability, and stabilize them. Promising advances in gene therapy and editing technologies have the ability to directly modify genes implicated in antioxidant defense systems, which could raise endogenous antioxidant enzyme levels or change pathways connected to OS[96,97]. Furthermore, studies explore bioactive substances derived from plants and other natural sources that possess strong antioxidant capabilities, offering possible treatments for disorders associated with OS. Research on metalloenzymes and redox-active metals aims to regulate OS by means of their therapeutic potential; they may function as modulators of redox signaling pathways or as catalysts for antioxidant processes. Optimizing therapy outcomes may involve customizing interventions based on unique genetic and environmental characteristics. The possible synergistic benefits of combining various antioxidants or antioxidant-based therapies with conventional treatments are being investigated.Developments in biomarker research allow for accurate, personalized evaluation of OS levels, which helps select the right therapies and enable real-time therapy monitoring. Clinical trials assessing new treatments aimed at OS show promise for being incorporated into clinical practice, highlighting the ever-changing field of OS management research and its potential to completely transform the treatment of related illnesses[95,96].

8.2 Personalized medicine in DMmanagement

Precision medicine, also known as personalized medicine, transforms healthcare by considering individual differences in illness susceptibility, progression, and response to therapy. It orients therapies for DM control to the unique features of each patient. Recent advances in genomic and molecular research have identified genetic variants and molecular markers associated with DM risks, subtypes, and treatment outcomes. This information is used in personalized medicine to classify people according to their molecular and genetic profiles[98,99]. Employing genetic and medical information, it determines a person's risk of developing DM. This allows for focused prevention through dietary changes, medication, and close monitoring of individuals who are more vulnerable. DM involves a variety of pathophysiological pathways, which is why customized therapy divides patients into several categories. This method customizes therapy regimens by taking into consideration lifestyle factors, comorbidities, metabolic profiles, and genetic markers. It simplifies the process of choosing a course of therapy for the highest level of tolerance and effectiveness by predicting a person's reaction to particular drugs based on their genetic and metabolic composition[99,100]. Exercise prescriptions and individualized nutrition regimens maximize the suggested intake of food and exercise, respectively. Digital health technologies offer real-time data for dynamic therapy modifications, such as wearables and smartphone apps. Early intervention options are made possible by considering a person's lifetime risk of complications associated with DM. Careful attention is required to ensure informed consent, data security, and ethical adherence in light of ethical and privacy considerations. Personalized medicine promises to improve patient satisfaction, results, and the burden of complications when it is used in DM care, which is a major improvement in clinical practice[100,101].

9. CONCLUSION

DM is often associated with OS, which is defined as an imbalance between the body's antioxidant defense systems and the generation of ROS. Its prevalence is not only associated with hyperglycemia but also affects cellular processes, insulin signaling, and the functioning of key organs through a variety of mechanisms. This imbalance is the starting point for a series of events that eventually result in inflammation, cellular damage, and the emergence of problems like retinopathy, neuropathy, nephropathy, encephalopathy, and cardiomyopathy.The field of DM and OS is constantly developing, and early management and treatment are becoming more and more essential. This entails developing novel treatments that deal with the underlying causes of OS in addition to the specialized utilization of antioxidants and changes in lifestyle. In conclusion, OS and DM are related through a dynamic and intricate interaction involving genetic, molecular, and environmental variables.An understanding of this link lays the groundwork for the creation of focused therapies that could revolutionize the way DM is managed. With research continuing to advance and customized treatments being more widely incorporated into clinical practice, there is hope that the impact

of DM-related complications will be significantly mitigated in the future, ultimately improving the quality of life for millions of people worldwide.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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