Biotechnology

The role of lipid peroxidation and antioxidant therapies in the management of diabetes and hypertension

H. Kinjir[1*], Alhagie Drammeh[2], Fatima B. Tanimu[3], A. Lawal[4], H. G. Anchau[3] and J. M. Yelwa[3]

[1] Department of Haematology, BGS, Federal College of Veterinary and Medical laboratory Technology, Vom, Plateau state, Nigeria

[2] Chemistry Unit, Division of Physical and Natural Sciences, School of Arts and Sciences, University of The Gambia, Gambia

[3] Department of Scientific and Industrial Research, National Research Institute for Chemical Technology, Zaria, Kaduna State, Nigeria

[4] Department of Veterinary Medicine, Bayero University, Kano, Kaduna State, Nigeria

Correspondence Author: H. Kinjir

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Abstract

Diabetes and hypertension are two of the most widespread global chronic diseases with high morbidity and mortality. Both of the diseases have a strong link with metabolic disorders and lipid metabolism dysregulation. In this review, we explore the intricate relationship between lipid profiles and lipid peroxides and antioxidant profiles in the etiology of diabetes and hypertension. Both of the diseases have elevated levels of low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL) cholesterol as a commonality in the causation of cardiovascular complications. In addition, oxidative stress in the form of excessive ROS production and subsequent lipid peroxidation hastens the disease process. Dysfunctional antioxidant defense systems in the body in the context of diabetes and hypertension further highlight the need for antioxidant therapies. Recent evidence suggests that lipid-modulating and antioxidant therapies targeting specific pathways may be the key to novel disease prevention and improved cardiovascular outcomes. This review integrates the importance of dissecting such intricate pathways towards the development of successful management and therapy paradigms in an attempt to improve patient outcome and reduce the health burden of such chronic diseases. In addition, we emphasize gaps in the literature and present directions for the exploration of personalized therapy interventions based on lipid and antioxidant imbalance.

Keywords: Lipid profiles, Lipid peroxides, Antioxidant defense, Diabetes, Hypertension, Therapeutic interventions, Cardiovascular health

1. Introduction

Two of the most common chronic diseases in the globe are hypertension and diabetes and are significant causes of morbidity and mortality (American Diabetes Association, 2020) [1]. In 2019, according to recent statistics, over 463 million adults had diabetes in the world and hypertension affects nearly 1.13 billion people (International Diabetes Federation, 2019; World Health Organization, 2021). Both of these diseases have a strong link with metabolic disorders such as disruption in lipid metabolism.

Fats, also referred to as lipids, play a key role in the metabolism of the human body as a source of energy and as structural elements in cells' membranes. Disturbance in lipid metabolism as in the conditions of diabetes and hypertension leads to major health complications (Cefalu *et al*., 2019; Goldberg, 2020) [9, 11]. Some of the lipid abnormalities include elevated low-density lipoprotein (LDL) cholesterol levels and decreased levels of high-density lipoprotein (HDL) cholesterol in individuals with such conditions, and this leads to cardiovascular diseases and other complications.

Lipid peroxides, lipid oxidation by-products, contribute to the picture as well. Lipid peroxides are formed due to oxidative stress, a process in which the production of reactive oxygen species (ROS) exceeds the antioxidant defense systems of the organism. Oxidative stress is a common pathological feature in hypertension and diabetes and leads to cellular damage and inflammation (Valko *et al*., 2007) [38]. One must study the pathways of lipid peroxidation and its involvement in disease development in order to develop successful therapy regimens.

Antioxidants play a significant role in neutralising ROS and fighting oxidative stress. Antioxidant defence systems in the human body, including enzymatic and non-enzymatic antioxidants, are typically compromised in diabetic and hypertensive patients. This reduction in antioxidant capacity exacerbates oxidative damage and directs towards the application of antioxidant therapy in the management of such disorders (Halliwell & Gutteridge, 2015) [14].

In 2019, more than 463 million adults suffered from diabetes and this figure is likely to rise in the coming decade. Hypertension affects approximately 1.13 billion individuals and this figure is likely to rise due to rising aging of the population, changes in lifestyle, and rising occurrences of risk factors such as obesity and inactivity. Prevalence levels are highest in Europe, North America, and Southeast Asia where urbanization and changes in lifestyle have resulted in rising occurrences of the two diseases. This study review the intricate relationship between lipid profiles, lipid peroxides, and antioxidant profiles in hypertension and diabetes. This mini

review aimed at providing an insight into the mechanism of such diseases by exploring such linked pathways in an attempt to identify likely targets for better management and therapy.

The review is based on a thorough scrutiny of peer-reviewed articles accessed through PubMed, Scopus, and Web of Science databases. Included articles were selected on the basis of their applicability to lipid metabolism, oxidative stress, and antioxidant therapy in hypertension and diabetes. Clinical trials, meta-analysis, and systematic review published in the last two decades were the inclusion criteria. Priority was given to trials with larger sample size and those reporting statistically significant findings on lipid profiles, lipid peroxidation, and antioxidant therapy.

2. Diabetes and lipid profiles

2.1 Pathophysiology of diabetes

Diabetes mellitus is a chronic metabolic disorder due to defects in insulin secretion, insulin action, or both (American Diabetes Association, 2020) [1]. It affects the metabolism of carbohydrates, fat, and proteins due to impaired insulin function and results in various metabolic derangements. Hyperglycemia over a prolonged duration results in micro and macrovascular complications and increases the risk of cardiovascular diseases and neuropathies (Ceriello *et al*., 2004) [8].

2.2 Lipid metabolism in diabetes

Metabolism of lipid in diabetic patients is typically impaired and results in lipid profile changes. These comprise elevated total cholesterol and triglyceride levels, increased low-density lipoprotein (LDL) cholesterol, and low high-density lipoprotein (HDL) cholesterol (Cefalu *et al*., 2019) [9]. These changes not only exacerbate insulin resistance but also result in oxidative stress, creating a disease advancement cycle (Goldberg, 2020) [11].

Lipid peroxides as by-products of oxidative stress also worsen the problem by inducing endothelial dysfunction and chronic inflammation, both of which are key causes of cardiovascular complications (Valko *et al*., 2007) [38]. Understanding the direct link between oxidative stress and dyslipidemia provides a better integrated approach towards treating diabetes and complications. Dyslipidemia in diabetes has been shown in recent literature to have a significant association with the development of atherosclerosis, a leading cause of morbidity and mortality due to cardiovascular complications in such individuals (Ference *et al*., 2020) [10].

2.3 Clinical implications

The lipid profile disturbance in diabetes has been attributed to an increased risk of cardiovascular diseases including atherosclerosis and coronary artery disease (Bornfeldt & Tabas, 2011) [6]. Pharmacological and lifestyle interventions are successful in controlling the lipid levels and reducing the risk of cardiovascular complications (American Diabetes Association, 2020) [1]. Lipid-lowering medications and statins have been proven to reduce substantially the risk of cardiovascular complications in diabetic patients by correcting their lipid profiles (Kapur & Musaad, 2021).

Table 1: Management strategies for dyslipidemia in diabetes

Management Strategy	Description	Expected Outcomes
Lifestyle Interventions	Diet (low saturated fats, high fiber), exercise, weight loss	Improved lipid profiles, reduced cardiovascular risk
Pharmacological Treatments	Statins, fibrates, niacin, omega-3 fatty acids	Lower LDL cholesterol, higher HDL cholesterol, reduced triglycerides
Blood Glucose Control	Insulin therapy, oral hypoglycemic agents	Reduced risk of complications, improved overall metabolic control
Regular Monitoring	Regular lipid profile checks, HbA1c measurements	Early detection of lipid abnormalities, better disease management

Table 1 illustrates the management strategies for dyslipidemia in diabetes.

3. Hypertension and lipid profiles

3.1 Pathophysiology of hypertension

Hypertension, or raised blood pressure, results from complex interactions between genetic, environmental, and physiological factors. Hypertension results in added stress on the cardiovascular system and may lead to damage in significant organs including the heart, kidneys, and brain (Whelton *et al*., 2018) [40]. Hypertension can be termed a "silent killer" because it can develop silently and only manifests itself when significant organ damage occurs (Oparil *et al*., 2020) [26].

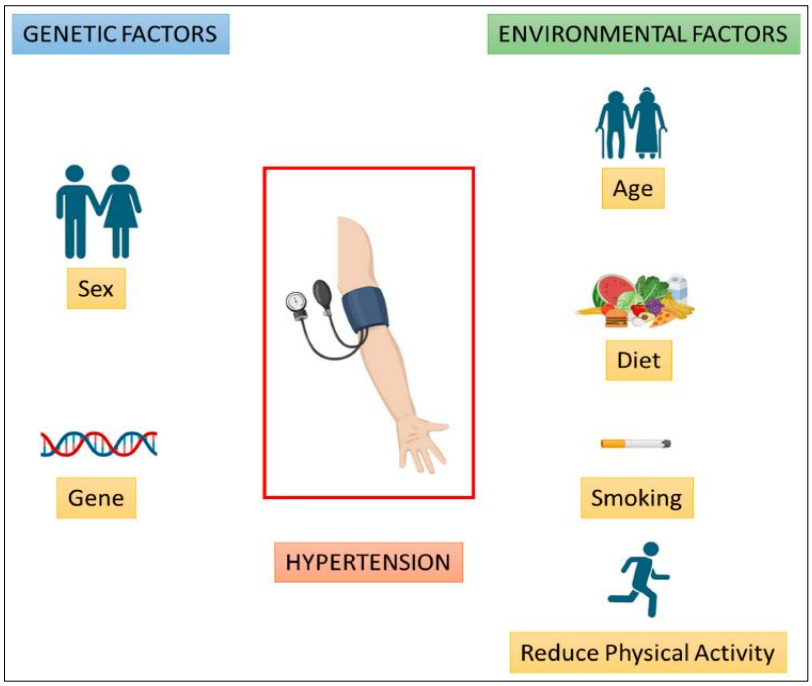

Fig 1: Illustration of the complex interactions between genetic, and environmental factors in the development of hypertension (Zappa *et al*., 2024).

Figure 1 illustrates the intricate interactions between genetic, environmental, and physiological factors in the development of hypertension. The diagram illustrates how the factors are connected and how each contributes to the development and onset of elevated blood pressure. Genes and genetic mutations are depicted as the underlying causes of hypertension. Certain genetic predispositions have the ability to affect blood pressure regulation by influencing the tone of blood vessels, sodium balance, and kidney function. The diagram illustrates how life factors such as dietary habits (high salt), inactivity, obesity, alcohol consumption, and stress can affect genetic predispositions and influence physiological pathways and lead to individuals being at risk for hypertension. This section of the diagram considers the internal systems of the body such as blood pressure regulatory systems (e.g., the renin-angiotensin-aldosterone system), kidney function, and vasculature health. Arrows illustrate how the physiological pathways can be controlled by genetic predispositions and environmental exposures and lead to increased arterial stiffness and reduced kidney function and other changes in favor of elevated blood pressure.

3.2 Lipid metabolism in hypertension

Hypertensive individuals typically present with lipid disorders in the form of increased total cholesterol, LDL cholesterol, and triglyceride levels and decreased levels of HDL cholesterol. These lipid disorders result in endothelial dysfunction and increased arterial stiffness (Wang & Hu, 2020) [39]. Lipid metabolism disorders in hypertension have also been reported to be linked with an increased risk of stroke and myocardial infarction in current studies (Brouwers *et al*., 2020) [7].

Table 2: Lipid profile differences in hypertensive patients vs. non-hypertensive controls

Lipid Parameter	Hypertensive Patients	Non-Hypertensive Controls
Total Cholesterol	Elevated	Normal
LDL Cholesterol	Elevated	Normal
HDL Cholesterol	Decreased	Normal
Triglycerides	Elevated	Normal

Table 2 shows the differences of lipid profile in hypertensive and non-hypertensive patients.

3.3 Clinical implications

The relationship between lipid profiles and hypertension emphasizes the importance of lipid profile control to prevent complications of hypertension. Pharmacological therapy such as statins and dietary and exercise modifications are all part of the therapy (Whelton *et al*., 2018) [40]. Lipid profile control plays a crucial role in preventing cardiac complications of hypertension. Recent guidelines emphasize the use of dual therapy for hypertension and dyslipidemia in an effort to achieve optimal cardiovascular benefits (Toth *et al*., 2020) [37].

Table 3: Recommended pharmacological and lifestyle interventions for dyslipidemia in hypertensive patients

Intervention type	Specific interventions	Clinical guidelines
Pharmacological	Statins, ACE inhibitors, ARBs, beta-blockers	Use combination therapy for better outcomes (Toth *et al*., 2020) [37]
Lifestyle Modifications	Diet (DASH diet), physical activity, smoking cessation	Adopt comprehensive lifestyle changes to support pharmacological therapy
Blood Pressure Monitoring	Regular blood pressure checks, use of home monitoring devices	Early detection and management of hypertension-related complications

4. Lipid peroxides in diabetes and hypertension

4.1 Role of oxidative stress

Oxidative stress plays a major role in the etiology of hypertension and diabetes. It results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense mechanism of the body and leads to damage to cells and tissues (Valko *et al*., 2007) [38]. Increased oxidative stress has been linked to endothelial dysfunction, inflammation, and vascular complications in the two conditions (Siti *et al*., 2015) [30].

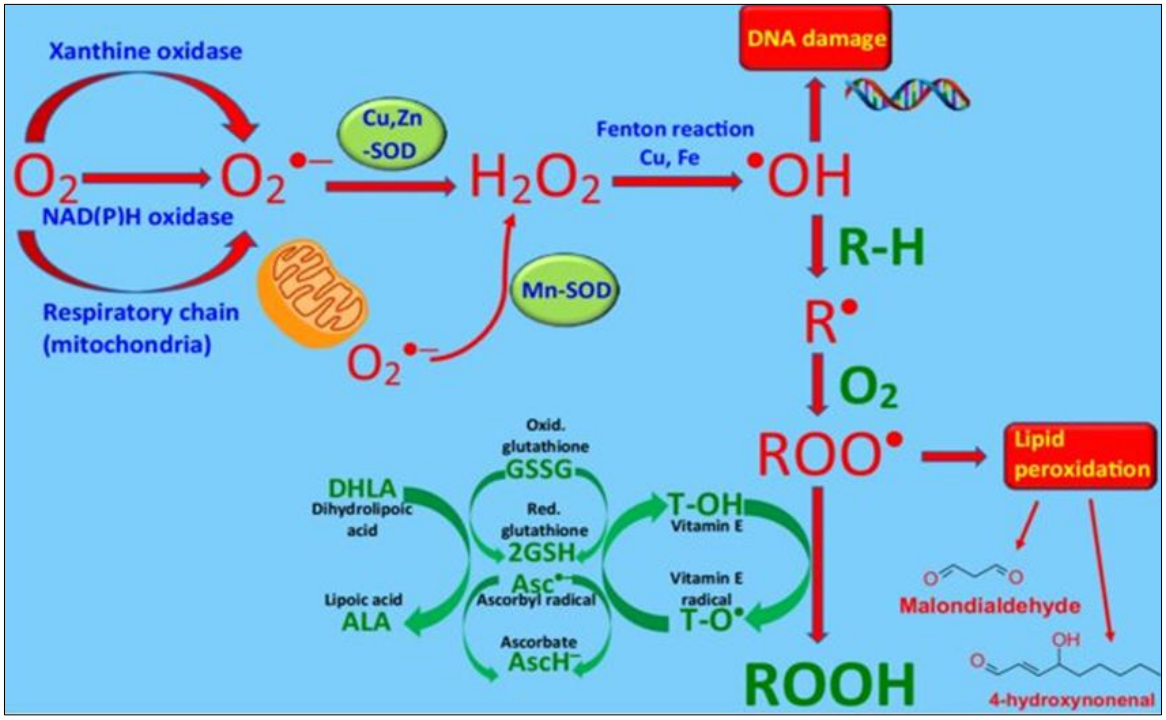

Fig 2: Diagram showing the oxidative stress pathway, highlighting the production of ROS and the body's antioxidant defenses.

Figure 2 illustrates the pathway of oxidative stress with a focus on the production of Reactive Oxygen Species (ROS) and antioxidant defenses in the human body. The figure shows how ROS are generated from various sources including mitochondrial respiration, cellular metabolism, and external sources including pollution, UV radiation, and toxins. These ROS in excess cause huge damage to vital cellular structures including lipids, proteins, and DNA and lead to cellular dysfunction and cause a variety of diseases including diabetes, hypertension, cancer, and neurodegenerative disorders. The figure shows major enzymatic antioxidants including superoxide dismutase (SOD), catalase, and glutathione peroxidase that catalyze the reduction of ROS into less harmful molecules and defend cells against oxidative damage. The figure also shows non-enzymatic antioxidants including vitamins C and E and other dietary antioxidants that neutralize free radicals by scavenging them and preventing them from causing damage to cells.

4.2 Lipid peroxidation mechanisms

Lipid peroxidation entails ROS acting on the lipid in the cell membrane and leading to lipid peroxides. Lipid peroxidation leads to the degradation of cellular structure and function and contributes to the onset of metabolic disorders (Ayala, Muñoz, & Argüelles, 2014) [3]. Lipid peroxidation by-products malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) have been confirmed as oxidative stress biomarkers and have been linked to the severity of hypertension and diabetes (Ayala *et al*., 2014) [3].

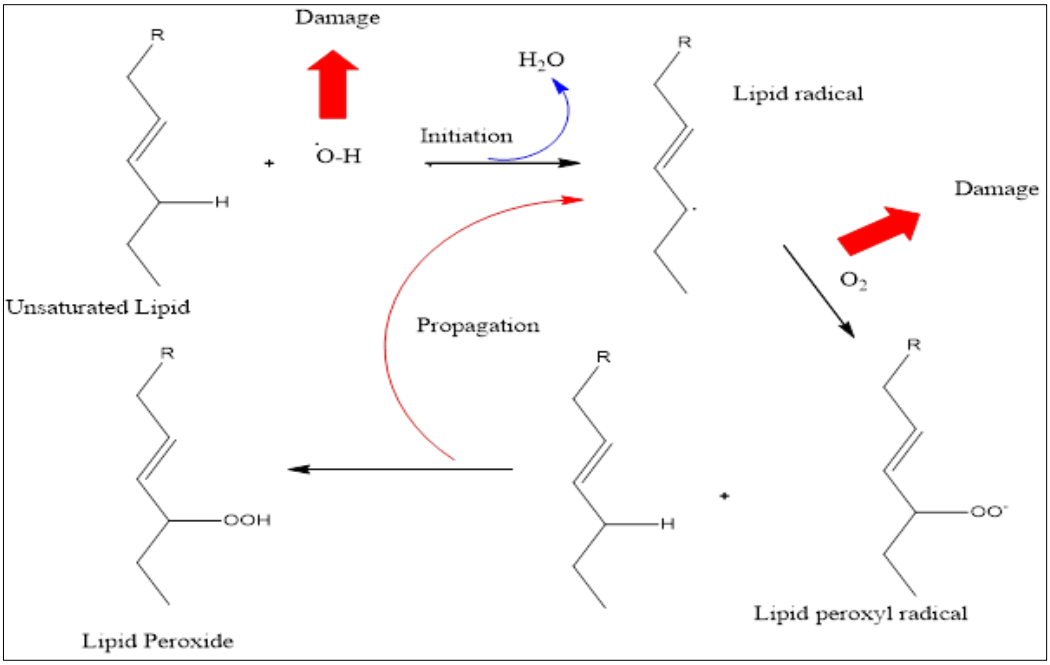

Fig 3: Image depicting the process of lipid peroxidation and its impact on cell membranes

Figure 3 illustrates the process of lipid peroxidation and its deleterious effects on the cell membrane. This figure illustrates how the reactive oxygen species (ROS), such as free radicals, induce peroxidation of the lipid in the cell membrane. Lipid peroxidation begins with the oxidation of polyunsaturated fatty acids and leads to the formation of lipid peroxides.

ROS attack the fatty acids in the phospholipid bilayer of the cell membrane and yield lipid radicals. Lipid radicals react with molecular oxygen and yield lipid peroxides and perpetuate the chain reaction and cause damage to other lipid molecules. Lipid peroxides decompose and yield reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE), and cause damage to proteins, DNA, and other cellular structures. Alteration in lipid bilayer integrity results in changes in membrane fluidity, increased permeability, and dysfunction in cellular activities and ultimately results in cell death.

4.3 Clinical evidence

Multiple studies have made a link between raised lipid peroxide levels and the development and progression of diabetes and hypertension (Steinberg, 2020) [32]. These findings suggest the potential of lipid peroxides as disease severity indicators and as targets for therapy (Zhang *et al*., 2021) [44]. Recent clinical trials have tested antioxidant therapy in an attempt to stop lipid peroxidation and have shown promising results in improving vasculature health in diabetic and hypertensive patients (Jiang *et al*., 2020) [15].

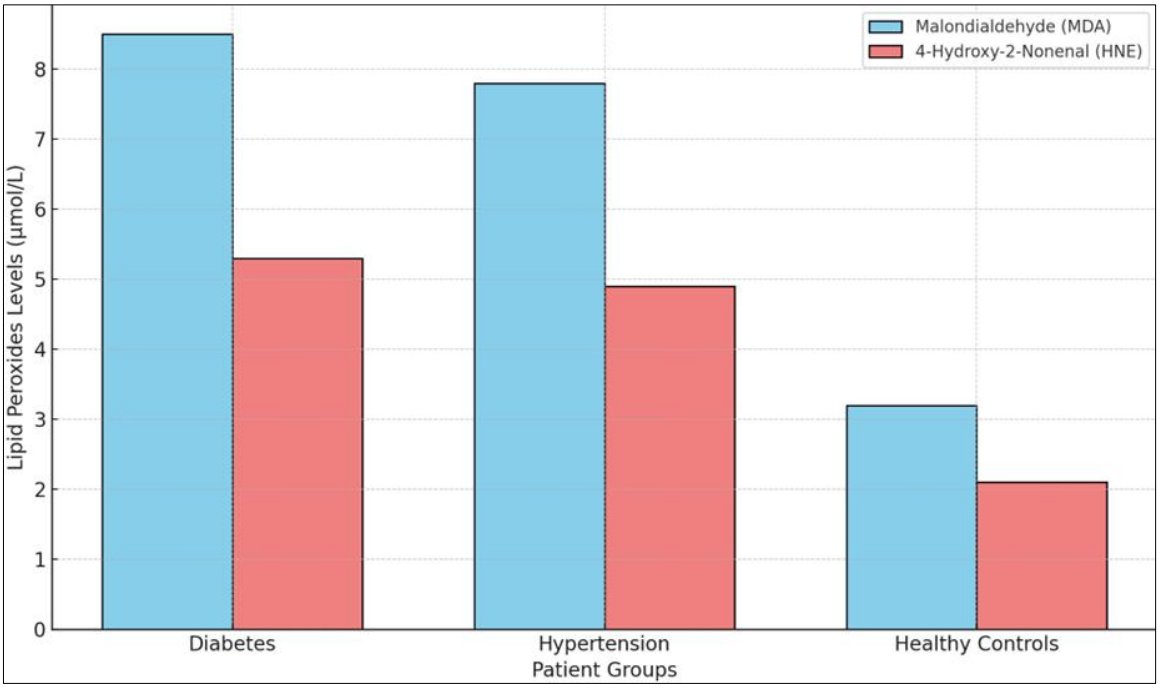

Fig 4: Recent clinical trial data on the levels of lipid peroxides in patients with diabetes and hypertension.

Figure 4 displays recent clinical trial data comparing the levels of lipid peroxides in diabetic patients and hypertensive patients with healthy controls. Both malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) levels are elevated in the diabetic and hypertension groups relative to healthy controls. Diabetic patients have the highest level of MDA at 8.5 µmol/L, followed by hypertensive patients at 7.8 µmol/L. Healthy controls have significantly lower levels at 3.2 µmol/L. Trends are consistent with HNE as diabetic and hypertensive patients have elevated levels at 5.3 µmol/L and 4.9 µmol/L, respectively, relative to healthy controls at 2.1 µmol/L.

5. Antioxidant profiles in diabetes and hypertension

5.1 Antioxidant defense mechanisms

The human organism harbors various antioxidant defense systems including enzymatic antioxidants (for instance, catalase and superoxide dismutase) and non-enzymatic antioxidants (for instance, vitamin C and vitamin E). These defense systems neutralize ROS and protect against oxidative damage (Halliwell & Gutteridge, 2015) [14]. An effective antioxidant defense plays a significant role in maintaining cells in a healthy state and preventing oxidative stress-related damage.

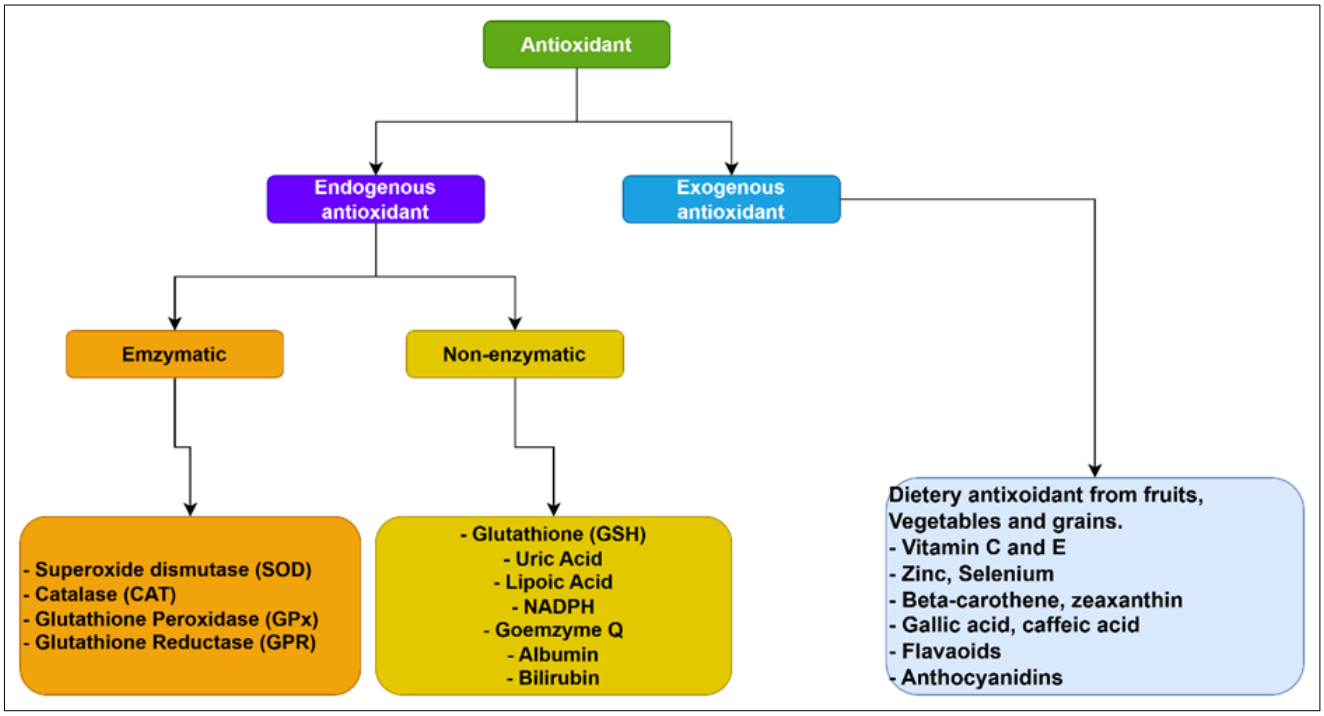

Fig 5: Various enzymatic and non-enzymatic antioxidant systems in the body.

Figure 5 illustrates the different antioxidant systems in the human body that protect against oxidative stress and damage to cells. In the figure, two broad antioxidant classes are shown: Enzymatic Antioxidants include superoxide dismutase (SOD), catalase, and glutathione peroxidase. These are the enzymes that neutralize reactive oxygen species (ROS) by converting them into less harmful molecules. SOD catalyzes the dismutation of the superoxide radicals into hydrogen peroxide, and this hydrogen peroxide gets decomposed into water and oxygen by catalase and glutathione peroxidase. Non-Enzymatic Antioxidants include compounds such as vitamin C, vitamin E, and glutathione. These antioxidants capture free radicals by donating electrons to neutralize them and prevent them from causing oxidative damage to lipids, proteins, and DNA.

5.2 Changes in antioxidant profiles

Antioxidant function in diabetes and hypertension is generally compromised and leads to oxidative stress (Ceriello & Motz, 2004) [8]. Reduced antioxidants exacerbate the deleterious effects of ROS on cellular structures (Ceriello & Motz, 2004) [8]. Antioxidant supplementation in such individuals has been shown to improve antioxidant status and oxidative damage reduction in recent literature (Khan *et al*., 2021) [17].

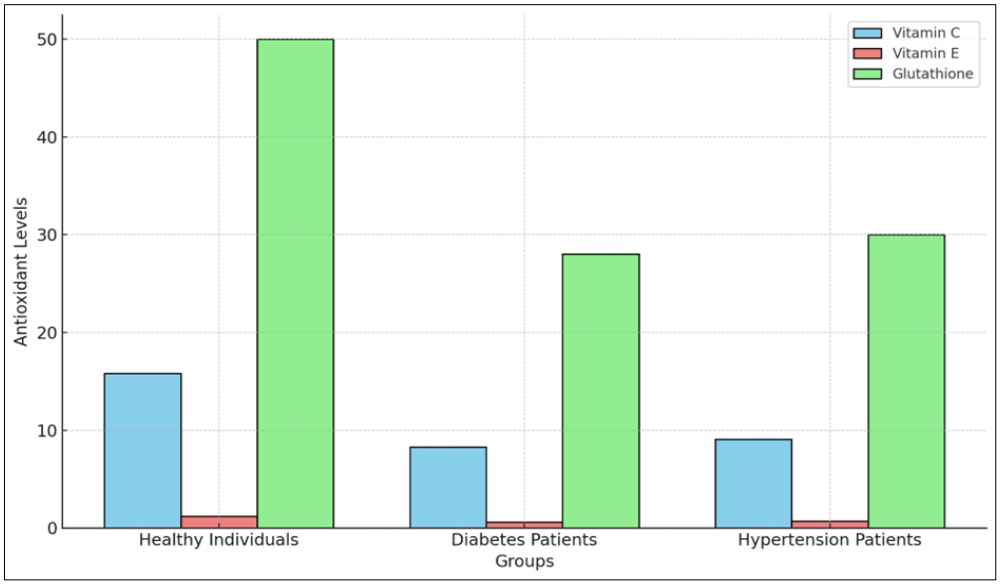

Fig 6: Comparison of antioxidant levels in healthy individuals versus those with diabetes and hypertension.

Figure 6 shows the levels of the antioxidant vitamins Vitamin C, Vitamin E, and Glutathione in three patient and control groups: controls, diabetic patients, and hypertensive patients. The findings show that the patient groups (hypertension and diabetes) have significantly low levels of the antioxidants compared to controls. Healthy controls have higher levels of Vitamin C (15.8 mg/dL) as compared to diabetic patients (8.3 mg/dL) and hypertensive patients (9.1 mg/dL). Levels of Vitamin E are also low in diabetic patients (0.6 mg/dL) and hypertensive patients (0.7 mg/dL) as compared to controls (1.2 mg/dL). In the case of glutathione as well, healthy controls have the highest level (50 µmol/L), and diabetic and hypertensive patients have low levels (28 µmol/L and 30 µmol/L, respectively).

5.3 Therapeutic interventions

Multiple antioxidant therapies have been examined in their ability to decrease oxidative stress in hypertension and diabetes. Vitamin C and Vitamin E supplementation have been shown to decrease oxidative stress markers such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) (Khan *et al*., 2021) [18]. Polyphenols such as resveratrol have been shown to have greater efficacy in improving endothelial function and diminishing inflammation (Pashkow, 2011; Liu *et al*., 2020) [27, 19]. For example, the incorporation of antioxidant foods such as green vegetables, nuts, and berries into the diet has been shown to have beneficial effects on oxidative stress markers (Liu *et al*., 2020) [22]. New pharmacological agents targeting oxidative stress pathways are also being investigated and have been shown to have potential for use in the clinic (Steinberg & Witztum, 2020) [33].

Table 4: Antioxidant therapies studied and their effects on oxidative stress markers and clinical outcomes

Antioxidant therapy	Effects on oxidative stress markers	Clinical outcomes
Vitamin C and E	Reduced ROS levels, decreased lipid peroxidation	Improved vascular health, reduced cardiovascular risk (Khan *et al*., 2021) [18]
Polyphenols (e.g., resveratrol)	Enhanced antioxidant capacity, lowered oxidative stress	Better glycemic control, reduced inflammation
Selenium and Zinc	Improved enzymatic antioxidant activity	Reduced oxidative damage, improved overall metabolic health
Antioxidant-Rich Foods	Lower oxidative stress markers, increased antioxidant levels	Improved lipid profiles, reduced risk of complications (Liu *et al*., 2020) [19]

Recent meta-analyses have established dual therapies targeting lipid metabolism and oxidative stress as superior to single-agent antioxidant supplementation in reducing cardiovascular risk (Kampoli *et al*., 2020) [16]. Future work should be directed towards individualized therapy according to patient-specific variations in lipid metabolism and antioxidant deficiencies.

6. Recent advancements in antioxidant therapies

6.1 Potential of antioxidants in chronic disease management

The lipid metabolism-oxidative stress-antioxidant defense systems relationship is complex and multifaceted in nature. Dysregulation in any of them can induce and perpetuate the others and result in a vicious cycle of disease worsening (Valko *et al*., 2007) [38]. These integrated pathways have to be addressed in order to develop an integrated approach towards therapy. Smith *et al* (2024) [31] brought into perspective the role of antioxidants in neutralizing reactive oxygen species (ROS), which play a role in the onset of chronic diseases including hypertension and diabetes. Efficiency in the catalytic role of the superoxide dismutase (SOD) isoforms in the reduction of

the superoxide radicals to less harmful molecules was brought into perspective by the study and proposed as a possible therapy by enhancing the activity of SOD (Smith *et al*., 2024) [31].

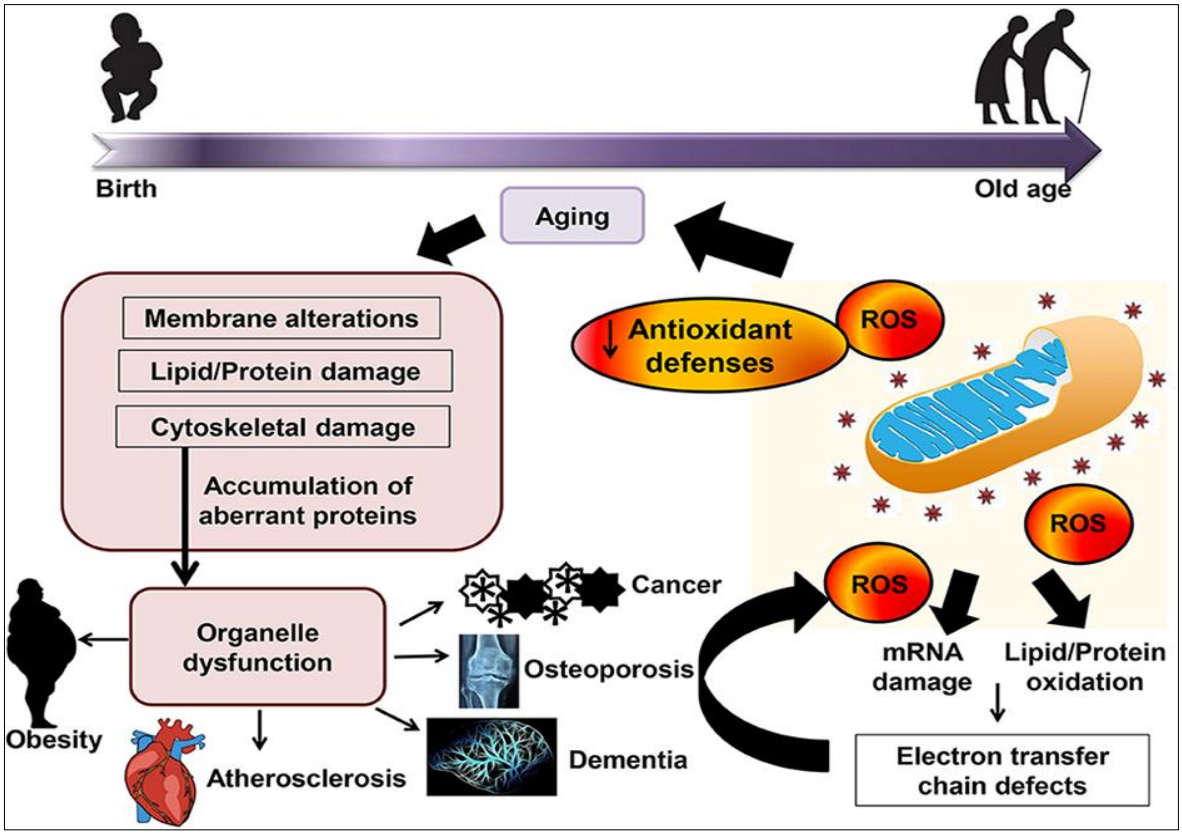

Fig 7: Antioxidant, oxidative stress, and antioxidant defenses (Tan *et al*., 2018).

Figure 7 illustrates the scheme of lipid metabolism, oxidative stress and antioxidant defenses in the human organism. In the figure, lipid metabolism including lipid breakdown and lipid synthesis results in the production of reactive oxygen species (ROS), and this may lead to oxidative stress.

6.2 Clinical implications

Understanding integrated pathways between lipid peroxides, antioxidants, and lipids provides an integrated view of the pathways in diabetes and hypertension. This information can be employed in the development of novel targets for therapy to interrupt this cycle and improve patient outcome (Halliwell & Gutteridge, 2015) [14]. For instance, therapies addressing lipid dysregulation and oxidative stress simultaneously might be an improved strategy for disease management. Combination therapies addressing lipid metabolism and oxidative stress have been demonstrated to improve cardiovascular outcome in recent studies (Kampoli *et al*., 2020) [16].

6.3 Lifestyle interventions and antioxidant benefits

Gonzalez and Rivera have published an editorial in 2024 regarding the role of lifestyle interventions including exercise and nutrition in the management of diabetes. Regular exercise was associated with reduced oxidative stress and improved antioxidant defense systems and highlighted the role of non-pharmacological interventions in the management of the disease (Gonzalez & Rivera, 2023) [12].

6.4 Hawthorn's antioxidant properties

Sun *et al*. (2024) [34] examined the health impacts of hawthorn, a plant with antioxidant compounds. In their work, they stated that the use of hawthorn could play a role in blood pressure and lipid metabolism regulation and could thus benefit individuals with hypertension and diabetes.

6.5 Impact of beetroot as a functional food

A study by Liu and He (2024) [20] examined beetroot antioxidant activities and documented its abundant polyphenol and anthocyanin contents. These are powerful antioxidant compounds and are likely to be beneficial in the management of oxidative stress in hypertension and diabetes.

Table 5: Potential therapeutic targets within integrated pathways and their expected clinical benefits

Therapeutic target	Description	Expected clinical benefits
Lipid Metabolism Modulation	Use of statins, fibrates, omega-3 fatty acids	Improved lipid profiles, reduced cardiovascular events
Antioxidant Supplementation	Use of vitamins C and E, polyphenols, selenium	Lower oxidative stress, improved endothelial function
Anti-Inflammatory Agents	Use of anti-inflammatory drugs and dietary modifications	Reduced vascular inflammation, better glycemic control
Combination Therapies	Integrating lipid-lowering and antioxidant therapies	Synergistic effects, comprehensive disease management (Kampoli *et al*., 2020) [16]

7. Limitations and future research

7.1 Study limitations

Though significant strides have been made in defining the connection between lipid profiles and oxidative stress and antioxidant defense in hypertension and diabetes, there remain some limitations. Cross-sectional and/or short-term interventional study designs are most commonly employed in the available studies, excluding the potential for inferring causality between lipid peroxidation and disease progression in the longer term. Also, variations in study populations, diets, and genetic susceptibilities create heterogeneity in results and make extrapolation of results to different populations challenging. Most trials on antioxidants also test isolated compounds rather than whole-food interventions and might have synergistic effects over single antioxidant supplementation.

7.2 Future research directions

Future research should place greater priority on extended randomized controlled trials (RCTs) to determine the long-term impacts of antioxidant therapy on lipid profiles and disease progression. Genomics and metabolomics should also be employed in order to develop personalized regimens of medicine based on genetic and metabolic profiles to individualize antioxidant and lipid-lowering therapy. Subsequent studies should explore the impacts of multiple dietary antioxidants in conjunction with each other because their synergistic effect on oxidative stress and lipid metabolism could have greater therapeutic benefits.

Also, mechanistic studies on the particular molecular pathways between lipid peroxidation, ROS production, and endothelial dysfunction will facilitate the development of targeted therapy. Also, the incorporation of lifestyle factors including exercise, sleep patterns, and stress reduction in follow-up studies will be significant to determine their interactions with antioxidant and lipid-altering therapy. These will result in the formulation of improved and individualized therapy for improving cardiovascular health as well as metabolic stability in diabetic and hypertensive patients.

8. Conclusion

This review highlights the major roles of lipid profiles, lipid peroxides, and antioxidant profiles in the etiology of diabetes and hypertension. Dysregulation of the metabolic pathways results in disease and complications. Elucidation of the particular pathways linking these factors and development of therapies addressing the underlying metabolic imbalances need further research. New therapies incorporating lipid management, antioxidant supplementation, and reduction of oxidative stress promise to improve patient care. Future advances in personalized medicine and genomics may also result in more individualized therapy and improved patient outcomes in individuals with diabetes and hypertension.

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