REVIEW ARTICLE

The Involvement of Reactive Oxygen Species in Causing Chronic Cardiovascular and Neurodegenerative Diseases and Some Cancers

Jasneet K Tiwana,[1] Anureet K Shah,[2] Naranjan S Dhalla[1]

Abstract

An increase in the occurrence of different infectious and chronic diseases as well as aging population has resulted in poor human health and decline in the quality of life all over the world. In fact, chronic diseases, which are partially resistant to currently available drugs are long lasting health hazards and require ongoing medical attention. Major causes of increase in these diseases are considered to be changes in the environment as well as diets and lifestyle. Particularly, there has been changes from a simple, nutritious, low- calorie diet and active lifestyle to a complex and processed food rich in high calories accompanied by a sedentary lifestyle and unhealthy living habits. Since high-calorie diets and inactive lifestyle are known to promote the production of reactive oxygen species (ROS) in the body, it is likely that oxidative stress and associated inflammation may be intimately involved in enhancing the resistance of several disorders to the existing therapeutic interventions and thus promoting the occurrence of chronic diseases. A thorough review of literature regarding the pathogenesis of some major chronic diseases including cardiovascular disease like heart failure, neurodegenerative disorder like Alzheimer's disease and various types of cancer has revealed that these health hazards are associated with increased oxidative stress, production of pro-inflammatory chemicals such as nitric oxide and some cytokines, as well as formation of some toxic substances such as advanced glycation end products. It is thus evident that extensive research work by employing genetic, immunological and nutraceutical approaches, needs to be carried out for developing some novel antioxidants with anti-inflammatory activities for reducing the incidence of chronic diseases. In the meantime, it would be prudent for patients with chronic diseases to pursue the preventive measures involving reduced intake of high calorie diet and following an active lifestyle.

Key words: Heart failure; Cancer; Alzheimer's disease; Oxidative stress; Inflammation; Low calorie diet; Active lifestyle.

1. Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada.
2. Department of Nutrition and Food Science, California State University, Los Angeles, USA.

Corresponding author:
NARANJAN S DHALLA
E: nsdhalla@sbrc.ca

Introduction

Chronic disease conditions are health hazards, which are long-lasting and persistent in their effects on diverse body functions. Such a terminology for chronic diseases has a large degree of variations in use within the professional community because the Center for Disease Control classifies heart disease, stroke, cancer, diabetes and obesity as chronic diseases, whereas Centers

for Medicare and Medicaid Services have a more extensive list of chronic diseases including neurodegenerative diseases. These differences have created a great deal of confusion in estimating the impact of chronic diseases, the cost of these disorders and interventional measures for reducing these health hazards.[1] It needs to be emphasised that chronic disease conditions are different from acute disease conditions as these affect multiple organs of the body and are not be fully responsive to various medications and treatments.[2] Chronic diseases require ongoing medical attention and limit daily life activities like social interaction, personal movements, eating or sleeping.[3] Some of the major examples of chronic diseases include arthritis, diabetes, hypertension, autoimmune diseases and acquired immunodeficiency syndrome, in addition to cardiac diseases, cancer and neurodegenerative disorders.

Chronic diseases are the leading cause of mortality worldwide and their occurrence is not confined to any particular social or religious class as well as any geographical region.[4] In fact, chronic diseases are generally considered to be the consequence of poor nutrition with modern foods. It may be noted that modern foods are high in calories, fats and salt but low in fibres[5] as compared to traditional foods, which are rich in micronutrients, macronutrients, carotenoids, fibres, vitamins and minerals.[6] The methods of preparing, processing and preserving modern foods are also considered to produce more toxic ingredients such as advanced glycation end products (AGEs) and reactive oxygen species (ROS) in comparison to the traditional procedures.[7,8] Other reasons include a sedentary lifestyle, excessive use of alcohol and tobacco, socioeconomic stress, genetics, race, ethnicity and religious habits.[9,10] The aging population suffering from multiple chronic conditions is adding to the existing burden on healthcare services all over the world.[11]

In view of the poor quality of life of patients with chronic diseases, it is crucial that special attention be paid to formulate some appropriate strategies to deal with this devastating health problem. Particularly, it is noteworthy that the rate of chronic diseases is becoming high due to aging population and most of these patients are more resistant to the existing pharmacotherapy. Thus, there is an urgent need not only to understand the pathogenesis of diverse chronic diseases but also to develop novel drugs for their treatment in aging population. It will also be prudent to con-

sider some alternative procedures and interventions such as nutritional and lifestyle modifying approaches for the purpose of preventive medicine. The present article is, therefore, intended to review the existing information regarding some of the chronic diseases namely, cardiovascular and neurodegenerative diseases as well as some types of cancer, which are major causes of mortality. Although the pathogenesis and modification factors for the development of chronic diseases are different from each other, the role of a few pathogenic mechanisms will be described to evaluate if there is any commonality for the occurrence of these health hazards. Some discussion will also centre around the effectiveness of newer pharmacotherapy for the treatment of each disease in addition to assessing the beneficial effects of some nutritional and lifestyle approaches.

Role of oxidative stress and inflammation in chronic diseases

a. Sources of ROS production

The production of ROS occurs due to leaking electrons from the mitochondrial electron transport chain during the metabolic process of energy production. The free oxyradicals thus formed react with other mitochondrial proteins to produce more ROS such as superoxide radicals, hydroxyl radicals and hydrogen peroxide.[6] ROS are also generated by the activation of NADPH oxidases,[12] which play important roles in many degenerative diseases. The excessive production of ROS leads to oxidative stress in the body.[13-15] The sources of ROS can be exogenous such as UV radiation; pollutants including paraquats, quinones, phenols; carcinogens and many chemotherapeutic drugs. In addition, ROS can also be produced endogenously in the body by intracellular enzymes like flavoenzyme ER01 in the endoplasmic reticulum, cytochrome p450 enzyme, lipoxygenases and nitric oxide (NO) synthase. These molecular targets are considered suitable for the development of interventions for disease prevention.[16] The activation of NO synthase leads to excessive production of NO, which reacts with superoxide radicals to form peroxynitrite for inducing nitrosative stress.[15] This pathogenic factor damages cells by oxidising free thiols and nitrating tyrosine residues leading to cardiovascular disease.[17] The

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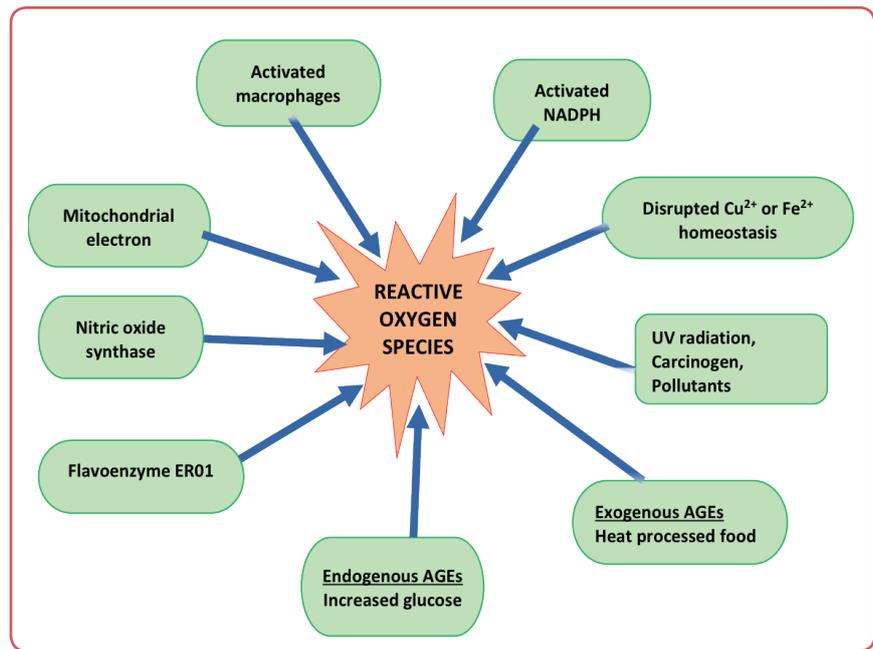
Figure 1: Various sources for the generation of reactive oxygen species
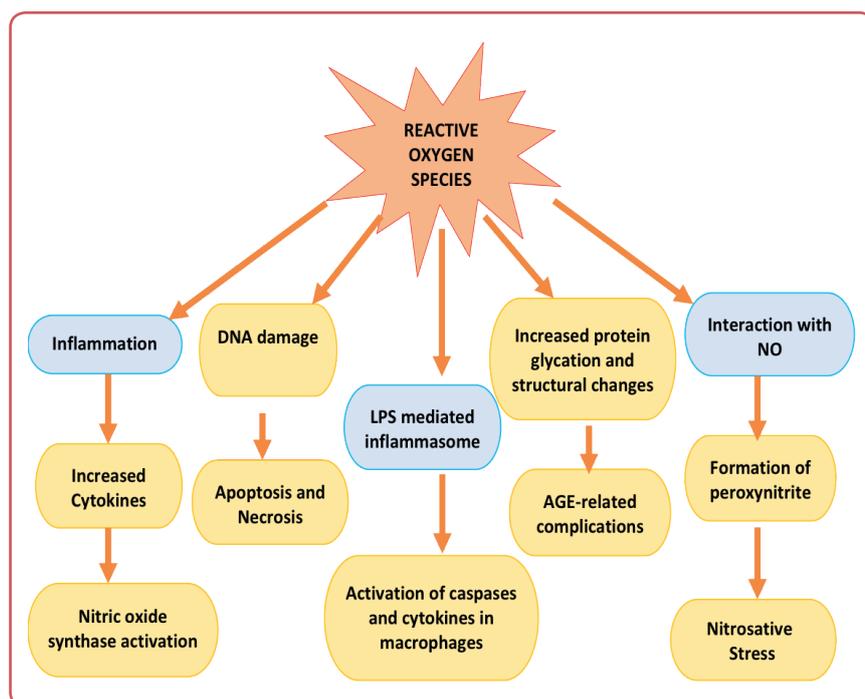*UV – ultraviolet; AGEs – advanced glycation end products;*

intracellular production of ROS in mitochondria occurs through enzymes like dihydroorotate dehydrogenase, glycerophosphate dehydrogenase, NADPH oxidase, monoamine oxidase, xanthine oxidase as well as Complex 1 and 3 of the electron transport chain.[18] There is also existing evidence that mitochondria have evolved as an antioxidant system which prevents these organelles from oxidative damage due to both internal and external ROS with the help of enzymes like superoxide dismutase and glutathione peroxidase.[15, 19] The mitochondrial antioxidant system allows only a small part of the endogenously produced ROS in mitochondria to escape from there to limit the production of oxidative stress in the cell.[19] The production of ROS from various sources is shown in Figure 1.

Moderate levels of ROS and NO have been observed to activate the intracellular signalling reactions for beneficial effects.[13-15] ROS are involved in ovulation[20] and T cell-mediated immunity in the body[21] whereas NO has been demonstrated to regulate cardiovascular and neuronal functions in addition to involvement in apoptosis and cell necrosis.[22] ROS have also been shown to oxidise cholesterol, proteins, carbohydrates and vitamins leading to the production of toxic and mutagenic compounds such as AGEs which are responsible for many diseases.[15, 23, 24] AGEs also undergo oxidation and dehydration to cause an increase in oxidative stress for the induction of chronic diseases.[22] AGEs are exogenously formed in heat-processed foods[25] as well as endogenous-ly formed by high amounts of sugars in the body, mostly fructose.[26] The carbohydrates-rich foods, as well as fish, legumes, vegetables, fruits and whole grains have been observed to contain lower levels of AGEs as compared to processed foods with high fat that lead to increased plasma ceramide levels.[26] The preparation of food at high temperatures for a longer period of time also leads to the production of a higher amount of AGEs as compared to other methods such as steaming and boiling.[25] It is pointed out that breakdown of homeostasis for metal ions, which are a part of many active sites in proteins has been reported to cause the production of uncontrolled amounts of AGEs in the body.[27]

b. Role of inflammation

It is now well known that chronic diseases are also caused by inflammation, which is an immune response of the body against foreign pathogens by the host cells. One of the main causes of inflammation is the activation of macrophages and cells like polymorphonuclear neutrophils (PMNs) that are involved in the cellular defences of the host. These also lead to the production of pro-inflammatory mediators for further increasing inflammation and oxidative stress by the formation of more ROS and reactive nitrogen species (RNS).[13] ROS are produced to clear the body of pathogens by causing an increase in inflammation but may also cause tissue injury to the host cell and an increase in the production of RNS to result in DNA damage and formation

Figure 2: Some effects of reactive oxygen species

LPS- lipopolysaccharide; NO – nitric oxide; AGEs – advanced glycation end products; DNA – deoxyribonucleic acid;

of AGEs causing dysfunction in cellular processes and leading to death of cells by apoptosis and necrosis.[28] Inflammatory cytokines cause activation of myeloperoxidase and NO synthase which also increase the nitrosative stress.[15] The dietary AGEs have been observed to be related to the levels of C-reactive protein and serum AGEs and these have been suggested to be responsible for inflammatory reactions during the development of several chronic diseases.[29] Some of the adverse effects of excessive amount of ROS are shown in Figure 2.

Excessive levels of NO have been shown to result in septic shock and cytotoxicity induced by activated macrophages in different chronic diseases.[30-32] Activated macrophages in the inflamed area are also known to produce ROS and tissue damage due to elevated levels of oxidative stress.[33] Increased oxidative stress and inflammation have also been shown to be related to various human diseases like diabetes mellitus, neurodegenerative diseases, cancer, rheumatoid arthritis, cataracts, cardiovascular diseases, respiratory diseases and aging.[34] Mitochondrial-derived ROS have been reported to be involved in the production of proinflammatory cytokines as well as in the regulation of inflammasome which activates inflammatory caspases in macrophages.[33] Different diseases also result from disrupted homeostasis of metals such as copper and iron which promote the formation of RNS and ROS. These metals are also responsible for lipid perox-

idation leading to the development of cancer and neurodegenerative diseases.[35] The regulation of glutathione both in reduced (GSH) and oxidised (GSSG) forms, is one of the most important antioxidant systems which, when compromised in the presence of excess ROS and RNS, result in an increase in disease conditions and symptoms.[12,36] Mitochondrial dysfunction has been shown to occur upon the generation of high levels of both oxidative stress and inflammation leading to mitosis and mitophagy.[18] Although it is difficult to indicate the cause-effect relationship between the development of oxidative stress and inflammation, it is evident that both these pathogenic processes are intimately involved in the genesis of several chronic diseases.

Role of oxidative stress in cardiovascular diseases

Cardiovascular diseases include many health disorders and syndromes such as angina, myocardial infarction, stroke, heart failure, arrhythmias, congenital heart disease, myocarditis and valvular heart disease.[36,37] Various factors are considered as the reasons for the onset of cardiovascular diseases, some of these include smoking, diabetes, high blood pressure, sedentary lifestyle, obesity, high- calorie foods, poor nutrition and high cholesterol levels.[36-39] Collectively, car-

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diovascular ailments are the number one cause of global deaths as an estimated 17.9 million deaths occurred in 2019.[39] Cardiovascular diseases are also the second leading cause of death in Canada.[40] Globally, 32 % of mortality is accounted for by cardiovascular diseases and the rate of spread is expected to increase due to high risk factors in low-income countries.[39-41] It is noteworthy that some studies have shown that an increase in oxidative stress is a causative factor for programmed and unprogrammed cell death of cardiomyocytes as well as molecular and cellular changes in the heart. Oxidative stress has also been associated with abnormalities related to calcium handling in cardiomyocytes and the loss of sensitivity of myofilaments to calcium. Nitrosative stress due to activation of NO synthase is one of the major causes of endothelial dysfunction seen in cardiac diseases. Palmitoyl carnitine oxidation which occurs due to increased fatty acid uptake by the myocardial tissue also results in increased ROS production and structural changes in mitochondria of cardiac cells.[15] Thus, it appears that high mortality due to cardiovascular disease may be related to increased levels of both oxidative and nitrosative stress in the body.

a. Production of oxidative stress in the heart

Mineralocorticoid receptors (MR) are corticosteroid receptors, the overactivation of which has been observed in many cardiovascular diseases.[42-45] The activation of these receptors occurs through the stimulation of Rac1 GTPase by increased oxidative stress in a ligand-independent manner. The activation of Rac1 induces an increase in the transcription of MR and development of cardiac dysfunction. Furthermore, the activation of Rac1 leads to increased translocation of MR causing accumulation of MR inside the nucleus.[42, 46] The activated MR then recruit NADPH oxidase (NOX), which increases the production of ROS to cause cardiac dysfunction.[46, 47] This process also produces DNA damage in the pressure-overloaded heart and is considered to be one of the major sources of increased oxidative stress in the failing heart.[15, 47] Increased production of ROS through the activation of Rac1 in cardiomyocytes forms a feed-forward loop, causing cardiomyocyte damage.[43] In addition, oxidative stress alters nuclear MR translocation through which MR signal transduction is activated to increase oxidative stress.[41, 42, 48] It should be noted that the family of NOX enzymes, which are transmembrane proteins, play very important roles

in the development of oxidative stress. Acute myocardial infarction and reperfusion injury are associated with activation of phagocytic NO synthase which also results in an increase in ROS.[15] The ROS thus formed act on various targets like protein tyrosine kinases, protein kinase C, protein tyrosine phosphatases, calcium channels as well as MAP kinases and transcription factors to produce a wide variety of cardiovascular abnormalities.[17] These ROS specific redox signals have been shown to cause cell death and apoptosis in cardiovascular diseases.[49]

Angiotensin II, catecholamines and the pro-inflammatory cytokine, TNF-a, have been reported to produce abnormal stimulation of nonphagocytic NO synthase, which can lead to collagen deposition, fibrosis and heart failure.[15] The activation of guanine protein- coupled angiotensin receptors (AT_1R) by angiotensin II also leads to the transactivation of endothelium growth factor (EGF) receptors through ROS.[49] When angiotensin II binds the AT_1R, it causes the receptor to get into the lipid raft and results in the formation of ROS from a complex involving Rac1. The increased ROS then promote phosphorylation of tyrosine residues of the EGF receptor in a calcium-dependent manner.[50] This phosphorylated EGF receptor acts as a scaffold for other signal molecules and forms a signalling platform, which activates extracellular signal-regulated kinase 1/2 (ERK1/2) as well as Akt, and leads to vascular hypertrophy.[17, 49, 51] Such a change results in the assembly of downstream signalling complexes, which also leads to vascular hypertrophy and hypertension.[49, 52, 53] Angiotensin II generates ROS by activating various signalling pathways associated with phospholipase C, phospholipase D and phospholipase A2. Activation of phospholipase A2 releases arachidonic acid which results in the production of ROS. When phospholipase C is activated, it leads to the hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG).[54] The formation of IP3 triggers the IP3-Ca^{2+} release pathway whereas DAG activates protein kinase C (PKC), both of which produce an increase in ROS by activating the NADPH oxidase complexes.[50] Oxidative stress has been demonstrated to cause more angiotensin II to bind to AT_1R and more intense intracellular accumulation of IP3 due to higher levels of activation of the phospholipase C pathway. Oxidative stress also increases AT_1R and sodium-hydrogen exchanger 3 in proximal tubular cells. Thus, oxidative stress makes phospholipase C more sensitive to angiotensin II ef-

fects and increases sodium retention in the body to elevate the blood pressure. Because there is an increase in the expression of AT_1R by angiotensin II, it has been suggested that the presence of a positive feedback loop for this hormone may also increase the blood pressure further.[55]

Angiotensin II has been observed to cause deletion in mitochondrial DNA and induce cardiomyocyte autophagy. High levels of circulating angiotensin II for a long time produce calcium overload in mitochondria, decrease mitochondrial function and increase oxidative stress.[15] It may be noted that monoamine oxidase in mitochondria is also a major source of ROS production and leads to the degradation of neurotransmitters like norepinephrine, dopamine, epinephrine and serotonin. Some heart diseases are associated with increased plasma levels of serotonin and catecholamines, which may be degraded by monoamine oxidase to increase the production of ROS and worsening the heart disease.[15] The vascular layers of the cell like endothelium and adventitia also produce ROS and thus play an important role in regulating vascular tone and inflammation. These ROS act as mediators and regulators of vascular functions[17, 51, 56] and when present in excess, these can lead to vascular cell damage, necrosis and apoptosis by directly oxidising the structural molecules.[17, 56]

b. Cardiac effects of oxidative stress

Both oxidative and nitrosative stress have been reported to produce calcium handling defects in subcellular organelles like mitochondria, sarcoplasmic reticulum and sarcolemma. In various cardiovascular diseases,[15] several changes are seen in the diseased myocardium which are associated with oxidative stress and these include elevated levels of inflammatory cytokines as well as reduction in antioxidant enzyme activities and the function of non-enzymatic anti-oxidant systems. The increased oxidative stress then leads to subcellular defects and cardiac dysfunctions through various downstream mechanisms such as lipid peroxidation, proteases activation, myocardial inflammation, inactivation of functional groups, alterations in gene expressions, changes in contractile proteins and mitochondrial calcium overload.[15] Oxidative stress causes changes in the sarcolemma and sarcoplasmic reticulum and induces intracellular calcium overload in cardiomyocytes. It also reduces the activities of Na^+-K^+ ATPase and Na^+-Ca^{2+} exchange systems to further increase the intracellular calcium. In addition, oxidative stress induces changes in the

ryanodine receptors (RyR1), in the sarcoplasmic reticulum and makes them leaky for releasing calcium into the cell and producing downstream muscle damage.[57] Prolonged oxidative stress and calcium handling abnormalities produce a loss of calcium sensitivity to myofibrillar ATPase which may cause myofibril degeneration and derangements. Functioning of mitochondria is impaired due to calcium overload whereas oxidative stress induces an increase in mitochondrial ATPase inhibitory factor 1 which worsens the calcium handling.[57] Calcium handling abnormality by the sarcoplasmic reticulum due to oxidative stress has been reported to result in the development of arrhythmias.[15]

It is noteworthy that heart failure is the most prevalent chronic cardiovascular disease which is associated with retention of fluid in the body, peripheral oedema and pulmonary congestion.[58] There are several underlying causes for heart failure and some of these include myocardial infarction, hypertension, cardiomyopathy and valvular heart disease. All these conditions induce structural changes in the heart and lead to impairment of its pumping ability.[58, 59] Blockade of coronary arteries results in reduced blood flow to some areas of the heart leading to cell death and causing myocardial infarction. Although the degree of heart failure due to myocardial infarction is dependent on infarct size, some other factors such as immune activation, inflammation, oxidative stress, changes in mitochondrial bioenergetics and autophagy are considered to be involved in the progression from cardiac hypertrophy to heart failure.[60-62] It is generally believed that an increase in ventricular wall tension as well as oxidative stress lead to cardiac remodelling and subsequent heart failure.[63] Various vasoactive hormones, which are released into circulation upon the blockade of coronary arteries also constrict small vessels in the hypertrophied heart and produce hypoxia for the development of oxidative stress.[64] It is also pointed out that cell death in myocardial infarction is caused by many defects including apoptosis, necrosis, pyroptosis and ferroptosis.[60] These pathways are interrelated but are induced through various factors such as oxidative stress and inflammation. Oxidative stress is considered to play a major role in the pathogenesis of ferroptosis whereas pyroptosis is mainly an inflammation-mediated cell death.[60, 65] Both these pathways of cellular damage involve canonical signalling which is associated with plasma membrane rupture and non-canonical signalling, which is related to

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changes in mitochondria or sarcoplasmic reticulum. Oxidative stress has also been observed to mediate insulin resistance through the necroptotic pathway and causes atherosclerotic damage. Some studies have shown that reduction in ROS led to a reduction of oxidative damage and necroptotic cardiomyocyte loss.[60] It is pointed out that hypertrophied hearts have an increased amount of antioxidants, but these are not enough to balance the amount of oxyradicals produced in the hypertrophied heart.[64] ROS oxidise cysteine thiols causing conformational changes that lead to increased release of calcium from the sarcoplasmic reticulum, thus reducing the amount of calcium present inside the sarcoplasmic reticulum; this is responsible for the dysfunctioning of excitation-contraction coupling in cardiomyocytes.[17, 66] Increased oxidative stress and calcium handling abnormalities in cardiomyocytes of the failing heart due to myocardial infarction modify myosin gene expression, decrease ATPase activity of myofibrils and impair the cardiac contractile force development.

Alterations in signalling pathways due to activation of the sympathetic nervous system and renin-angiotensin- aldosterone systems are responsible for the progression of heart failure.[58] Plasma levels of vasoactive hormones such as catecholamines and angiotensin II are increased in pathological conditions and these hormones increase the cardiac muscle mass and produce cardiac hypertrophy for decreasing the ventricular wall tension. However, prolonged exposure of the hypertrophied heart to these vasoactive hormones has been shown to produce calcium handling abnormalities and other subcellular defects for the induction of heart failure.[64] ROS are also responsible for the activation of several signalling kinases and transcription factors in hypertrophied hearts.[67, 68] Furthermore, ROS are known to cause extracellular matrix remodelling by stimulating cardiac fibroblast proliferation and activating matrix metalloproteinases.[69] In fact, the activation of both the sympathetic nervous system and the renin-angiotensin system has been reported to increase the level of oxidative stress which contributes to the progression of heart failure.[70] Failing hearts have also been observed to show an increase in the expression of genes, which code for cytokines and increase the activation of both innate and adaptive immune systems; this observation indicates that inflammation is linked to the development of heart failure.[71]

Pharmacotherapy and intervention strategies for the treatment of cardiovascular disease

Important pathological events in the development of heart failure include elevated levels of vasoactive hormones, activation of the immune system, inflammation, oxidative stress, insulin resistance, formation of toxic substances, alterations in mitochondrial bioenergetics and autophagy.[72-81] These events have thus been considered to be the targets for drug developments and interventions in the treatment of cardiovascular diseases including heart failure. It has been found that blocking of lectin-like oxidised LDL receptor-1 (LOX-1) with an antibody produces inhibition of ROS generation and prevention of mitochondrial damage in heart failure; this is because the binding of ox-LDL to LOX-1 leads to the generation of ROS through activation of a series of downstream reactions.[82, 83] Mitochondria are one of the major producers of endogenous ROS and thus blocking of mitochondrial ROS by using mitoSNO has been observed to prevent cardiac dysfunction.[67] Some natural synthetic antioxidants have been studied for the treatment of cardiovascular diseases. A compound called resveratrol, a natural phytoalexin, has been identified to suppress the high glucose-induced generation of superoxide anion by increasing the phosphorylation of adenosine monophosphate-activated protein kinase. It has also been observed to elicit endothelium-dependent vasodilatations and alleviate endothelial dysfunction due to high glucose levels.[84] However, resveratrol has been reported to have varying levels of effects on cardiometabolic diseases or shows no to very little effect in some other diseases. On the other hand, olive polyphenols like oleuropein and hydroxytyrosol have shown significant results in preclinical trials. Most of the clinical studies have been performed to observe the effects of olive oil for its therapeutic actions on cardiovascular and cardiometabolic health. However, specific studies employing olive phenols as pure compounds have not been performed and thus more research is needed to know about the effects of olive polyphenols. Different preclinical trials in animals have also been carried out to show the therapeutic effects of other natural compounds like quercetin, catechins, curcumin, organosulphur compounds, melatonin, folic acid and glutathione on

cardiometabolic and cardiovascular diseases but well- organised detailed clinical trials are needed to support their effects in humans.[85-87]

Some studies have been conducted to examine synthetic compounds for anti-oxidant properties and their therapeutic effects in cardiovascular diseases. N – acetylcysteine (NAC) has shown some beneficial actions in improving cardiac function in preclinical trials but showed differing effects in various cardiometabolic diseases.[88] Thus, more research is needed to identify the role of NAC as a therapeutic option. Other synthetic compounds include superoxide dismutase mimetics (SOD mimetics) which have shown favourable effects in animal models but there is a lack of clinical studies to indicate their therapeutic use.[89] Probucol is another synthetic compound which has been reported to show significant preclinical and clinical results. Some clinical studies have indicated that probucol may be used as an additive for the treatment of cardiometabolic diseases but further research needs to be performed to examine its long- term benefit and safety.[85, 88, 89] There has been some developments to target mitochondrial abnormalities using small molecules as well as peptides and thus prevent heart failure; these interventions were found to help in mitochondrial detoxification and prevention of heart failure.[90]

Since accumulation of free iron within mitochondria is known to produce an excessive amount of ROS mitochondria- permeable iron chelators like deferiprone has been identified as a new intervention in cardiac disease prevention.[91] Other interventions include anti-oxidative therapies to target oxidative stress in the body by various methods.[92] At present, the best therapy in this regard seems to be the inhibition of xanthine oxidase by allopurinol or oxypurinol.[93, 94] Future antioxidative therapies in heart failure are considered to include increasing endogenous antioxidant capacity and increasing expression of antioxidant- producing enzymes.[92] MicroRNAs are also examined for their ability to act as regulators of endogenous oxidative stress in cardiovascular diseases but their application in humans needs more research.[85] Supplementation with precursors of major cellular antioxidants like GSH and NAD$^+$ has been shown to increase the endogenous antioxidant capacity.[93, 95] Another approach would be to improve the expression or activity of glutamyl cycle and NAD$^+$ producers to reduce oxidative stress.[96, 97] The inhibition of necroptotic pathways in cardiomyocytes has also been suggested to reduce cell death.[60] Likewise, various intermediates of the canonical and non-canonical pathways have been targeted by interventions such as protein kinase inhibitors like RIP1kinase inhibitors (necrostatins) and RIP3 inhibitors (GSK'872, HS-1371) for improving cardiac function.[60] In this regard, necrostatin-1 (Nec-1) has been observed to prevent remodelling in acute myocardial infarction as well as, post-myocardial infarction heart failure. It also blocks an enzyme in the inflammatory pathway and thus reduces inflammation- related cell death. Another drug necrosulfonamide, that inhibits MLKL in the canonical pathway has also been reported to depress oxidative stress.[60] Some studies have indicated that the signalling pathways that lead to cell damage under high oxidative stress conditions in right ventricular are different from those in the and left ventricular heart failure and thus further research is needed to incorporate the antioxidant therapy into the heart failure treatment options.[98]

Role of oxidative stress in neurodegenerative diseases

Neurodegenerative diseases occur when the nerve cells or neurons in the brain and spinal cord get damaged and eventually die. The degree of symptoms of neurodegeneration such as memory loss, hallucinations and loss of motor control is considered to depend upon the number of neurons which become damaged during the development of this disorder. These diseases strike in mid to late life and thus the condition of patients is expected to worsen as the population ages.[99] It is pointed out that neurodegenerative disorders affect millions of people all over the world and their rate is increasing for the most common diseases such as Alzheimer's disease and Parkinson's disease. The causes for these diseases are genetic factors, environmental conditions and lifestyle attributes.[100] It is also noteworthy that oxidative stress in the nervous system develops due to the large amounts of ROS and RNS produced by the activated microglia and endothelial cells.[101] The increase in oxidative stress in the nervous system leads to death of neuronal cells by apoptosis and excitotoxicity.[102, 103] RNS however have also been observed to be important biological messengers and thus play critical role in the transmission of signals in the nervous system.[104, 105] Neuronal

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damage in some neurodegenerative diseases has also been observed to be due to the activation of glutamate receptors; the excessive activation of these receptors leads to a marked influx of calcium into neurons leading to overstimulation of normal activity and neuronal damage.[106, 107]

It should be emphasised that mitochondria release various apoptotic factors in response to different environmental or internal body signals. These apoptotic factors are also responsible for neuronal cell death in neurodegenerative diseases.[108-110] Excessive oxidative stress can cause mitochondrial DNA damage and genetic mutations which are considered to be associated with neurodegenerative diseases. Genetic aberrations such as single gene disease, proteasome dysfunction and protein misfolding are some conditions which are responsible for neurodegenerative diseases. In addition, complex interactions among multiple predisposing genes have been shown to result in various disease states and worsen the existing neurological disorders.[105, 111] It should also be mentioned that NO is known to play an important role in the transmission of signals throughout the nervous system. It is involved in the regulation and proliferation of vascular smooth muscle cells, leukocyte adhesion, angiogenesis, thrombosis and hemodynamics.[105, 112] Excessive amount of NO leads to the production of reactive nitrogen species in the body and thus can lead to nitrosative stress and neuronal damage. High concentrations of NO are toxic as these combines with tyrosine residues in the body which are needed for proper functioning of the ribonucleoside diphosphate reductase system.[105, 112, 113] Furthermore, several sources of ROS in the nervous system are the excitatory amino acids and neurotransmitters in the brain and neuronal tissue. These amino acids get metabolised and produce ROS which increase oxidative stress. ROS attack glial cells, which maintain homeostasis, protect neurons and form myelin in the nervous system and thus cause neuronal damage.[108, 114]

One of the major neurodegenerative diseases is Alzheimer's disease (AD), which is characterised by abnormal deposition of amyloid beta peptide especially in the hippocampus. The intracellular accumulation of neurofibrillary tangles and hyperphosphorylated T proteins result in the loss of synapses and dendritic spines, as well as hypoperfusion and hyperaemia. The oligomeric amyloid beta peptide is responsible for the symptoms seen in AD and also serves as the diagnos-

tic criteria of this diseases upon the estimation of oxidative stress.[115-117] Mitochondrial defects also play an essential role in the neuron degeneration in AD by generating excessive amounts of ROS, activating mitochondrial permeability transition pores, excitotoxicity, impaired production of adenosine triphosphate and altered homeostasis of calcium.[118-119] Since metal ions like copper and iron play some critical roles in the production of neurodegenerative diseases, iron has been observed to react with hydrogen peroxide and generate ROS in lysosomes to cause oxidative damage.[120] The presence of increased levels of redox-active iron has also been observed to trigger amyloid plaque formation. Another pathway by which iron generates oxidative stress is ferroptosis which has been identified as the major cause of neuronal cell death in neurodegenerative diseases. Ferroptosis refers to programmed cell death which is caused by accumulation of lipid peroxides in the cell.[121-123] Loosely bound metal ions like copper act as catalysts for the production of ROS and in fact an increase in the amount of loose copper ions has been detected in AD. Copper ions bound to amyloid plaques have also been demonstrated to contribute to oxidative stress.[124-126] It may be noted that increased oxidative stress in the neuronal cells has been reported to oxidise some proteins and reduce the activities of enzymes like creatine kinase, glutamine synthetase and glutamine synthase in AD.[118, 127, 128] Oxidation of proteins is also responsible for the hyperphosphorylation of T proteins through microtubule-associated protein kinase pathway and activation of transcription factor nuclear factor. This thus leads to formation of neurofibrillary tangles which are one of the major characteristics of AD.[105, 129]

Pharmacotherapy and intervention strategies in treatment of neurodegeneration

Antioxidant therapies are one of the major areas of research in the treatment for neurodegenerative diseases and thus several studies have discussed the mechanisms and identification of targets for preventing the impact of oxidative stress in inducing neurodegeneration.[130-142] Therapeutic

options for upstream oxidative stress include enzymes and antioxidants to reduce the generation of free radicals and interrupt the interaction between neuronal protein and oxidative stress.[143, 144] Downstream antioxidant therapy in neuronal disorders due to oxidative stress includes preventing neuronal inflammation and scavenging the free radicals produced.[144-146] The use of antioxidants to prevent oxidative damage caused by Fenton-like reactions involving iron is also considered to be a therapeutic intervention.[121] G- protein coupled receptors (GPCR) are the largest family of transmembrane receptors and have been observed to be involved in the pathology of many neurodegenerative diseases. Allosteric modulators of GPCR and neuropeptides have also been used for the treatment of neurodegenerative diseases.[147, 148] A study has also been observed to minimise plaque production in AD by genetic deletion of mGluR5 receptor which belongs to the GPCR family.[149] Targeting of serotonergic receptors such as serotonin- 6 receptor ($5-HT_6R$) has also been identified as an intervention for the treatment of AD.[150, 151] Other types of intervention strategies include the use of iron chelators such as deferiprone which targets iron metabolism.[152]

Currently used treatment of AD is based on cholinergic hypothesis, according to which deficiency of acetylcholine (ACh) is observed in the central nervous system in patients suffering from this disease. Thus, the current approach is the cholinergic replacement strategy which was attempted to use muscarinic and nicotinic cholinergic ligands and acetylcholinesterase inhibitors.[153, 154] Other treatments used are dual-binding site AChE inhibitors, dual-binding AChE and BACE-1 inhibitors and AChE inhibitors and calcium channel blockers. Non-AChE directed multitarget drug developments and multitarget bioavailable metal chelators are also under study in the treatment of AD.[154] Some examples of drugs in use for the treatment of AD include aducanumab and tacrine. Aducanumab is a human monoclonal antibody which has been observed to enter the brain, bind to parenchyma beta plaques and reduce soluble and insoluble amyloid beta plaques in a dose-dependent manner in AD.[155, 156] Tacrine is a non-selective AChE inhibitor and was the first approved drug for AD. It is however no longer in use because it was observed to have some adverse effects and dose-dependent hepatotoxicity. A derivative of tacrine called HLS-3 has been found to show similar central effects and lesser peripheral adverse effects as compared to oral tacrine.[157-159]

Role of oxidative stress in some cancers

Cancer is rising worldwide as it caused approximately 10 million deaths in 2020.[160] According to WHO, 18.08 million cases of cancer were diagnosed with cancers of lung, breast and prostate being the most frequent; lung cancer in men and breast cancer in women are most frequently diagnosed. The most deadly cancers are of lung, liver and stomach and these are the most common cause of mortality for men. In women, breast cancer has the highest rate of mortality followed by lung and stomach cancers. It has been estimated that the mortality rate of cancer will become greater than the mortality rate of ischaemic heart disease by 2060.[161] Common causes of cancer are tobacco use, high body mass index, alcoholism and sedentary lifestyle. Cancer can also be caused by some infections like hepatitis and human papillomavirus (HPV) which account for about 30 % of cancer cases in low and lower-middle income nations.[160]

ROS have been identified to have distinct effects on cellular components and have both pro-tumorigenic and antitumorigenic effects.[162] Since ROS are involved in normal cell metabolism and cell signalling as well as ageing and diseases due to irreversible damage to lipids, DNA and proteins,[163] ROS have been observed to promote proliferation and survival of cancer cells, angiogenesis and metastasis in mouse cell models and human cell lines.[162, 164, 165] ROS also activate stress-induced signalling pathways that can induce cell cycle arrest, senescence and cancer cell death.[164] Autophagy helps to maintain genomic stability not only by suppressing chronic tissue damage but may also promote tumour growth by suppression of p53 response which prevents the diversion of tumours to benign oncocytomas.[163-166] Autophagy removes damaged organelles like mitochondria and limits ROS amplification.[167-169] Increased levels of ROS have been shown to cause oxidation of guanine and irreversible cysteine modification in addition to acting as carcinogenic and promoting genomic instability.[164-170] Environmental carcinogens such as cigarette smoke have been observed to have very high amounts of ROS which are involved in cells mediated by oncogenes or loss of tumour suppressors as is seen in the downregulation of p53.[163] ROS are also believed to promote tumour through the activation of mitogenic

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signalling pathways like PI3K/AKT/mTOR and MAPK/ERK signalling cascades.[171-173] ROS have been reported to be involved in the loss of cell-to-cell adhesion due to which the tumour cells break through the cell basement membrane and cause metastasis.[164-174] Endogenous oxidants have been shown to prevent initiation of tumour; GPX3 suppresses tumour initiation in mouse models of colon cancer,[175] SOD gets localised to mitochondria and block cancer cell proliferation[176] and peroxiredoxin inhibits cancer cell growth.[177] Exogenous antioxidants such as N-acetyl cysteine, vitamin E[178] and vitamin C have also been observed to have antitumour as well as some tumour proliferating effects.[179] Amino acids were shown to regulate ROS balance in cancer cells and act as protective factors against cancers. Glutamate and methionine were demonstrated to modify levels of NADPH in cancer cells and helped to maintain ROS levels below the toxic threshold along with cysteine which has strong antioxidant properties.[180-182] Some genetic alterations like ectopic expression of oncogenes Ras,[183] loss of tumour suppressor p53[184] and genetic ablation of the gene encoding breast cancer (*Brca1*)[185] have been observed to increase ROS levels and induce tumorigenesis. These observations suggest that the development of oxidative stress plays a critical role in the genesis of some types of cancer.

Pharmacotherapy and intervention strategies for the treatment of cancer

Since ROS are the major cause of cancer progression, many treatments target ROS to prevent the development of cancer. Several natural antioxidants and phytochemicals have been introduced as anti-cancer therapies as they have anti-proliferative and pro-apoptotic effects.[186, 187] However, there are studies which have indicated that targeting ROS by antioxidants to reach normal cell concentrations for destroying tumours presents many problems which need to be addressed.[180] Cancer cells are known to thrive on ROS levels which are moderately higher than those in normal cells. Thus, therapeutic strategies are being developed to elevate ROS levels that do not exceed the redox adaptation of the cell and induce oxidative stress which is incompatible with cellular life.[188] In order to increase ROS levels and cause cell death, motexafin, gadolinium and anthracyclins have been used in cancerous cells.[189, 190] Antioxidant product inhibition can be achieved by depletion of GSH activity as is seen in the case of buthionine sulfoximine which inhibits GSH synthesis.[191] Imexon is used in the treatment of advanced stages of cancer as it disrupts GSH activity by binding to the thiol functional group of reduced GSH and thus depletes the GSH pool for antioxidant activity.[192, 193]

There are studies targeting cysteine metabolism and ferroptosis to limit tumour growth; however, there are many cancer cell lines which show resistance to this treatment and thus it is important to develop efficient drug-targeting methods.[180, 194, 195] Another therapeutic method is nanomedicine which involves many biocompatible and biodegradable systems that deliver conventional chemotherapeutic drugs in the body. These interventions help to increase the availability of drugs around the tumour tissue and improve their release. Nanoparticles have also been used in the diagnosis as well as treatment of cancer.[186, 196] Targeted therapy helps to modulate the specific site like tumour vasculature or intracellular organelles and leave the surroundings unaffected. This would help to make the treatment of cancer more specific and reduce the drawbacks of the treatment.[197] Gene therapy and expression of genes which trigger apoptosis and wild-type tumour suppressors are also considered to be good interventions and thus have been investigated.[198] Thermal ablation of tumours and magnetic hyperthermia are considered to be tools for precise medication and serve as substitutes for more invasive options like surgery.[199] Some fields still under study include targeted silencing mediated by siRNAa, radiomics and pathomics.[186] Phytochemicals which are secondary plant metabolites have been observed to potentiate the efficiency of chemotherapeutic agents by exacerbating oxidative stress in cancer cells.[200] Thus, these are the basis for the development of novel interventions for the protection and treatment of cancer.

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Conclusion

Change in the diet and unhealthy lifestyle have been a major cause of cardiovascular diseases, neurodegenerative diseases and cancer. The excessive production of ROS and the presence of excessive amounts of AGEs in modern diets cause an increase in the oxidative stress that leads to many chronic diseases, three of which were discussed in this review. There are commonalities among the pathogenic factors like ROS, AGE and NO that may cause these diseases. All these factors when present in excess create abnormalities in the metabolic pathways of the body by inducing an increased oxidative stress which further leads to many other problems like inflammation in the body organs as well as causing DNA damage or lipid deposition. The increased levels of ROS and AGEs result in activation of the immune system that leads to inflammation, which is also a common factor in these chronic diseases. The preventive strategies for all the three diseases include following a healthy lifestyle with moderate exercise and also intake of nutritious foods rich in antioxidants such as fresh fruits and vegetables. Antioxidants such as vitamins A, C and E; beta-carotenes and bioflavonoids are helpful in the reduction of oxidative stress. Consumption of foods rich in calories and high content of AGEs should be reduced as a common preventive strategy for cardiovascular and neurodegenerative diseases as well as cancer. Development of prevention strategies based on natural food resources and traditional medicines should be encouraged to prevent the occurrence of many chronic diseases. In addition, it is of great importance to develop more effective antioxidants with anti-inflammatory activities and other interventions for some combination therapies, if we have to improve the outcome of patients with chronic diseases.

Ethics

This study was a secondary analysis and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Conflicts of interest

The authors declare that there is no conflict of interest.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Jasneet K Tiwana (JKT):
0009-0008-7168-926X
Anureet K Shah (AKS):
0000-0003-1765-0942
Naranjan S Dhalla (NSD):
0000-0002-4894-4727

Author contributions

Conceptualisation: NSD
Validation: AKS
Data curation: JKT
Writing - original draft: JKT
Writing - review and editing: AKS, NSD

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