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Review Article

The Role of Antioxidants and Anti-Inflammatory Agents in Cardiometabolic Disease

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ABSTRACT

Cardiovascular diseases remain a major cause of morbidity and mortality worldwide. Cardiovascular diseases associated with metabolic disorders are collectively referred to as Cardiometabolic Diseases (CMDs). Oxidative stress and inflammation are key contributors to the development and progression of CMDs. Antioxidants and anti-inflammatory agents have garnered significant attention as potential therapeutic strategies for preventing and managing cardiovascular disorders. To better understand the complex interactions between oxidative stress, inflammation, and cardiovascular health, this review paper will focus on the mechanisms of action and potential advantages of antioxidants and anti-inflammatory drugs in reducing the risk factors associated with CVDs and enhancing cardiovascular health in general.

1. Introduction

Cardiovascular disease (CVDs) remains a significant global health issue with a high burden of morbidity and mortality. In general, CVDs continue to be a significant worldwide cause of health loss, impacting every country across the globe. Estimates indicate approximately 8,092.4 instances per 100,000 people in Asia and 7,241.7 cases per 100,000 people worldwide.[1] Globally, there are 245.1 instances of CVDs per 100,000 people; however, in Asia, the number of cases per 100,000 people is estimated to be 516.9.[1] . Targeted treatments and ongoing studies are required to reduce the prevalence of CVD and enhance global health outcomes.

The mechanisms of hypertension, atherosclerosis, and cardiovascular diseases such as coronary artery disease (CAD) and cerebrovascular disease are the subjects of numerous studies. Cardiovascular diseases associated with metabolic diseases (diabetes mellitus, genetic metabolic diseases, atherosclerosis, obesity, etc.) are referred to as Cardiometabolic Diseases (CMDs). A complex mechanism involving metabolic and molecular alterations in oxidative stress, inflammation, endothelial dysfunction, and lipid metabolism plays a significant role in the development of various disease processes.[2] The initial step in the pathophysiology of CVDs is endothelial damage, which exposes the cell layers to dangerous inflammatory processes that lead to the creation of lesions.[3]

Cellular oxidative stress (OxS) is a factor in the pathology of CMDs due to the release of harmful free radicals by endothelial cells and vascular smooth muscle cells. The reactive oxygen species (ROS) have an unpaired free electron in the outermost orbital, known as free radicals. In order to become stabilized, they interact with elements of the cell, such as protein, DNA, or lipid. The two main oxidants that significantly affect cardiovascular disease are superoxide and nitric oxide. Oxidative stress is brought on by an imbalance in the body's defensive mechanisms against ROS generation. Antioxidants reduce the damage produced by oxidative stress by quelling reactive oxygen radicals.[3]

One chronic condition that affects the elderly and has been linked to oxidative stress and inflammatory cytokines is atherosclerosis. It is a chronic inflammatory disease that progresses slowly and can result in angina, myocardial infarction, stroke, and unexpected death. Its defining feature is localized arterial lesions that eventually clog the blood vessels. The conventional list of risk factors for atherosclerosis includes diabetes, obesity, smoking, high blood pressure, and advanced age. Persistent inflammation has recently been connected to the development of atherosclerosis.[4]

2. Oxidative Stress and Cardiometabolic Diseases

The deleterious effects of OxS have an impact on the pathophysiology of most cardiac disorders, including cardiometabolic disorders. Myocardial contraction-relaxation cycle disruptions and electrical instability brought on by OxS can lead to arrhythmias, poor

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cardiac function, and cardiac arrest. When it comes to the etiology of macroangiopathy, microangiopathy, fibrosis, microvascular blockage, and structural remodeling in non-myocyte heart tissue, OxS can play a role.[5]

The heart's reduced electrical stability is caused by a number of molecular pathways, such as direct disturbances of the homeostasis of Na^+, K^+, and $Ca2^+$; modifications to gap junctions that exacerbate oxidative damage by associated Ca2+-induced ROS production; and ROS-induced ROS release, which may encourage ventricular arrhythmias. One of the supraventricular arrhythmias, atrial fibrillation (AF), has been associated with an imbalance in defense mechanisms between pro- and anti-oxidants, leading to an increase in hydrogen peroxide and superoxide produced by NADPH oxidase isoforms 4 and 2. Additionally, patients with diabetes have a higher incidence of arrhythmias.[6]

Risk factors linked to the development of AF and the inability to maintain sinus rhythm include metabolic syndrome, hyperuricemia, obesity, and atherosclerosis. It is hypothesized that during cardiac excitation and contraction, OxS affects both cardiac non-myocytes and cardiac cells, providing a paradigm of widespread cardiac dysfunction in CMDs. In these patients, arrhythmias are often observed, accompanied by remodeling of the heart's structure and function due to fibrosis, hypertrophy, etc.[6]

Mechanistically, OxS has been linked to diabetes and metabolic syndrome, promoting cardiomyopathy and cardiac contractile dysfunction by inhibiting Ca^{2+}-regulating proteins and contractility enzymes, impairing myofibril sensitivity to Ca^{2+} ions, and altering gene expression.[7]

Direct oxidation of contractile proteins may also contribute to the heart failure associated with hypercholesterolemia. Furthermore, high levels of oxidized cholesterol in the blood have detrimental effects on cation transporters, membrane fluidity, and enzyme activities in vascular smooth muscle, cardiomyocytes, and endothelial cells. This impairs their capacity to adapt to stress and jeopardizes cardiac vascular and myocardial functions.[8]

Therefore, OxS exacerbates structural and functional heart abnormalities in the presence of CMDs. As a result, strategies that target various pathways, such as the imbalance of the redox system, could be employed to prevent or treat cardiac injury in CMDs.[5]

Heart dysfunction is a result of the various redox signaling pathways that CMDs affect in cardiomyocytes. They entail the suppression of mitochondrial MnSOD as well as endogenous enzymes that regulate antioxidants such as glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD). The activation of protein kinase C (PKC), uncoupled nitric oxide synthase (NOS), xanthine oxidase (XO), and NADPH oxidase (NOX) by CMDs also increases the production of ROS, causing oxidative stress in cardiomyocytes.[5]

Additionally, OxS-mediated damage brought on by CMDs impairs the performance of ion transporters located at the membrane, such as Na^+/Ca^{2+}-exchanger (NCX), sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), Na^+/K^+-ATPase, and Ca^{2+}-ATPase, disrupting ion homeostasis and leading to Ca^{2+} overload (elevating the concentration of intracellular Ca^{2+}).[5]

Increased intracellular Ca^{2+} levels trigger the synthesis of ROS-inducing enzymes like XO or PKC. OxS also causes mitochondrial ROS synthesis, known as ROS-induced ROS release, which exacerbates cardiac damage from oxidative stress. CMDs also block the translation of genes involved in the defense of intracellular antioxidants, including heme oxygenase 1 (HO-1), by inhibiting the redox signaling pathway and mitochondrial ATP-sensitive K^+-channels (mtKATP), which are mediated by nuclear factor erythroid 2-related factor 2 (Nrf2).[5]

Organelle (SR, sarcolemma, mitochondria, myofilaments) damage, DNA fragmentation, decreased synthesis of ATP in mitochondria, and increased apoptosis are all caused by these OxS-mediated mechanisms, which affect the myocardium and lead to contractile failure and arrhythmias in the heart (Figure 1).[5]

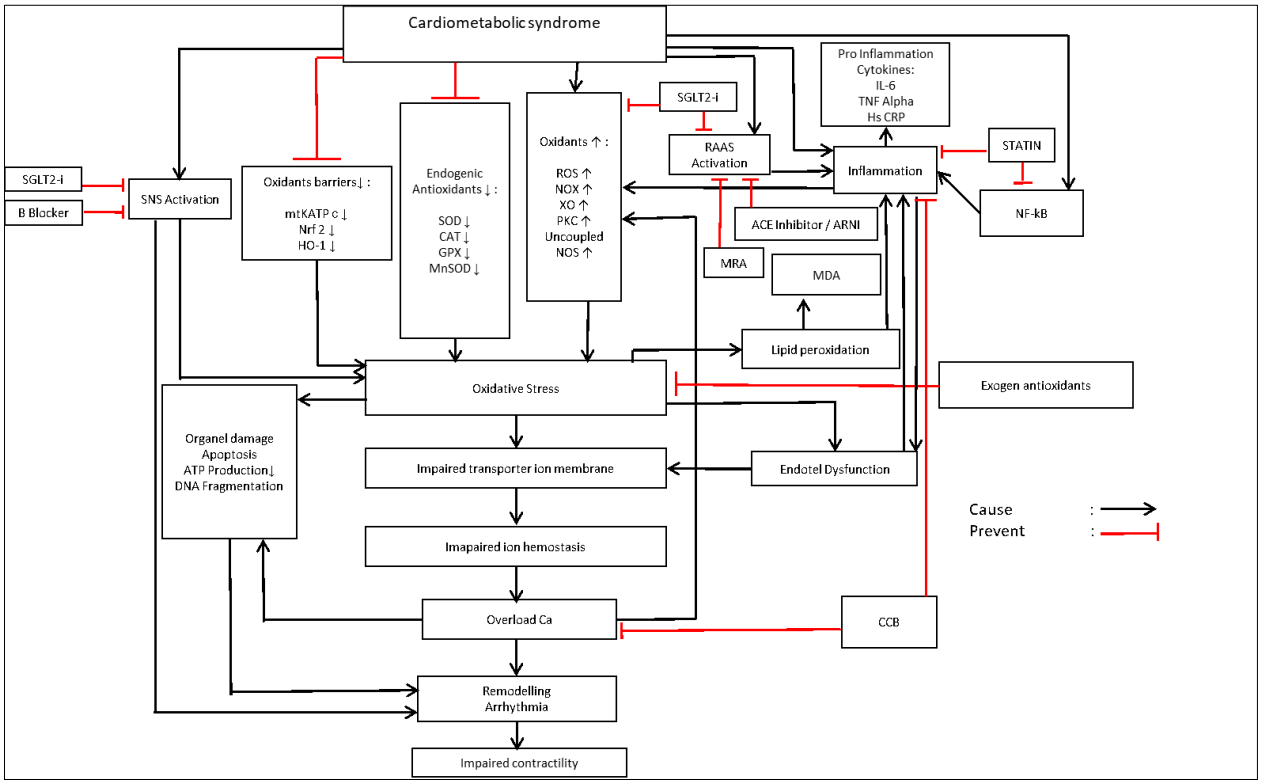

Figure 1 – Role of oxidative stress and inflammation towards cardiac dysfunction in cardiometabolic syndrome. Some cardiac drugs that often prescribed also mentioned.

3. Inflammation and Cardiometabolic Diseases

An increasing amount of evidence indicates that immunological dysregulation, systemic inflammatory cytokines, and circulating metabolic substrates are involved in the multi-organ disease process that results in alterations in the form and function of the heart in patients with cardiometabolic conditions. There is a prevalent belief that excess food consumption results in the production of pro-inflammatory mediators by extracardiac tissues, which subsequently causes systemic and cardiac inflammation (Figure 1).[9] Furthermore, circulating inflammatory cytokines, such as TNF-α and IL-6, which activate nuclear factor (NF)-κB and c-Jun N-terminal kinase (JNK), as evolutionarily conserved regulators of inflammation, reduce systemic and cardiac insulin sensitivity.[9] The condition known as "metabolic inflammation," or "meta-inflammation," is characterized by persistent low-grade inflammation that is mostly brought on by obesity and other metabolic issues. [10]

Contrary to acute inflammatory responses to cardiac tissue damage, which are crucial regeneration processes, chronic inflammation alters the metabolic program of the heart and contributes to adverse remodeling and functional impairment.[11] The main cause of obesity-related systemic inflammation is the production of certain chemokines from adipocytes, such as leukotriene B4 (LTB4) and C-C motif chemokine ligand 2 (CCL2). These chemokines stimulate monocyte trafficking to adipose tissue. After being attracted by the C-C motif chemokine receptor 2 (CCR2) to adipose tissue, monocytes transition toward a pro-inflammatory macrophage phenotype and produce their own pro-inflammatory cytokines, attracting more monocytes and aggravating inflammation both locally and systemically. [12]

Saturated fatty acids also trigger the release of TNF-α, IL-1, IL-6, and CCL2 as inflammatory mediators by macrophages through methods reliant on Toll-like receptor (TLR)4, a pattern recognition receptor. This results in a continuation of cardiac inflammation. [13]

In patients with diabetes mellitus and obesity, the overproduction of adipocyte-derived aldosterone and neprilysin encourages immunological dysregulation and macrophage recruitment, hastening the breakdown of natriuretic peptide. Together, these components influence low-grade myocardial inflammation and renal sodium reabsorption. Notably, increased body fat mass is tightly correlated with increased aldosterone secretion from the adrenal glands, which is directly caused by the adipokine leptin. [14]

Cardiac inflammation and remodeling in CMDs are brought on by the activation of the renin-angiotensin-aldosterone system (RAAS), as indicated by a significant release of angiotensinogen by the liver and adipose tissue. Angiotensin-converting enzyme (ACE) converts angiotensin (Ang) I in the bloodstream to angiotensin (Ang) II, which, when paired with aldosterone, activates NF-κB in endothelial cells and cardiac fibroblasts. This upregulates vascular adhesion molecules, attracts immune cells, and increases the synthesis of extracellular matrix (ECM). Leukocyte migration, the production of proinflammatory cytokines, fibrosis, and insulin resistance are all decreased by the conversion of Ang I into Ang-(1-7) by ACE2 through the activation of the Mas receptor in the counterregulatory RAAS pathway. [15]

Another mechanism that links heart inflammation with systemic glucometabolic disorders and hypertrophy is the formation of advanced glycation end products (AGEs). Chronic hyperglycemia can cause AGEs to accumulate in the cardiac extracellular matrix (ECM), where they can then activate the AGE receptor (RAGE) to increase the production of pro-inflammatory mediators like IL-6, TNF-α, ICAM-1, and CCL2. It should be noted that AGEs also contribute to cardiac inflammation through the RAGE/NF-κB pathway, directly activating macrophages. [16]

The inflammatory myocardial environment and disruption of cardiac tissue homeostasis are caused by paracrine signals from recruited immune cells, systemic cytokines, increased substrate availability, and ECM alterations. Maladaptive myocardial remodeling can therefore be considered a chronic cardiac inflammatory syndrome that is closely related to food metabolism in patients with obesity and type 2 diabetes.[17]

4. Anti-oxidants and Anti-Inflammatory Effects in Cardiometabolic Diseases

Since OxS is thought to be a main factor that contributes to the progression and development of CMDs, many antioxidants, including natural compounds or synthetic antioxidants and antiperoxidants, have been suggested for use as strategies potentially employed in the treatment or prevention of CMDs. Therapies that target endogenous antioxidant systems, or indirect antioxidants, in addition to exogenous antioxidants, have grown in importance for the treatment or prevention of CMDs.[5]

The heart and/or circulation may activate endogenous antioxidant systems in response to certain exogenous substances, and some of these chemicals have also demonstrated cardioprotective efficacy in clinical situations. However, these drugs' antioxidant activity may not be the only important mechanism underlying how they continue to sustain CMDs cardioprotection. Despite the fact that pharmaceuticals that block the ROS-producing enzymes are neither direct nor indirect antioxidants, they have a well-researched and promising potential therapeutic effect to reduce OxS in CMDs; nevertheless, this is outside the focus of the current review. The benefits of formulations, several antioxidant-rich plant or nutritional products like nuts, oils, vegetables, or fruits on the heart have been studied. [5]

Endogenous antioxidants administered to CMDs stimulate a number of intracellular processes in cardiomyocytes that enhance redox equilibrium and lessen the damage to the heart caused by CMDs. One of the activated pathways is the Nrf2/Keap1/HO-1 redox pathway, which is also dysregulated in CMDs. Another activated route is the endogenous antioxidant systems, such as SOD, catalase (CAT), and glutathione peroxidases (GPX), which are reduced in CMDs. Additionally, antioxidant therapies stimulate several PI3K/Akt-mediated cardioprotective pathways, including Akt/eNOS/PKC and Akt/eNOS/PKG, both activating SERCA and improving intracellular Ca2+ homeostasis. These pathways raise NO levels and activate mtKATP channels. Antioxidants also prevent apoptosis by blocking the Akt/SIRT-1/NF-κB or Akt/FoxO3 pathways. Antioxidants modify these mechanisms and lower OxS in the cardiomyocytes, increasing heart function and reducing cardiac illnesses in CMDs.[5]

A connection between inflammation and metabolism is also suggested by the anti-inflammatory characteristics of medicines intended to lower cardiovascular risk factors, such as glucose- and cholesterol-lowering drugs. These methods can simultaneously treat inflammatory and metabolic stress, providing a therapeutic justification for addressing these pathogenetic processes simultaneously.[10]

Endomyocardial biopsies from HFpEF patients who are on statins show decreased cardiomyocyte hypertrophy and myocardial nitrosative stress. According to research, HFpEF patients using statins have a decreased risk of developing AF. Other supporting data for this hypothesis has been provided by studies that show statins are linked to better outcomes in HFpEF, decreasing mortality in the absence of CAD. Despite that, some of the harmful metainflammatory pathways present in HFpEF will be attenuated by the pleiotropic anti-inflammatory actions of these drugs. [10]

Along with statins, several other glucose-lowering drugs have also been shown to lessen inflammation, suggesting possible therapies for HFpEF. New research demonstrating the benefits of SGLT2 inhibitors in HF, in the absence of diabetes, has made it possible to test these drugs in HFpEF. While the precise mechanism behind the cardiovascular benefits of SGLT2 inhibition are yet unknown, it has been hypothesized that they may focus on metabolic inflammatory pathways. [10]

It should be noted that metainflammation is a mild, systemic condition. Inconsistent results were seen in the past when pro-inflammatory cytokines were suppressed in HF. Direct anti-inflammatory methods may increase the chance of unintended immune response suppression, according to one theory. The diversity of immune cell subsets found in the human heart further demonstrates the intricacy of immune system responses in creating circulatory adaptations to stress. [10]

Recent study suggests that a focused anti-inflammatory strategy may be more effective in managing inflammatory processes in cardiovascular illness. This could potentially alter the therapeutic effects of stem cell therapy post-MI, with a focus on cardiometabolic syndrome. [10]

5. Conclusion

Oxidative stress and inflammation contribute to cardiometabolic diseases, promoting atherosclerosis and plaque instability. Antioxidants and anti-inflammatory drugs can improve heart health, but effective treatments require understanding mechanisms, tailored approaches, and rigorous trials.

6. Declaration

6.1 Ethics Approval and Consent to participate
Not applicable.

6.2. Consent for publication
Not applicable.

6.3 Availibility of data and materials
Data used in our study were presented in the main text.

6.4 Competing interests
Not applicable.

6.5 Funding Source
Not applicable.

6.6 Authors contributions
Idea/concept: TA. Design: TA. Control/supervision: DS, AFR, CTT. Data collection/processing: DS. Analysis/interpretation: TA, DS. Literature review: TA, DS. Writing the article: TA. Critical review: DS, AFR, CTT. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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