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REVIEW ARTICLE

"OXIDATIVE STRESS MARKERS IN TYPE 2 DIABETES MELLITUS"

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Abstract

Insulin resistance and high blood glucose are hallmarks of type 2 diabetes mellitus (T2DM), a serious global health concern. In the pathogenesis of T2DM, oxidative stress—a mismatch between antioxidant defenses and reactive oxygen species (ROS)—is a major factor. The mechanisms causing oxidative stress and its clinical consequences are highlighted in this review, which offers a thorough overview of oxidative stress markers in T2DM. We classify oxidative stress according to its origins, pathways, impacted biomolecules, and related illnesses. We stress the significance of keeping an eye on indicators of oxidative stress, including glutathione (GSH), catalase, advanced oxidation protein products (AOPPs), protein carbonyls, malondialdehyde (MDA), and superoxide dismutase (SOD). Comprehending these indicators is crucial for formulating focused treatment approaches to reduce oxidative stress and enhance clinical results in individuals with T2DM.

Introduction:-

Type 2 diabetes mellitus (T2DM) is a rapidly increasing global health concern that affects millions of people worldwide. T2DM is now acknowledged as a major public health concern that has a big impact on healthcare expenses as well as the general well-being of people [1]. Insulin resistance, a disease characterized by decreased insulin responsiveness and inadequate insulin secretion from pancreatic islet β-cells, is a hallmark of T2DM [2]. As per the World Health Organization (WHO), diabetes mellitus is a chronic metabolic disease characterized by elevated blood sugar levels that last for an extended period of time and have an adverse impact on the heart, blood vessels, eyes, kidneys, and nerves.

The term "oxidative stress" was first used by Helmut Sies in 1985 to describe a state in which pro-oxidants and antioxidants are out of balance and leaning toward each other. Since then, the science has flourished with a wealth of new findings that have revealed intricate details, such as the targets that reactive oxygen species (ROS) can affect and the complex biochemical pathways that determine how cells respond to ROS challenges [7]. As a result, this definition was revised and is now stated as follows: Oxidative stress is a state in which the normal equilibrium of ROS in cells is momentarily or persistently elevated. This leads to disturbances in cellular metabolism and its regulatory mechanisms, which ultimately results in damage to vital cellular constituents [3]. ROS are essential for many biological functions, including migration, differentiation, proliferation, and the control of necrosis and

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apoptosis [4]. Overproduction of ROS causes oxidative stress, which in turn causes oxidative damage to different parts of the cell, such as DNA, lipids, and carbohydrates [5]. Increased blood sugar levels in people with type 2 diabetes (T2DM) cause ROS to be produced through a variety of pathogenic pathways, and coexisting medical conditions may make oxidative damage worse [6].

In this review, we provide a thorough summary of human studies that outline the etiology and pathophysiology of oxidative stress in T2DM, examine different indicators of oxidative stress, and attempt to develop a systematic categorization for this complex phenomenon.

Types of Oxidative Stress

Because ROS are reactive, it is extremely difficult to detect their levels directly in living creatures, whether in laboratory settings or inside cells. Due to the complexity of these species, researchers frequently rely on oblique hints left by ROS-related processes, which creates a great deal of uncertainty and is akin to peeking into the unknown. There is currently no exact way to precisely analyze ROS processes directly [3]. We have only begun to explore the myriad significant roles that ROS play in numerous essential processes. It is also challenging to adequately categorize the many forms of oxidative stress due to their complexity. Aware of these difficulties, we're starting the process of developing a classification system in an effort to increase awareness and clarity in this area. Based on essential elements, two classification schemes have been proposed in an attempt to address this: First, it is temporally based; second, it is intensity/density based. As Figure 1 shows, these two types can be further divided into a number of groups. A categorization system for oxidative stress has also been presented; it is suggested to classify the phenomenon according to multiple characteristics, such as its sources, the mechanisms involved, the biomolecules impacted, or the diseases linked to it. Here are a few typical steps taken to arrive at this classification:

(A) Based on Sources:

1. **Endogenous Oxidative Stress:** Occurs naturally during regular cellular metabolism; the majority of the body's ROS are produced by the mitochondria, for instance. More electrons can leak to oxygen at specific locations (complexes I and III) when the mitochondrial electron transport chain is blocked, producing more $O_2^{\cdot-}$ and H_2O_2. Because of this, certain inhibitors of this chain are employed to induce apoptosis in tumor cells by releasing ROS [8].
2. **Exogenous Oxidative Stress:** Cells can produce more ROS in response to environmental stimuli such as sunshine, metals, cigarettes smoke, allergies, medicines, pollution, pesticides, and bug sprays. This can ultimately result in oxidative stress [9]. Radicals are transformed into organic peroxides by ionizing radiation. These peroxides have additional oxidative effects when they interact with metal ions such as Fe and Cu. After exposure to UV light, riboflavin, porphyrins, and NADPH-oxidase undergo reactions that produce 8-oxo-guanine and lower intracellular glutathione (GSH) levels, which then rise back to normal. Through a variety of processes, heavy metals such as iron, copper, cadmium, nickel, arsenic, and lead cause free radicals, which affect antioxidant enzymes and lipid peroxidation. Lead raises the quantity of glutathione peroxidase and influences the lipid peroxidation of brain tissue. Nitric oxide, superoxide, and peroxides are produced when arsenic is present, but antioxidant enzymes are inhibited. DNA bases can be changed by these processes. Exposure to ozone impairs lung function in both healthy individuals and others by causing inflammation in the respiratory epithelium [10].

(B) Based on Mechanisms:

1. **ROS/RNS (Reactive Oxygen/Nitrogen Species) Production:** Classifying according to the particular ROS/RNS (superoxide anions, hydroxyl radicals, peroxyl radicals, alcoxy radicals, and hydroxyl peroxyl radicals) produced as well as the processes involved in their synthesis [11].
2. **Antioxidant Defense System:** Based on the effectiveness or ineffectiveness of the body's antioxidant defense systems, which comprise repair enzymes, antioxidant chemicals, and antioxidant enzymes [14].

Based on Affected Biomolecules:

1. **Lipid Peroxidation:** Concentrating on lipid oxidative damage and the products of lipid peroxidation [13].
2. **Protein Oxidation:** Centered on changes in structure and function caused by oxidative damage to proteins [13].
3. **DNA Damage:** Taking into account DNA mutations and lesions caused by oxidative stress [12].

Based on Associated Diseases:

1. **Diabetes, cardiovascular diseases, neurodegenerative disorders, and cancer:** Classifying illnesses according to the pathophysiology of which oxidative stress is a major factor [12].

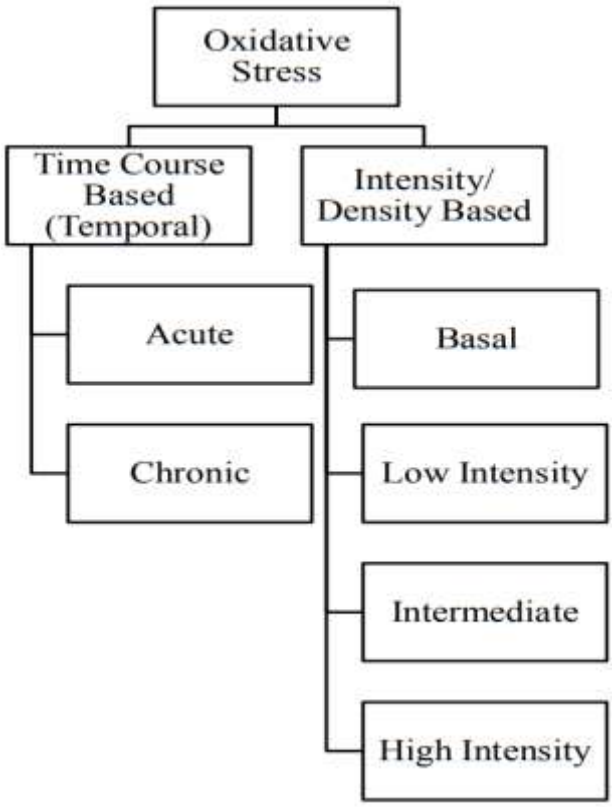

Figure 1:- Types of Oxidative Stress, Based on Two Fundamental aspects.

Time course based (Temporal):

Regarding oxidative stress, the body attempts to keep the steady-state level, or equilibrium of ROS, within a normal range. Acute oxidative stress is caused by sudden spikes in ROS brought on by outside stimuli, but if the body's defenses are robust enough, ROS levels quickly return to normal [15]. However, ROS levels might stay high for extended periods of time if the body is unable to handle this abrupt spike, which can result in chronic oxidative stress. Prolonged stress may activate genes linked to stress and result in long-term alterations. Interestingly, ROS levels can fall below the normal range in a situation known as chronic reductive stress, which is a little more understood [16]. Think of these stress levels as the body's stations; persistent stress might occasionally create a new quasi-stationary level that becomes the new normal. It is helpful to classify these stresses according to their severity, ranging from mild to severe oxidative stress. Severe stress, also known as oxidative distress, overwhelms the body and damages it, whereas mild stress, also known as oxidative eustress, is controllable and causes no harm. The body responds differently to different degrees of stress, which could have long-term consequences [17].

Intensity/ Density based:

The below graph shows the relationship between the dose or intensity of an external factor that initiates the stress response and the levels of oxidative stress. The graph is divided into four areas, each of which represents a distinct degree of oxidative stress depending on the influence of ROS (Reactive Oxygen Species).

1. Region I - Basal Oxidative Stress (BOS): This area displays the body's reaction to low concentrations or dosages of the stressor. In this instance, ROS levels are not much different from the typical range known as the steady-state level. The reason it's dubbed "basal" is that the changes are too tiny to pick up on with the tools available today.
2. Region II - Low Intensity Oxidative Stress (LOS): Measurable alterations in ROS and the body's reaction occur as the stressor's intensity rises. Substances affected by ROS (ROMS) progressively rise, suggesting a reaction to the stressor. In the meantime, after peaking, ROS-inducible ROS-sensitive parameters (ROSISP) first increase before declining. The zero equivalent point (ZEP), which is represented by this drop, denotes the point at which no observed effect (NOE) happens.

3. Region III - Strong Oxidative Stress (SOS): Here, ROSISP levels significantly decline from baseline, indicating a weakened state of the body's antioxidant defenses. The fact that ROMS levels are still rising suggests more oxidative damage.
4. Region IV - Very Strong Oxidative Stress (VOS): Due to widespread inactivation brought on by the elevated ROS levels, ROSISP reaches its lowest values at the stress inducer's maximal dose or concentration. On the other hand, when cellular components vulnerable to ROS alteration run out, ROMS levels surge.

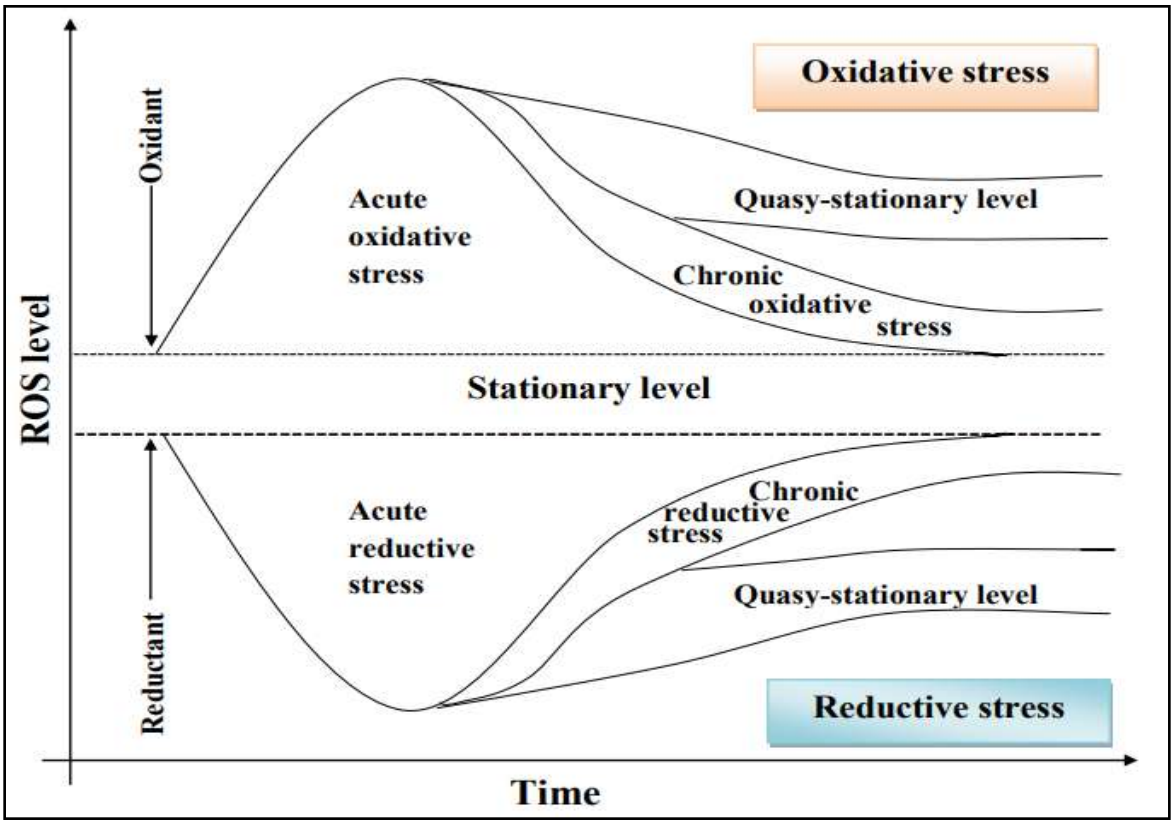

Figure 2:- Time Course Based (Temporal) Oxidative Stress.

Causes of Oxidative Stress in T2DM and its Pathology

The etiology of oxidative stress in type 2 diabetes mellitus (T2DM) is attributed to an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant capacity of the body. There are multiple variables that lead to this condition:

1. Hyperglycemia: Increased blood glucose levels increase the generation of ROS via multiple pathways:

- Glucose auto-oxidation: Extra glucose generates superoxide radicals through non-enzymatic processes.
- Activation of the polyol pathway: This pathway's increased glucose flux weakens antioxidant defenses by reducing NADPH, a vital component for antioxidant renewal.
- Advanced glycation end products (AGEs): The generation of AGEs is a result of hyperglycemia. AGEs interact with their receptors (RAGE) to cause oxidative stress by activating NADPH oxidase and producing superoxide radicals [18].

2. Mitochondrial Dysfunction: One of the main causes of ROS in T2DM is mitochondrial dysfunction. An imbalance in the electron transport chain during oxidative phosphorylation causes electrons to leak and superoxide radicals to develop, which causes an excess of ROS [19].
3. Inflammation: In people with T2DM, persistent inflammation makes oxidative stress worse. Pro-inflammatory cytokines like TNF-α and IL-6 boost the generation of ROS by igniting immune cells and intensifying the oxidative burst meant to eradicate infections. But in the case of diabetes, this results in more ROS buildup and tissue damage [20].

4. Protein Kinase C (PKC) Activation: When PKC is activated by hyperglycemia, NADPH oxidase, a major ROS generator, is upregulated. Additionally, this stimulation causes endothelial dysfunction, which is a prelude to diabetic vascular problems [21].
5. Hexosamine route: Under hyperglycemic circumstances, this route becomes hyperactive and produces UDP-GLCNac, which alters transcription factors and encourages the expression of genes linked to fibrosis and inflammation, hence exacerbating oxidative stress [22].
6. Lipid Peroxidation: Elevated lipid levels in T2DM may experience peroxidation. This process produces malondialdehyde and other reactive aldehydes, which worsen oxidative stress and cause more cellular damage [23].

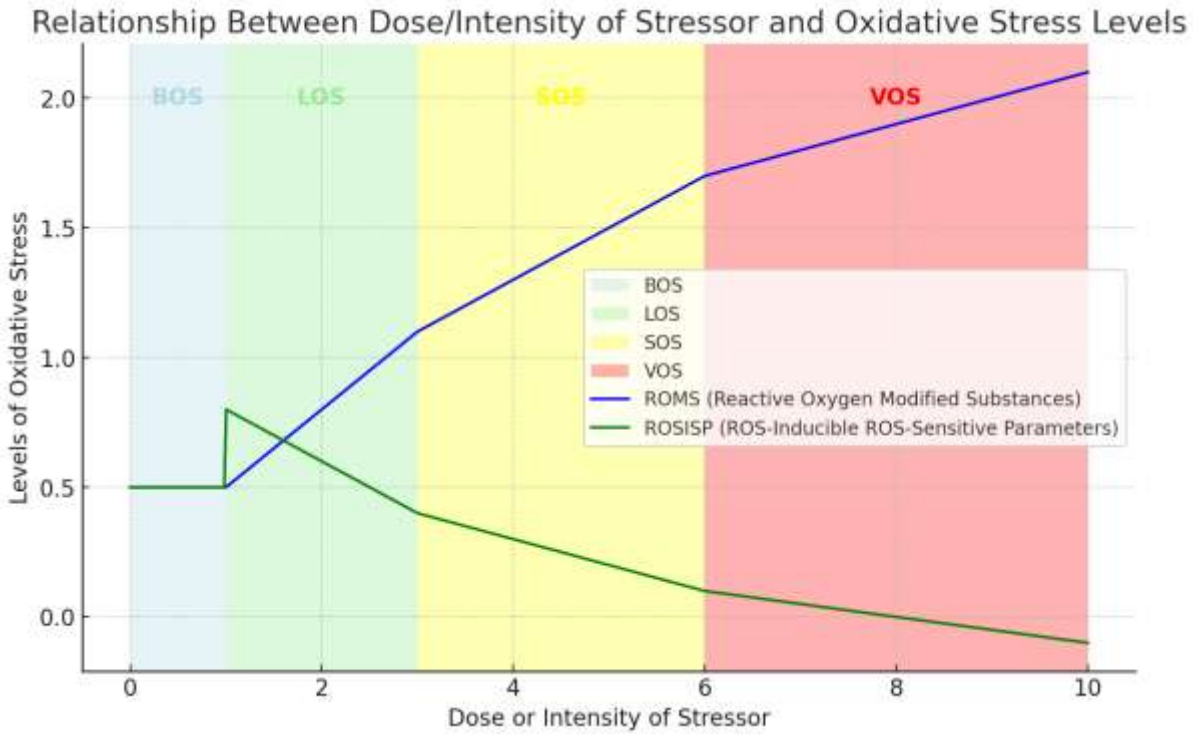

Figure 3:- Intensity/ Density Based Oxidative Stress.

Pathology of Oxidative Stress in T2DM

The deleterious effects of oxidative stress in type 2 diabetes mellitus are extensive and have a substantial influence on numerous organs and systems:

1. ß-Cell Dysfunction: ROS directly harm ß-cells in the pancreas, impairing their ability to secrete insulin and accelerating their death. This leads to a vicious cycle of oxidative stress and ß-cell destruction, exacerbating hyperglycemia [24].
2. Insulin Resistance: Insulin signaling pathways are disrupted by oxidative stress, which leads to insulin resistance. Tissue glucose absorption is hampered by ROS because they block downstream signaling and the insulin receptor substrate (IRS) proteins [25].
3. Vascular Complications:
    - Diabetic Retinopathy: Increased vascular permeability, hemorrhages, and eventually vision loss are caused by oxidative stress damaging retinal blood vessels [26].
    - Diabetic Nephropathy: Proteinuria and progressive renal failure are caused by ROS-induced damage to the glomeruli and renal tubular cells [27].
    - Cardiovascular Diseases: In diabetic patients, oxidative stress greatly raises the risk of cardiovascular events by promoting endothelial dysfunction, atherosclerosis, and hypertension [28].
4. Neuropathy: ROS cause peripheral nerve injury, which results in diabetic neuropathy, a condition marked by pain, numbness, and loss of feeling. Oxidative damage to the nerve cells and supporting tissues acts as a mediator in this [29].

5. Inflammation and Immune Dysfunction: Insulin resistance and ß-cell dysfunction are made worse by low-grade inflammation that is maintained by chronic oxidative stress. Additionally, it suppresses the immune system, which increases the susceptibility of T2DM patients to infections [30].

Markers of Oxidative Stress in T2DM

ROS can be identified by their effects on lipids, proteins, carbohydrates, and nucleic acids, which result in the formation of unique molecules. These substances act as suggestive "markers" or "biomarkers" of oxidative damage since they are specific to the formation caused by ROS activity and cannot be replicated through other processes [31].

In T2DM, oxidative stress is a major factor in the onset and advancement of diabetic complications. Significant indicators of oxidative stress in diabetes circumstances include the following markers:

1. Lipid Peroxidation

One of reactive oxygen species' main targets is lipid peroxidation (ROS). Malondialdehyde (MDA), one of the highly reactive aldehydes produced by the process, damages cell membranes and is regarded as one of the main indicators of oxidative stress. Patients with diabetes have been found to have elevated MDA levels, which may indicate that MDA plays a role in diabetic consequences such as atherosclerosis and neurological diseases [32].

2. Protein Oxidation

ROS can oxidatively modify proteins, resulting in the production of advanced oxidation protein products (AOPPs) and protein carbonyls. Diabetes problems like nephropathy and cardiovascular illnesses are linked to elevated levels of these oxidized proteins. The amount of carbonyl present in proteins is a reliable indicator of oxidative stress since it shows protein damage that might impair cellular processes [33].

3. Glutathione Levels

Reduced levels of glutathione (GSH), an essential antioxidant in cells, are a sign of oxidative stress in diabetes. GSH detoxifies dangerous radicals and aids in maintaining redox balance. Reduced GSH/GSSG (oxidized glutathione) ratios are frequently observed in T2DM, suggesting compromised antioxidant defense and elevated oxidative stress [34].

4. Catalase Activity

The enzyme catalase reduces oxidative damage by breaking down hydrogen peroxide into oxygen and water. Patients with diabetes frequently experience changes in its activity, which adds to the oxidative stress linked to T2DM [35].

5. Superoxide Dismutase (SOD)

Superoxide dismutase (SOD) is an additional essential antioxidant enzyme that facilitates the conversion of superoxide radicals into hydrogen peroxide and oxygen. SOD's importance as a measure of oxidative stress is highlighted by the fact that changes in its activity can impact the oxidative balance in people with diabetes [36].

Conclusion:-

Measuring these biomarkers—MDA, protein carbonyls, AOPPs, GSH, catalase, and SOD—offers important information on the state of oxidative stress in type 2 diabetes mellitus. Keeping an eye on these indicators can aid in comprehending oxidative damage and formulating plans to lessen the consequences linked to diabetes.

The relevance of oxidative mechanisms in the pathophysiology of diabetes and its complications is highlighted by this synthesis of oxidative stress markers in type 2 diabetes mellitus, providing prospective targets for therapeutic intervention.

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