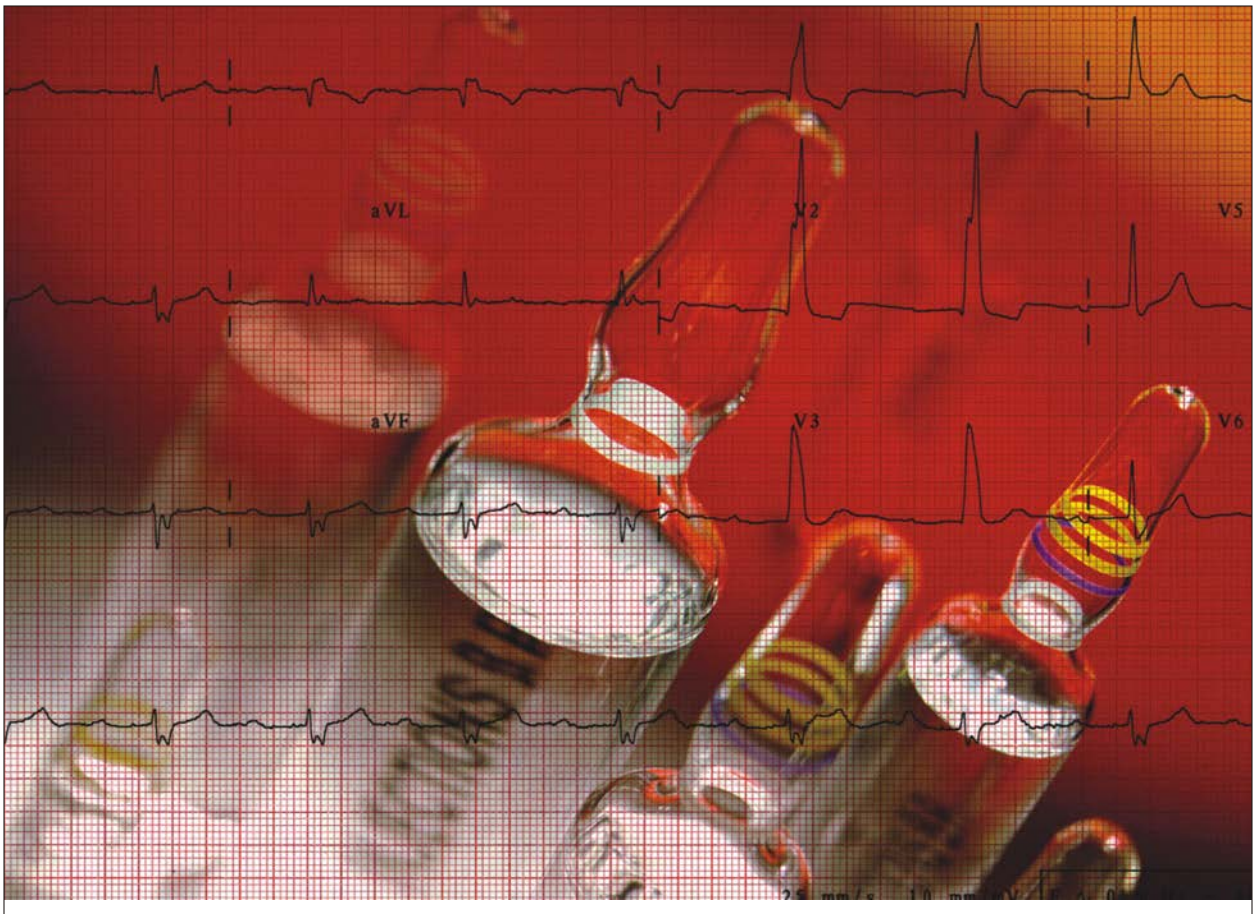

Current Research in **Cardiovascular Pharmacology**

ISSN 2152-193X

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OPEN ACCESS Current Research in Cardiovascular Pharmacology

ISSN 2152-193x
DOI: 10.3923/crcpaj.2017.1.16

Review Article
Physiological, Biochemical and Molecular Role of Oxidative Stress in Cardiovascular Disease: A Comprehensive Study

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Abstract

The metabolic disorder affects about 30% of the US population with escalating prevalence. In this study, the relationships between the metabolic disorder and the occurrence and rigorousness of cardiovascular disease in common and coronary artery disease in particular were explored. The impression of metabolic disorder on outcomes of coronary revascularization therapies and coronary collateral development was specifically compiled. Besides, the association between the metabolic disorder and its individual component pathologies and oxidative stress were also examined. Researchers discuss the apparent lack of encouraging influence of antioxidants on cardiovascular consequences in enormous clinical trials with stress on some of the restrictions of these trials. Lastly, researchers highlight verification for booming application of antioxidant assets of pharmacological agents, including metformin, statins, angiotensin II type I receptor blockers and angiotensin II converting enzyme inhibitors for preclusion and management of the cardiovascular impediments of the metabolic disorder.

Key words: Angiotensin II, coronary artery disease, metabolic disorder, oxidative stress

Received: August 18, 2016 Accepted: November 06, 2016 Published: December 15, 2016

Citation: Sanjay Mishra, Amit Kumar Mani Tiwari and Abbas Ali Mahdi, 2017. Physiological, biochemical and molecular role of oxidative stress in cardiovascular disease: A comprehensive study. Curr. Res. Cardiovas. Pharmacol., 6: 1-16.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Metabolic disorder is an ailment of energy exploitation and storage, recognized by a co-occurrence of three out of five of the following medical state of affairs: Abdominal (central) obesity, raised blood pressure, elevated fasting plasma glucose, high serum triglycerides and low high-density cholesterol (HDL) levels. The metabolic disorder upsurges the danger of emerging cardiovascular disease, predominantly diabetes and heart failure[1]. Certain studies have revealed the prevalence in the USA to be an approximate 35% of the adult population[1] and the prevalence increases by means of age. Further, metabolic disorder defines a group of self-determining risk factors, most likely aggregating the likelihood of cardiovascular disease[2-4]. This disorder affects about 30% of the United States population with escalating occurrence[5]. Although an accord norm has not been attained for diagnosing metabolic disorder, it is recommended screening to be considered as insulin resistance, central obesity, dyslipidemia and high blood pressure[6]. Additional factors such as pro-thrombotic and pro-inflammatory states have also been taken together with metabolic disorder[7].

Increased cardiovascular risk in the metabolic disorder is the consequence of a multi-faceted communication of the individual risk factors that is still obscure. For example, although central obesity is a defining feature of the metabolic disorder, a study of middle aged men with metabolic disorder brings into being that cardiovascular risk is also augmented autonomously of body mass index with the metabolic disorder[8]. Furthermore, an association of increased risk of ischemic heart disease as well as ischemic stroke in metabolic disorder was pragmatic in a study concerning with less obese metabolic disorder patients[9]. In human vascular diseases, endothelial dysfunction is a systemic pathological state of the endothelium and can be largely defined as an imbalance between vasoconstricting and vasodilating substances created by/or acting on the endothelium[10]. Customary functions of endothelial cells comprise mediation of coagulation, platelet adhesion, immune function and control of volume and electrolyte content of the intravascular as well as extravascular spaces. Endothelial dysfunction can contribute to a number of disease processes, as takes place in hypertension, hypercholesterolaemia, diabetes, septic shock, Behcet's disease and it can also outcome from environmental factors, e.g., from smoking tobacco products and exposure to air pollution[11]. Endothelial dysfunction is more prevalent in shift workers, identified to have a greater menace for cardiovascular diseases[12]. Nevertheless, most of these studies on human participants have tangled the percentage flow-mediated dilation (FMD%) index as the investigation product that has just been exposed to be inconsistent without suitable statistical contemplation. Further, endothelial dysfunction is a crucial physiopathological mechanism, foremost coronary artery disease and other atherosclerotic diseases[13]. Thus, metabolic disorder upsurges the possibility of cardiovascular disease to a magnitude more than the possibility of conferring by any of its individual components. Amplified oxidative stress has arisen as playing a principal accountability in metabolic disorder and its component pathologies and may probably be a unique feature in the development of this disease. Reactive Oxygen Species (ROS) are known to be extremely reactive derivatives of oxygen metabolism. These short-lived molecules play key roles in normal physiological, biochemical and molecular processes viz., gene expression and signal transduction. In a healthy condition, ROS are sustained at an optimal level due to an equilibrium between their creation and removal by enzymatic (superoxide dismutase, glutathione, catalase and peroxidase) and non-enzymatic (vitamins C and E) antioxidants. In a pathological state such as the metabolic disorder, an augmented oxidant capacity combined with declined antioxidant capacity generates an uneven environment resulting in oxidative stress[14]. Increased ROS levels established during oxidative stress have toxic effects on cells and tissues through augmented oxidation of carbohydrates, lipids and proteins. The ROS have been observed to play a foremost role in the development and progression of cardiovascular disease[15-17]. Moreover, oxidative stress has been recognized as a major mechanism of micro- and macro-vascular complications in the metabolic disorder[18].

COMPONENT PATHOLOGIES OF METABOLIC DISORDER AND OXIDATIVE STRESS

Oxidative stress is a characteristic of the metabolic disorder: Patients with metabolic disorder frequently develop sophisticated atherosclerosis. Oxidative stress acts as innermost role in the initiation and progression of atherosclerosis. The NAD(P)H oxidases are the major source of ROS in the vasculature. Augmented expression and activity of the phagocytic NAD(P)H oxidases with a corresponding increase of oxidized LDL (oxLDL) and nitrotyrosine levels accompanied by thickened intima to media ratio in the carotid arteries, pinpointing an early subclinical atherosclerosis have been established in metabolic disorder patients[19]. It has moreover been found that sub fractions of small HDL cholesterol particles, which are usually shielding, possesses

poorer antioxidant capacity in the metabolic disorder[20]. Increased oxidative stress coupled with increased production of ROS[14] is augmented by decreased expression of antioxidant enzymes. Investigations in a diet-induced rat model of metabolic disorder found augmented oxidative stress followed by endothelial dysfunction. This study further demonstrated increased ROS creation competence by the NAD(P)H oxidase along with down-regulation of key superoxide dismutase (SOD) isoforms representing a disrupted antioxidant protection system in metabolic disorder[21]. Reports of the 'Third National Health and Nutrition Examination Survey', pin-point diminished concentrations of the antioxidants vitamins C, E and numerous carotenoids in spite of adjusting for lower vegetable and fruit consumption in participants with metabolic disorder[22]. Therefore, it is obvious that the human metabolic disorder is characterized by oxidative stress precipitated by surplus generation of ROS and diminished antioxidant resistance[14].

Oxidative stress versus obesity: Recently, there have been a number of efforts to describe the contribution of the individual components of the metabolic disorder to oxidative stress marked in the patients. Obesity is a nuclear component in the expansion of metabolic disorder playing a vital role in amplified oxidative stress. Obese patients have exposed oxidative stress-induced decreased vasodialatory reaction to acetylcholine, inversely correlated to body mass index, waste to hip ratio, fasting insulin and insulin resistance[23]. Obesity in children, without any other metabolic disorder components has been repetitively connected with increased oxidative stress and endothelial dysfunction[24]. Weight loss (10% of body weight) by moderate diet restriction and moderate-intensity aerobic exercise in metabolic disorder patients has been revealed to perk up markers of oxidative stress[25]. These findings put forward that a general inflammatory stress state coupled with childhood obesity, remarkably with abdominal fat deposition may play a vital role in the progress of the most primitive stages of pro-atherosclerotic inflammatory processes followed by vascular dysfunction. These fluctuations might be partially reversible by short-term diet and exercise involvement, even though patients do not attain model body weight. In contrast, data from an intensive 21-day residential diet and exercise program in overweight or obese patients exposed a decrease in oxidative stress and development in other markers of cardiovascular risk connected with metabolic disorder even before noteworthy weight loss[26]. This cause could have been mediated by a reduction in oxidative stress through exercise-mediated progress in endothelial function and Nitric Oxide (NO) production or up-regulation of antioxidant defenses. In various animal models, ROS creation in adipose tissue of obese mice was abridged by treatment with the NAD(P)H oxidase inhibitor apocynin resulting in progress in glucose and lipid metabolism independent of body weight[27]. Long-term studies are needed to see if these short-term effects render to long-term cardiovascular outcomes.

Oxidative stress versus insulin confrontation: The isolated contribution of insulin resistance to oxidative stress is complicated one and investigations probably addressing the question of oxidative stress in type II diabetes characteristically do not differentiate between the study participants on the basis of obesity or their lipid profile. This presents a noteworthy obstruction with respect to confirming whether insulin resistance on its own elevates oxidative stress in humans. Similarly, the animal models of insulin resistance are obese and the insulin resistance develops secondary to obesity. Augmented ROS have also been shown to have a causal role insulin resistance[28]. Both Tumor Necrosis Factor-α (TNF-α) and dexamethasone decreased Akt phosphorylation and thus glucose uptake into cultured muscle cells which was inverted by antioxidant treatment (N-acetyl cysteine (NAC), SOD, catalase, manganese (III) tetrakis (4-benzoic acid) porphyrin (MnTBAP)). The similar study moreover projected that glucose uptake was compromised in obese (db/db) mice *in vivo* ensuing in increased blood glucose and antioxidants lowered blood glucose[28].

Oxidative stress versus hyperglycemia: While hyperglycemia *per se* is not an important parameter of the metabolic disorder, hyperglycemia resulting from primary β-cell devastation in lack of any other gears of the metabolic disorder, has been shown to link with prominent oxidative stress (decreased glutathione, GSH/GSSG ratio) in type I diabetes[29]. Conversely, this may or may not be relevant to the metabolic disorder, wherever hyperglycemia develops secondary to the development of insulin resistance.

Oxidative stress versus dyslipidemia: Dyslipidemia specified by prominent LDL and triglycerides and lowered HDL is moreover a common component of the metabolic disorder phenotype. A positive relationship between elevated LDL and triglycerides and low HDL and oxidative stress in animal models is well recognized. The LDL receptor-deficient mice fed a cholesterol-enriched diet developed elevated LDL levels and thus oxidative stress[30]. These annotations widen to human studies. High plasma oxidative stress markers certainly interrelated with increased plasma triglycerides and inversely correlated with low HDL[31] in a group of metabolic disorder patients with end-stage renal disease, after all other factors

(presence of obesity, hypertension and/or type II diabetes) were accustomed. Lipid peroxidation, as an index of oxidative stress, interrelated with low HDL levels, regardless of age, gender and presence of the other metabolic disorder components[32]. It is furthermore accepted that the several positive impacts of some statings in the cardiovascular system are independent of their lipid-lowering effect and a result of a direct decline in oxidative stress. For example, short-term pravastatin treatment reduced Myocardial infarction (MI) size in hypercholesterolemic rabbits through decrease in peroxynitrate and nitrotyrosine formation[33]. Corresponding results, with respect to the atherogenic index were obtained with rosuvastatin that decreased oxidative stress by elevating the expression of antioxidant enzymes (SOD, catalase and glutathione peroxidase), LDL, triglycerides, C-reactive protein (CRP) and HDL[34].

Oxidative stress versus hypertension: Hypertension is another component of the metabolic disorder that is independently connected with increased cardiovascular risk. While animal models of hypertension have also been quite constantly associated with elevated oxidative stress, whether hypertension by itself increases oxidative stress in humans is a bit controversial. An investigation found no distinction in markers of oxidative stress as comparing hypertensive and normotensive patients[35], while various studies monitored elevated oxidative stress in hypertensive patients[36,37]. A study in metabolic disorder patients revealed that other metabolic disorder components (low HDL, triglycerides, abdominal obesity and fasting glucose) had least contribution to elevated oxidative stress, whereas hypertension by itself was accountable for increased oxidative stress in these patients[38]. This investigation, however, used the International Diabetes Federation (IDF) definition for metabolic pattern that employs Body Mass Index (BMI) as an indicator of central obesity and has been criticized for under diagnosing metabolic disorder patients[39]. The Adult Treatment Panel (ATP) III metabolic syndrome definition that uses waist circumference as a measurement of central obesity has been demarcated to be a better forecaster of mortality than the IDF description[40]. It is not apparent how the effects of hypertension were alienated from the effects of the other risk factors in the recognized pathology of the metabolic disorder in this study. In another study viewing a positive link between hypertension and oxidative stress, apparently imperative hypertension was found to in fact be secondary to insulin confrontation[41,42]. These studies exemplify that attempts to recognize the etiology of oxidative stress in human metabolic disorder where hypertension is a constituent are complicated by the propensity of additional metabolic disorder components and thus interpretation of the study consequences as perplexing factors so that the isolated contribution of hypertension to oxidative stress becomes complicated to settle on.

Additionally, unlike the other component pathologies of the metabolic disorder, hypertension is itself a multifactorial disease with a variety of possible etiologies. Oxidative stress has been exposed to upsurge deoxycorticosterone acetate-(DOCA-) salt[43], angiotensin II-(Ang II-)-infusion[44] and 2-kidney-1-clip-induced[45] as well as in genetic animal models of spontaneous hypertension (SHR). Though, norepinephrine-induced hypertension does not escalate oxidative stress in a rat model[46]. These studies may point out whether or not human hypertension is connected with oxidative stress and hinges on the predominant etiology of the disease in the individual patient. This may explain the apparent discrepancy among the studies sketched above.

Lesion from children with metabolic disorder: Though, a definition of the metabolic disorder in children has not been agreed upon, progress of characteristics of metabolic disorder is progressively more prevalent in children and adolescents. Childhood obesity has been linked with progress of cardiovascular risk elements[47]. Autopsies of young people exposed that increased number of cardiovascular risk elements consequences in augmented severity of coronary and aortic atherosclerosis[48]. A swine model of obesity revealed that early obesity is linked with vascular oxidative stress and endothelial dysfunction even before progress of insulin confrontation or systemic oxidative stress[49]. This was confirmed in obese children, where obesity without any other metabolic disorder components has been repetitively interrelated with increased oxidative stress and endothelial dysfunction[23,24]. Additional components of metabolic syndrome further increased oxidative stress in overweight children[50], possibly signifying that compounding the component pathologies of the metabolic disorder multiplies oxidative stress by some as yet vacillating factor.

Interaction among metabolic disorder, its constituent pathologies, environment and lifestyle elements: Cigarette smoke and air pollution are the most noteworthy external sources of oxidative stress. Epidemiological studies have revealed a clear association between increased air pollution and human morbidity and mortality. Production of ROS is the major mechanism, mediating these disadvantageous effects[51]. Short-term exposure to urban air pollution in healthy young adults caused in increased oxidative stress, which is not

restricted to respiratory system, especially the lungs[52]. The main arbitrators of air pollution-derived effects are aromatic hydrocarbon and metal-containing inhalable nanoparticles, penetrating the alveolar septal barrier and thus produce oxidative stress both via activation of alveolar macrophage and systemic vascular oxidases including the NAD(P)H, mitochondrial and xanthine oxidases[53,54]. Aromatic hydrocarbons produce ROS through redox cycling of quinone-based radicals by forming complex(s) of metals occasioning in increased electron transport and by depletion of antioxidants by reactions between quinones and thiol-containing compounds. Metals directly support electron transport to produce oxidants and also reduce levels of antioxidants[51]. Besides, cellular responses to oxidative stress after nanoparticle exposure contribute to the overall damage[55]. Oxidative stress initiates activation of proapoptotic signal transduction cascades and release of inflammatory mediators, which ultimately lead to cell death, particularly of endothelial cells. Endothelial cell damage and death is a significant event in the progress and worsening of CAD and other vascular pathologies[55].

Cardiovascular consequences of cigarette smoke versus metabolic disorder: Smoking and air pollution intermingle with the metabolic disorder in ways, which are as yet inadequately understood but evidently merge to deliver a cardiovascular risk factor being greater than the sum of its parts. Smokers and ex-smokers are more likely to have higher rates of both metabolic disorder and its individual constituents than non-smokers[56,57]. Both cigarette smoking and the metabolic disorder are strong independent risk factors for cardiovascular disease; however, smoking too potentiates the negative cardiovascular effects of the metabolic disorder[58], principally mediated via ROS generation[59].

Cardiovascular concerns of environmental pollution versus metabolic disorder: Secondary to several studies having reported similar impacts[60,61], a scientific proclamation issued by the American Heart Association in 2010 implicated particulate matter air pollution as a trigger for cardiovascular disease. Studies exposed increased cardiovascular risk in both short- and long-term exposure with higher particulate matter air pollution related death risk for cardiovascular than for pulmonary diseases. Air pollution has been linked with an augmented risk of myocardial infarction[62]. Obese community may be at an increased risk[63]. In Sao Paulo, Brazil, cardiovascular disease emergency room visits were 20% greater in patients with type II diabetes than in non-diabetics representing that diabetics may be more vulnerable to the adverse effects of air pollution[64]. It is uncertain whether the patients could be classified as metabolic disorder or not. Another investigation reported a two-fold increased risk of MI in diabetic patients versus non-diabetics exposed to the same quantity of environmental pollution[65]. In both studies, end-points (emergency room visits and incidence of MI) were normalized to population statistics in areas of lesser air pollution. Nanoparticle and carbon monoxide air pollution elicited autonomic nervous system dysfunction that manifested in significant heart rate variations in metabolic disorder but not in normal subjects[66].

Additionally, studies in animal models and humans suggest that long-term exposure to environmental pollutants escalates progress of insulin resistance, hyperglycemia, hypertension, obesity and the metabolic syndrome. Workers in refineries and residents in surrounding areas have been found to have high incidence of the metabolic disorder[67-69]. Benzene derivatives, major byproducts of petrochemical reactions, induce hyperinsulinemia in a dose-dependent mode in animal studies, which could make available a mechanism of enlargement of insulin resistance in the metabolic disorder. Bisphenol A, an essential ingredient in plastic polymer production found in noteworthy quantities in the urine of about 95% of the US population, at doses 1000-fold less than those allowed by the Environmental Protection Agency (EPA) reduces glucose tolerance and induces insulin resistance[70] by decreasing glucose transporter 4 (GLUT-4) expression[71]. Long-term exposure to lead has been repetitively interrelated with hypertension[72]. Sub toxic levels of arsenic in drinking water have been correlated with high prevalence of type II diabetes in numerous studies across the world[73-76]. Arsenic inhibits Akt phosphorylation[77], an event critical for GLUT-4 transporter translocation to the membrane and glucose uptake. A study in mice revealed that long-term exposure to air pollutants may promote development of insulin resistance, obesity and thus metabolic disorder[78]. Thus, not only do air pollution and environmental toxins aggravate cardiovascular complications in patients with existing metabolic syndrome but they also uphold the development of the metabolic disorder.

Effect of diet on oxidative stress in the metabolic syndrome: Certain studies have been shown to explore a role for dietary stimulus on oxidative status. Mediterranean-style diet intervention consisting of increased intake of whole grains, fruits, vegetables, nuts and olive oil for about 2 years resulted in decreased CRP levels as well as improved insulin

resistance and endothelial function[79]. The CRP levels have been exposed to be increased by increased oxidative stress[80,81]. Advantageous effects of the Mediterranean diet are more supported by findings revealing increased consumption of virgin olive oil to upgrade antioxidant status with decreased oxidative stress[82]. In contrast, 'The Oxford Fruit and Vegetable Study Group' reported only a small upsurge in antioxidant concentration with accompanying reduction in blood pressure with increased consumption of fruit and vegetables in the diet of healthy subjects[83] signifying a greater benefit of dietary interventions for the metabolic syndrome population. Green tea supplementation reduced body weight and BMI and had an advantageous impact on lipid peroxidation in obese metabolic syndrome patients[84]. Consequences from a recent study support that sufficient dietary intake of dairy leads to an improvement in markers of oxidative stress in metabolic disorder[85].

METABOLIC SYNDROME AND ITS INDIVIDUAL COMPONENT PATHOLOGIES ON SEVERITY OF CARDIOVASCULAR DISEASE

Metabolic syndrome versus incidence and severity of coronary artery disease: Metabolic disorder patients have a considerably greater risk for the progress of cardiovascular disease in general and Coronary Artery Disease (CAD) in particular. A number of studies report a connection between metabolic disorder and carotid atherosclerosis[86]. The clustering of abdominal obesity with two or more constituent pathologies of the metabolic disorder without hyperglycemia resulted in an ~2.5 times (range 1.5-6.2) higher prevalence of elevated carotid intima-media thickness, an early indicator of subclinical atherosclerosis, whereas in those with hyperglycemia the prevalence was ~6 times (range 2.6-12.1) higher[87]. Elevated blood glucose on the background of abdominal obesity strongly connected with CAD development in women, while low HDL on the background of abdominal obesity was a stronger predictor for CAD progress and severity in men[88]. Even abdominal obesity alone, without supplementary metabolic disorder constituents, appears to predict future cardiovascular risk in men but not in women[89]. Additionally, increased occurrence of CAD, the metabolic disorder is linked with more severe ischemic CAD and a higher number of the metabolic disorder constituents have been connected with worse CAD by coronary angiography[90,91]. Patients with insulin resistance and hyperglycemia are ~2 times more probable to die of CAD than patients with CAD but without insulin resistance or hyperglycemia. Patients with all constituent pathologies of the metabolic disorder are ~3.6-4.4 times more probable to die of CAD[92,93].

The etiology for these phenomena may be associated with elevated oxidative stress in the metabolic disorder. Augmented oxidative stress has been strongly connected with atherosclerosis leading to CAD[94]. In fact, a specific element essential in the initiation of atherosclerosis, oxLDL has emerged as the single strongest predictor of CAD compared with the conventional lipoprotein profile (LDL, HDL and triglycerides) and other traditional risk factors (BMI or waist circumference, individual component pathologies of the metabolic syndrome or metabolic syndrome and smoking). Elevated oxLDL confers a 4.25 greater probability of CAD development[95] and has been found to directly link with HDL levels but fascinatingly to be independent of any other components of the metabolic disorder as well as age, gender and inflammatory markers. Thus, elevated oxLDL confers a similar risk to that imparted by the metabolic disorder but not by any of its individual constituents.

Metabolic disorder versus results of treatments for CAD: In addition to more severe CAD with worse long-term prognosis, current revascualrization therapies, Coronary Artery Bypass Grafting (CABG) and Percutaneous Transluminal Coronary Angioplasty (PTCA) in metabolic disorder patients are connected with higher procedural risk and poorer long-term consequences[96-98]. In a study of the 551 metabolic disorder patients who underwent coronary revascualrization by either CABG or PTCA, 256 underwent revascualrization within 10 years and 221 died within that time period (118 due to cardiovascular events)[99]. Metabolic disorder patients have been revealed to have an augmented inflammatory retort following PTCA than both healthy patients and patients with diabetes mellitus[99]. Besides, in a study in which patients were followed for 4 years after PTCA using sirolimus-eluting stents, occurrence of in-stent thrombosis after PTCA was as good as between metabolic disorder patients without insulin resistance or hyperglycemia and patients without metabolic disorder as 0.6 and 0.3%, respectively; however, annual death rates were 3 times higher in the metabolic disorder patients, i.e., 3%. In metabolic disorder patients with insulin resistance and hyperglycemia, in-stent thrombosis was six times higher (6.1%) and annual mortality 5 times higher (5.6%)[100,101]. Following CABG, metabolic syndrome patients have an augmented occurrence of adverse cardiac events and re-appearance of angiographically noteworthy lesions in 2 or

more vessels, due to either graft failure or new lesion formation, within 2-5 years. This effect appears to correlate closely with prominent triglycerides and blood glucose[102-104]. A recent study based on data from the research study accomplished at the Cleveland Clinic, USA over the last 20 years reflected HDL levels to be the most significant predictor of endurance in post-CABG patients[105]. This is appealing in light of low HDL being the only parameter that strongly interrelated with up surged oxLDL also appearing to most precisely predict CAD risk growth.

Impact of the metabolic disorder on consequences of treatments for CAD: With the restricted effectiveness of the current treatments for occlusive CAD in the metabolic disorder patient population, noteworthy effort has been aimed at developing alternative resources for coronary revascualrization. Tapering of the coronary arteries due to accumulation of atherosclerotic plaque pointers to decrease in blood flow to distal tissue. In response to augmented myocardial oxygen demand, heart tissue distal to the occlusion undergoes transient, Repetitive Ischemia (RI) as in steady angina pectoris. The physiological retort of the heart is to enlarge native collateral arterioles to conduit vessels in a process termed coronary collateral growth or arteriogenesis[106]. This protects the heart from ischemic damage by restoring blood supply to heart tissue distal to the occluded artery. However, the ability to enlarge native collaterals is impaired in metabolic syndrome patients[106]. The metabolic disorder remained an independent risk factor for poor coronary collaterals even after adjusting for type II diabetes[107]. The number or type of metabolic disorder constituents other than diabetes was not differentiated in this study. Sasmaz and Yilmaz revealed that an increasing number of component pathologies of the metabolic disorder correlated with increasingly poorer coronary collateral progress by angiography using the Cohen and Rentrop grading systems[108]. Besides, it has been resoluted that of the individual components of the metabolic disorder hyperglycemia, hypertension and insulin resistance negatively linked with coronary collateral development with hyperglycemia having the strongest negative link and insulin resistance the weakest[109]. Thus, refurbishment of coronary collateral development is a potential noninvasive strategy for treating occlusive CAD in this patient population.

Studies in animal models of diabetes and the metabolic disorder support the findings in humans. Coronary collateral growth in response to coronary artery occlusion has been exposed to be impaired in rat models of the metabolic disorder[110,111] and a dog model of dextrose infusion[112]. However, normal collateral development has been reported in a swine model of the metabolic disorder[113]. The most noticeable difference between the rat and dog models and the swine model is that the studies in the rat and dog models used transient, repetitive coronary artery occlusion to arouse collateral progress that mimics the situation in the human, whereas the swine model is a model of progressive chronic ischemia. As the exact spell of coronary occlusions has been connected with the extent of collateral growth[114,115], this difference between the two animal models is the possible explanation for the different aftermaths between the rat and dog versus the swine models.

Oxidative stress is evolving as a major underlying mechanism of impaired collateral growth in the metabolic disorder. It has now been clear for several years that an optimal amount of ROS or an optimal redox state of the cell (redox window) is absolutely required for coronary collateral growth. This topic was recently extensively reviewed[106]. Briefly, certain clinical research groups have confirmed that reduction of ROS below the lower boundary of this window reduces collateral growth but increasing ROS above the upper boundary of this window is likewise incompatible with collateral development[106,110,116]. Either decreasing superoxide with a flavin-containing oxidase inhibitor [diphenyleneiodonium (DPI)] or increasing with an SOD inhibitor [diethyldithiocarbamic acid (DETC)] abrogated coronary collateral growth in normal, healthy rats[116]. Furthermore, decreasing oxidative stress by apocynin or Ang II type I receptor blockade in normal rats diminished coronary collateral growth but meaningfully improved coronary collateral growth in the metabolic disorder rat model where basal and repetitive occlusion-induced oxidative stress is raised[109,110]. Consequently, in normal healthy animals, the amount of ROS produced by repetitive coronary occlusion is essential for coronary collateral growth. However, in the metabolic disorder animals where baseline levels of ROS are raised up, the amount of ROS produced by repetitive coronary occlusion is much higher and is not attuned with coronary collateral growth[105,106]. This mechanism might underlie the diminished coronary collateral progress in the metabolic disorder patients.

Of the probable sources of ROS, the sources most significant for the regulation of coronary collateral development have not yet been entirely resolved. Strong evidence now points to the mitochondrial sources of ROS. In a recent study, the mitochondria-targeted antioxidant MitoQ nearly completely reinstated coronary collateral development in a rat model of the metabolic disorder, the Zucker obese fatty rat (ZOF)[117]. Several studies propose that membrane

NAD(P)H oxidases are also important sources of ROS within the context of collateral growth[118,119]. Whether the crosstalk between membrane NAD(P)H oxidases and the mitochondria, phenomenon known as ROS-induced ROS release is functionally pertinent in collateral growth remains to be determined.

IMPACT OF ANTIOXIDANT THERAPIES ON THE METABOLIC DISORDER AND ITS INDIVIDUAL CONSTITUENT PATHOLOGIES

Lesions from antioxidant clinical trials: Consequences from clinical trials for improving cardiovascular results by antioxidant therapy, however have been changeable and confusing. Antioxidant supplementation in humans has not been as successful as expected although some studies have been encouraging. The HOPE and HOPE-TOO clinical trials evaluated long-term vitamin E therapy in patients at least 55 years old who had either vascular disease or diabetes mellitus. There was no improvement in cardiovascular consequences. Distressingly, there was an upsurge in heart failure and heart-failure-related hospitalizations[120]. Parallel results were achieved in the MRC/BHF heart protection study. In contrast, a collective analysis of nine cohort studies found that vitamin C but not vitamin E reduced incidence of major coronary heart disease[121].

However, multiple factors complicate the interpretation of the results of these trials. First, whether the antioxidant involvements truly succeeded in reducing oxidative stress in patients enrolled in the HOPE and the MRC/BHF trials was never ascertained[122]. As many of the patients enrolled in these trials were already on drugs with known oxidative stress lowering impacts, including Angiotensin Converting Enzyme (ACE) inhibitors or Ang II type I receptor inhibitors (ARBs), metformin and statins, it is possible that there was in fact no additional effect of antioxidants on ROS levels. In support of this proposition, vitamin E failed to lower oxidative stress in double-blind studies in healthy individuals with intact antioxidant defenses signifying that antioxidants are ineffective under conditions where there is no oxidative stress[123]. Furthermore, in animal studies, treatment with antioxidants decreased ROS levels and improved coronary collateral growth in metabolic disorder animals with raised basal oxidative stress but essentially reduced coronary collateral development in healthy animals with no evidence of basal oxidative stress[118], representing that administering antioxidants on the background of normal ROS levels does not converse a beneficial cardiovascular impact. Therefore, antioxidant supplementation does not decrease the risk of developing metabolic disorder in healthy subjects[124] and shortage of cardiovascular benefits found in the large scale clinical trials may not be evocative of untreated metabolic disorder patients. However, supplementation may recover cardiovascular risk in patients with established metabolic disorder as these are patients with a decreased antioxidant capability[125,126]. In metabolic disorder patients, infusion of vitamin C reduced oxidative stress markers and enhanced arterial flow-mediated dilation[127]. Daily cranberry juice for 8 weeks increased antioxidant capacity and reduced lipid oxidation in metabolic disorder women[128]. Second, the effectiveness of antioxidants used in clinical trials is low. Both vitamins E and C have really been revealed to have some pro-oxidant effects *in vitro*[129, 130] and are at the doses administered in the clinical trials, unlikely to affect plasma or tissue ROS levels[131]. Besides, vitamin E does not inhibit some substantial elements of ROS-induced damage in the metabolic disorder, for example, myeloperoxidase-induced lipid peroxidation[132]. Especially with respect to ischemic heart disease, evolving evidence recommends that reduction in mitochondrial oxidative stress may be critical for myocardial adaptations to ischemia, including collateral development and other aspects of ischemic preconditioning; the antioxidants in these trials were not targeted to the mitochondria and thus could not have reduced mitochondrial oxidative stress. Correspondingly, collateral development and myocardial perfusion *per se* were not the end-points in these trials; therefore, a multitude of additional factors, most probably heart failure, contributed to total consequences.

Antioxidant characteristics of metformin, statins, ARBs and ACE inhibitors: The advantageous effect of dropping oxidative stress on cardiovascular results in metabolic disorder patients can perhaps be further supported by beneficial impacts of the drugs characteristically used to treat the metabolic disorder and/or its various constituents, especially metformin, statins, ARBs and ACE inhibitors. All of these pharmacological agents have been observed to have valuable cardiovascular effects independent of their original purpose, that is glycemic control (metformin), lipid lowering (statins) and blood pressure regulation (ARBs and ACE inhibitors). These beneficial cardiovascular effects may be mediated by their antioxidant characteristics. Metformin has been presented to decrease intracellular ROS by up regulating thioredoxin in cell culture[133]. In human umbilical vein endothelial cell (HUVEC) culture, metformin inhibited advanced glycation end-product-(AGE-) induced ROS formation[134], also signifying a possibility that its protective effects on the vasculature are mediated via its direct antioxidant effects. In the rat kidney, metformin increased antioxidant defenses by upregulating catalase and

glutathione, accounting for noteworthy protection against diabetic nephropathy[135]. In a clinical trial study, metformin decreased carotid intima-media thickness, plasma indexes of inflammation and oxidative stress and ultimately arterial stiffness in a group of metabolic disorder patients[136].

It is also now accepted that the various positive effects of some statins in the cardiovascular system are mediated autonomously of their lipid-lowering effect via a direct decline in oxidative stress. As mentioned earlier, short-term pravastatin treatment reduced MI size in hypercholesterolemic rabbits through reduction in peroxynitrate and nitrotyrosine formation[33]. Parallel results, with regards to the atherogenic index were achieved with rosuvastatin, lowering oxidative stress by elevating the expression of antioxidant enzymes, superoxide dismutase, catalase, glutathione and glutathione peroxidase in addition to lowering LDL, triglycerides and CRP and elevating HDL[34].

A number of clinical trials have recognized beneficial effects of ARBs and ACE inhibitors on cardiovascular end-points in type II diabetic and metabolic disorder patients without hypertension. The HOPE study showed a 22% reduction in cardiovascular events (MI, stroke, cardiac arrest, revascualrization, heart failure and death) in metabolic disorder patients and without hypertension treated with an ACE inhibitor, ramipril versus metabolic disorder patients without hypertension not treated with an ACE inhibitor[137]. Almost matching results were obtained with an ARB, telmisartan (ONTARGET trial)[138]. The Ang II is a potent producer of vascular and myocardial ROS through the activation of NAD(P)H oxidases[139,140]and as a result likely mitochondrial ROS generation via the phenomenon of ROS-induced ROS release. ARBs and ACE inhibitors have been revealed to down regulate ROS in cell culture and *in vivo* with ARBs, while much less frequently used, showing a statistically considerably greater impact. Losartan reduced oxidative stress generation and progress of pressure overload-induced left ventricular hypertrophy in a rat model[141]. An ACE inhibitor, quinapril, reduced plasma markers of oxidative stress in metabolic disorder patients[142]. Olmesartan, today's most frequently used ARB for patients at risk for CAD development as a consequence of its strong anti-inflammatory nature, added to an ACE inhibitor led to a greater decrease in oxidative stress and a noteworthy improvement in cardiac function in advanced diastolic heart failure in hypertensive patients[143].

In addition to lowering oxidative stress, Ang II blockade has been revealed to have marked positive impacts on insulin resistance, glucose tolerance and the lipid profile. In a rat model of insulin resistance and renin-angiotensin system (RAS) over activity, the TG(mREN2)27 rat, administration of an ARB improved insulin sensitivity, motivated glucose transport into muscle and lowered oxidative stress[144]. The ARBs likewise reduced insulin resistance in the obese and insulin resistant ZOF rats by rising GLUT-4 transporters and glucose uptake[145]. *Post hoc* analysis of the HOPE trial confirmed a 32% reduction in the occurrence of growth of new-onset diabetes (insulin resistance and hyperglycemia) in patients treated with the ACE inhibitor, ramapril. A further study reported parallel results in ZOF rats, where not only insulin and glucose but all metabolic parameters including LDL, HLD and triglycerides as well as oxidative stress and vascular dysfunction were considerably improved in retort to ACE inhibition; however, these parameters were not improved nearly as much in the Zucker diabetic fatty rat (ZDF), representing that overt hyperglycemia is more defiant to Ang II inhibition[146]. A clinical study also revealed a noteworthy reduction not only in fasting blood glucose but also in LDL cholesterol and an increase in HDL cholesterol following 6 months of ARB or ACE inhibitor (losartan or enalapril) treatment[147].

These effects are likely also indirectly mediated through the Ang II-generated oxidative stress, as Ang II has been revealed to inhibit Akt phosphorylation and as a result, GLUT-4 transporter translocation to the plasma membrane in an NAD(P)H oxidase-dependent way via tyrosine nitration, most likely through formation of peroxynitrate[148]. In fact, another study has confirmed that Ang II impairs insulin signaling and GLUT-4 translocation to the membrane in muscle fibers via production of ROS that could be inverted by ARBs or antioxidant treatment[148]. Thus, the positive effects of ARBs and ACE inhibitors in the cardiovascular system, away from lowering blood pressure thus reducing hypertrophic vascular remodeling and after load on the heart can likely be ascribed to their direct antioxidant impacts as well as lowering in blood glucose and connected benefits, most remarkably reduction in AGEs and associated vascular remodeling (reduced compliance) and upgrading in the lipid profile, particularly HDL levels which have a tendency to correlate with oxLDL, actually the most predictive factor for CAD progress[148].

Never-the-less, Nitric Oxide (NO) produced by endothelial NO synthase has been well recognized as a central anti-inflammatory and anti-atherogenic principle in the vasculature[149,150]. Epidemiological and clinical studies have demonstrated that a growing list of natural products, as components of the daily diet or phytomedical preparations may get better vascular mechanism by upgrading NO

bioavailability. Besides, it has been investigated antioxidant impacts of propolis on certain biochemical parameters citing in kidney and heart tissues of acute NO synthase inhibited rats by Nω-nitro-L-arginine methyl ester (L-NAME).

CONCLUSION AND FUTURE RECOMMENDATIONS

Conclusively, it is clear that metabolic disorder is associated with increased oxidative stress. It appears that some constituent pathologies of the metabolic disorder contribute to a higher percentage of total oxidative stress than others; however, additional studies are needed to conclude the exact contribution of individual constituents to total oxidative stress. It is also clear that the metabolic syndrome is a strong risk factor for the progress and increased severity of cardiovascular disease in general and occlusive CAD in particular and confers a higher risk than the sum of its individual constituents. However, the presence of which individual constituent or what exact amalgamation of individual constituents confers the greatest risk for CAD development remains an issue of debate and may be gender-specific with abdominal obesity in combination with low HDL and prominent oxLDL conferring the maximum risk for men, whereas hyperglycemia provides the utmost risk factor for women. Besides, air pollution and cigarette smoke pose a larger risk of unfavorable cardiovascular events for people with the metabolic disorder probably because of the augmented oxidative stress in the metabolic disorder that is further up surged by the aromatic hydrocarbon and metal nanoparticle constituents of these environmental pollutants resulting in activation of recognized detrimental cascades of events, which connect oxidative stress to exacerbation of cardiovascular disease. Lastly, it may be assumed the antioxidants probably being valuable for treatment and prevention of cardiovascular disease in metabolic disorder patients. It is therefore critical that therapeutic endeavors aimed at resolution of CAD in the metabolic disorder, including coronary revascularization be considered in animal (including human) models of the metabolic disorder.

SIGNIFICANT STATEMENT

The major significance of this study is how to explore the antioxidants probably being valuable for treatment and prevention of cardiovascular disease in metabolic disorder patients. It is therefore critical that therapeutic endeavors intended at resolution of CVD in the metabolic disorder.

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