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Cardiac Dysfunction and Oxidative Stress in the Metabolic Syndrome: an Update on Antioxidant Therapies

Olesya Ilkun and **Sihem Boudina***
Division of Endocrinology, Metabolism and Diabetes and Program in Molecular Medicine, University of Utah School of Medicine, Salt Lake City, Utah 84112

Abstract

The metabolic syndrome (MetS) is a cluster of risk factors including obesity, insulin resistance, dyslipidemia, elevated blood pressure and glucose intolerance. The MetS increases the risk for cardiovascular disease (CVD) and type 2 diabetes. Each component of the MetS causes cardiac dysfunction and their combination carries additional risk. The mechanisms underlying cardiac dysfunction in the MetS are complex and might include lipid accumulation, increased fibrosis and stiffness, altered calcium homeostasis, abnormal autophagy, altered substrate utilization, mitochondrial dysfunction and increased oxidative stress. Mitochondrial and extra-mitochondrial sources of reactive oxygen species (ROS) and reduced antioxidant defense mechanisms characterize the myocardium of humans and animals with the MetS. The mechanisms for increased cardiac oxidative stress in the MetS are not fully understood but include increased fatty acid oxidation, mitochondrial dysfunction and enhanced NADPH oxidase activity. Therapies aimed to reduce oxidative stress and enhance antioxidant defense have been employed to reduce cardiac dysfunction in the MetS in animals. In contrast, large scale clinical trials using antioxidants therapies for the treatment of CVD have been disappointing because of the lack of efficacy and undesired side effects. The focus of this review is to summarize the current knowledge about the mechanisms underlying cardiac dysfunction in the MetS with a special interest in the role of oxidative stress. Finally, we will update the reader on the results obtained with natural antioxidant and mitochondria-targeted antioxidant therapies for the treatment of CVD in the MetS.

Keywords

Cardiac dysfunction; mitochondrial dysfunction; reactive oxygen species; antioxidants; oxidative stress; substrate utilization; metabolic syndrome; insulin resistance

INTRODUCTION

The metabolic syndrome (MetS) represents a cluster of cardiovascular risk factors that includes abdominal obesity, dyslipidimia, hypertension, and impaired glucose tolerance. The MetS increases the risk for type 2 diabetes (T2D) and cardiovascular disease (CVD). Thus, people with the MetS have a five-fold higher risk of T2D and a two to three-fold higher risk

*Address correspondence to this author at the Division of Endocrinology, Metabolism and Diabetes, Program in Human Molecular Biology & Genetics, 15 N 2030 E Bldg # 533 Rm. 3410B, Salt Lake City, Utah 84112; Tel: (801) 585-6833: Fax: (801) 585-0701; sihem.boudina@hmbg.utah.edu.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

of atherosclerotic CVD than those without [1–2]. The etiology of CVD in patients with MetS may involve: coronary atherosclerotic disease, arterial hypertension, left ventricular (LV) hypertrophy, diastolic dysfunction, endothelial dysfunction, coronary micro-vascular disease and autonomic dysfunction. The pathogenesis of CVD in the MetS is multifactorial as it can be caused by one or more factors associated with this condition such as the systemic abnormalities, insulin resistance, diabetes and/or inflammation. One common characteristic of CVD in the MetS and the insulin resistant state is increased oxidative stress in the heart [3–4]. Indeed, patients with the MetS have elevated systemic oxidative damage as a result of overproduction of ROS and decreased antioxidant protection [5–6]. In this review, we will first summarize the contribution of each component of the MetS to cardiac dysfunction and then highlight the underlying mechanisms with a special focus on the contribution of oxidative stress. Finally, we will summarize and discuss past and current studies using antioxidant therapies to treat CVD in the MetS.

CARDIAC DYSFUNCTION IN THE METABOLIC SYNDROME

Each component of the MetS is known to independently affect cardiac structure and function, but their combination under this syndrome seems to carry additional risk [7–8]. Thus, cardiac dysfunction can occur in patients with normal coronary artery disease or other etiologies, suggesting the existence of specific cardiomyopathies such as obesity-related cardiomyopathy, diabetic cardiomyopathy and insulin resistance-related cardiac dysfunction. As summarized in (Fig. 1), common mechanisms responsible for cardiac dysfunction are shared between obesity, diabetes and insulin resistance, however unique mechanisms characterize each component of the MetS.

MECHANISMS FOR OBESITY-RELATED CARDIOMYOPATHY

Obesity itself or in association with dyslipidimia promotes hearts failure in humans [9–10]. Several mechanisms have been proposed to explain cardiac dysfunction in obesity including increased hemodynamic load, cardiac hypertrophy, increased lipid accumulation and altered substrate metabolism. For example, an association between myocardial triacylglycerol (TG) content and concentric LV hypertrophy with subtle reduction in systolic function was reported in humans [11]. Similarly, a higher cardiac TG content was observed in heart of obese or T2D patients [12], suggesting the involvement of cardiac lipid accumulation in the pathogenesis of cardiac dysfunction in the MetS (See Review by Kusminski *et al.* [13]). In addition to the above mentioned mechanisms, it was recently suggested that adipose-derived factors and adipokines such as leptin, adiponectin, resistin and fatty acid binding protein 4 (FABP4) can directly affect cardiac structure and function. Indeed, elevated circulating leptin levels are predictors of worse outcome in patients with CVD and heart failure [14]. Furthermore, leptin treatment of neonatal ventricular myocytes promotes cardiac hypertrophy through the regulation of actin dynamics [15]. In contrast, leptin treatment of the leptin-deficient (*ob/ob*) or the leptin receptor-deficient (*db/db*) mice completely normalized cardiac hypertrophy [16], suggesting rather an antihypertrophic role for leptin. Depressed plasma adiponectin levels correlated inversely with the MetS and T2D and increased the risk of myocardial infarction and heart failure [17–19]. Similar to findings with leptin, adiponectin also has antihypertrophic properties as its reduction in mice promotes the development of LV hypertrophy [20]. Moreover, serum resistin levels are usually high in mouse models of the MetS and in humans with heart failure [21–24]. Resistin affects both the structure and the function of the heart. Indeed, *in-vitro* and *in-vivo* studies have suggested a role for resistin in promoting cardiac hypertrophy and reducing contractility [21, 25]. Finally, adipocytes-derived fatty acid binding protein 4 (FABP4) levels were found to correlate positively with the MetS in a cross-sectional study [26] and

this fat-specific factor reduced cardiac function through modulation of intracellular calcium [27–28].

MECHANISMS FOR DIABETIC CARDIOMYOPATHY

Since its first introduction by Rubier *et al.* [29] forty years ago, the existence of a unique diabetic cardiomyopathy has been confirmed in numerous studies (see reviews by Boudina and Abel [30–31]). Indeed, diabetes increased the risk for heart failure even after adjusting for age, blood pressure, weight, cholesterol and coronary artery disease. Thus, CVD is 2–3 times more common, and survival is worse in subjects with diabetes in comparison with age-matched and sex-matched counterparts [32–34]. According to the molecular theory of diabetic cardiomyopathy, hyperglycemia is the main pathogenetic factor, which causes abnormalities at the cardiac myocyte level, eventually leading to structural and functional abnormalities [35]. Diabetic cardiomyopathy is characterized by an initial diastolic dysfunction that occurs before altered systolic function [36–37]. One proposed mechanism for altered diastolic function in diabetic myocardium is enhanced deposition of glycosylated glycogen, which is known to promote cardiac stiffness via increased fibrosis [38–40]. In parallel, hyperglycemia was shown to directly alter components of calcium homeostasis, leading to diastolic dysfunction (See review by Dobrin and Lebeche [41]). Indeed, the activity and the content of the sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) is decreased in diabetes [42–43] and the hemodynamic dysfunction is prevented by up-regulation of SERCA in a rat model of the MetS [44]. In addition to reducing left ventricular relaxation time, SERCA2a gene transfer therapy reduced oxygen cost for contraction in a mouse model of type 2 diabetes [45], highlighting the importance of calcium in metabolic regulation. The mechanisms by which hyperglycemia affects SERCA activity are through (1) oxidative stress-mediated oxidation of its cysteine thiols which interferes with the ATP binding site, making it unable to hydrolyze ATP [46] and (2) through direct cross-linking of collagen with SERCA, which inhibits its activity. More recently, a role of micro RNAs in cardiac dysfunction caused by diabetes has emerged [47]. Indeed, the expression of miR133, the most abundant micro RNA in the heart, was reduced by diabetes, and hyperglycemia-induced cardiac hypertrophy was prevented by miR133 over-expression in cardiac myocytes *in-vitro* [48].

MECHANISMS FOR INSULIN RESISTANCE-RELATED CARDIAC DYSFUNCTION

The MetS and insulin resistance are associated with abnormal LV diastolic function and structure independently of age, gender, blood pressure and fasting plasma glucose [49]. Furthermore, insulin resistance predicts the incidence of heart failure independently of other established risk factors, including diabetes and obesity [50]. Moreover, the contribution of insulin resistance to cardiac dysfunction without the systemic abnormalities associated with the MetS has recently been studied using a mouse model of cardiac insulin resistance obtained by deletion of insulin receptors specifically in cardiomyocytes (CIRKO mice) [51]. Whereas at baseline, these mice exhibit mild alterations of cardiac performance, their response to pressure overload [52], isoproterenol treatment [53] or myocardial infarction [54] is altered, suggesting that insulin resistance increased the susceptibility for the development of cardiac dysfunction independently of obesity or diabetes. The mechanisms involved in insulin resistance-mediated cardiac dysfunction include altered substrate metabolism, persistent expression of the fetal beta-myosin heavy chain isoform, reduced angiogenesis and mitochondrial dysfunction.

COMMON MECHANISMS BETWEEN OBESITY, DIABETES AND INSULIN RESISTANCE

1- Altered Cardiac Substrate Metabolism

The mammalian heart possesses the capacity of oxidizing any available substrate to maintain a steady level of ATP required for contraction. Although, oxidation of fatty acids (FA) is predominant in the adult heart, the use of glucose, lactate and ketones can be enhanced in certain pathological condition (See review by Duncan JG [55]. This flexibility in substrate use is important for normal cardiac function and its alteration by the MetS contribute to cardiac dysfunction. Thus, obesity, diabetes and/or insulin resistance independently or in combination affect this flexibility due to alteration in substrate availability or to impairment in transcriptional regulation of oxidation pathways. For example, obesity in mice enhances cardiac FA oxidation and reduces glucose oxidation independently of diabetes [56]. The mechanisms for obesity-related alteration in cardiac substrate utilization are not completely understood but involve enhanced FA and reduced glucose availability and leptin resistance [57]. Similarly, type 1 and type 2 diabetes enhanced FA oxidation and uptake whereas glucose utilization was reduced [58–60]. The mechanisms for increased cardiac FA uptake and oxidation in the MetS include impaired glucose transport, enhanced long-chain FA uptake through relocation of the FA transporter CD36 in the sarcolema [61] and increased mitochondrial CPT-1 activity [62]. Whereas, altered cardiac substrate metabolism is evident in the MetS, there was no correlation between impaired substrate use and LV diastolic dysfunction in type 2 diabetic patients, thus excluding a causal role in the development of cardiac dysfunction during the MetS [60]. Finally, insulin resistance without confounding systemic abnormalities was shown to reduce both glucose and FA oxidation in the heart possibly via a reduction in the expression of genes involved in FA oxidation and by impairing mitochondrial oxidative capacity [51, 63].

2- Altered Cardiac Mitochondrial Function and Biogenesis

Mitochondrial dysfunction plays a crucial role in the pathogenesis of cardiac dysfunction in the MetS. Indeed, each component of the MetS is known to independently modulate mitochondrial function, proteome and biogenesis. Whereas most studies examining changes in mitochondrial function in the MetS in humans have been performed in skeletal muscle, the results cannot be extrapolated to the heart due to its higher mitochondrial oxidative capacity and content. Thus, most of what we currently know about mitochondrial function in the heart comes from animal models of the MetS with the exception of few indirect studies looking at cardiac oxygen consumption, phosphocreatine (Pcr)/ATP ratios or atrium mitochondrial oxygen consumption in obese or T2D patients. These studies associated mitochondrial uncoupling and/or dysfunction with increased cardiac oxygen cost for contraction in obese individuals [64], decreased high energy phosphate metabolism in the diabetic heart [65–66] and reduced mitochondrial maximal capacity to oxidize FA and glutamate in T2D patients [67]. In contrast to human studies, mitochondrial dysfunction in the heart of genetically obese *db/db* mice was first reported in the 80s by Kuo *et al*. [68] and then confirmed by a recent study [69]. Furthermore, impaired mitochondrial function and biogenesis was identified in other mouse models of obesity and insulin resistance such as the leptin-deficient *ob/ob* mice [70] and UCP-DTA mice [71]. The mechanisms for impaired cardiac mitochondrial function and biogenesis in the MetS and the insulin resistant state have been extensively reviewed [3, 72–74] and include enhanced FA-induced mitochondrial uncoupling [69], increased mitochondrial oxidative stress [67, 75–76], impaired mitochondrial calcium handling [77–78], enhanced mitochondrial DNA damage [79], altered mitochondrial proteome [80–84] and deregulation of mitochondrial biogenesis [72–73, 85].

3- Impaired Cardiac Autophagy

Although autophagy, which is a physiologic process by which a cell clean damaged proteins and organelles, has been known since the 60s, its role in CVD has been recently introduced. Thus, defect in autophagy causes cardiac dysfunction and heart failure particularly under increased cellular stress such as ischemia/reperfusion (I/R) [86]. Furthermore, autophagy plays a central role in cardiac dysfunction during aging and its modulation might represent a promising way to treat cardiac senescence [87–89]. Similarly, long-term caloric restriction enhances autophagy and preserves cardiac function in otherwise healthy mice [90]. Although autophagy has been implicated in various pathologies of the heart, it is until recently that the pathophysiologic role of autophagy in the MetS has been introduced [91–92]. Thus, autophagy is reduced in the hearts of OVE26 mice, a mouse model of severe type 1 diabetes that develop diabetic cardiomyopathy, an effect that was exacerbated by the inhibition of AMPK and alleviated by metformin treatment [93]. More recently, autophagy was found to be deregulated in the heart of high fat-fed mice (a mouse model of the MetS), rendering them more susceptible to I/R injury [94]. The mechanisms underlying the deregulation of autophagy and whether it can be targeted to treat cardiac dysfunction in the MetS require more work.

4- Increased Cardiac Oxidative Stress

Oxidative stress (OS) is defined as an excess formation or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [95]. Many aspects of the relationship between OS and endothelial dysfunction in the MetS and diabetes have been previously reviewed [96–97], this review will focus on the role of OS in cardiac dysfunction in the MetS. Increased systemic OS, as evidenced by reduced serum vitamin C and α-tocopherol concentrations and decreased superoxide dismutase activity, has been previously documented in patient with the MetS [5–6, 98]. Furthermore, a positive correlation between systemic OS and the development of insulin resistance and diabetes was found in the Framingham Offspring Study [99]. Thus, hydrogen peroxide (H_2O_2) emission was found to be higher in right atrial appendages obtained from patients with T2D undergoing non-emergent coronary artery bypass graft surgery [67]. In contrast to the fewer human studies, many studies have confirmed the existence of OS in the myocardium of animal models with one or more components of the MetS. Thus, succinate-supported H_2O_2 production as well as lipid and protein oxidation markers were increased in the heart of *db/db* mice [69]. Furthermore, insulin resistance enhanced cardiac ROS generation independently of hyperglycemia, hyperlipidemia and hyperinsulinemia in mice [63], and superoxide production was elevated in the myocardium of high fat-fed spontaneously hypertensive (SHR) rats [100]. Furthermore reduced GSH/GSSG ratio was shown in *ob/ob* hearts [101] and decreased cardiac expression of manganese superoxide dismutase (MnSOD), glutathione peroxidase I (GPxI) was observed in high fat-fed and obese Zucker rats [102–103]. Although an association between elevated OS and cardiac dysfunction in the MetS has been established, a causal role for OS in the development of myocardial dysfunction has not been proven yet but one could emphasize that ROS-mediated damage to proteins, DNA and RNA may exacerbate cardiac dysfunction. Furthermore, OS is involved in the pathogenesis of apoptosis as it can directly activate pro-apoptotic signaling pathways such as JNK, p38 and ASK-1 [104–105]. In addition, increased mitochondrial ROS can lead to cytochrome c release and the initiation of apoptosis [106]. The induction of apoptosis by OS plays an important role in cardiac remodeling and fibrosis.

THE SOURCES AND THE MOLECULAR MECHANISMS OF INCREASED OXIDATIVE STRESS IN THE METS

1- Mitochondrial Sources

Mitochondrial function is particularly important in the heart since it provides over 90% of myocardial ATP [107]. In the process of normal respiration, 0.4 to 4% of oxygen consumed by mitochondria is incompletely reduced and form ROS [108]. As illustrated in (Fig. 2), ROS are generated at several sites of the electron transport chain (ETC), where electrons leak to O_2 to generate superoxide [109]. A significant amount of superoxide is produced at the level of complex I and III of the ETC. Complex I produces superoxide in the matrix [110] whereas its production by complex III happens both in the matrix and in the inter-membrane space [111]. In addition to complex I and III, other less important sources of mitochondrial superoxide have been documented and include pyruvate dehydrogenase, 2-oxoglutarate dehydrogenase, the electron transferring flavoprotein ubiquinone oxidoreductase (ETF-QOR) (receiving electrons from the β-oxidation) and the glyceraol 3-phosphate dehydrogenase [112–113]. Because of the susceptibility of mitochondrial membranes and DNA to oxidative damage, detoxifying systems are in place to reduce superoxide accumulation. This detoxification is achieved by the conversion of superoxide to H_2O_2 by MnSOD [114–115] and peroxide reduction by GPx1 and GPx4, thioredoxin reductases (Trx2), glutaredoxin (Grx2) and peroredoxins (Prdx3 and Prdx5), which are all expressed in the mitochondria [116].

Mitochondrial-generated H_2O_2 was documented in the hearts of genetically obese and diabetic *db/db* mice and in CIRKO mice lacking insulin receptors in cardiac cells [63, 69]. One common finding between these mice is enhanced FA oxidation, which can promote ROS formation. Indeed, a study by St-Pierre *et al*. [111] demonstrated that mitochondrial H_2O_2 production in the heart is enhanced when mitochondria are respiring on the FA substrate palmitoylcarnitine compared to other substrate such as glutamate or pyruvate. This is possibly due to enhanced superoxide generation from the ETF-QOR, as a result of accelerated electrons flux through the β-oxidation. This is further confirmed by the association of enhanced activity of enzymes involved in β-oxidation with mitochondrial generation of H_2O_2 in *db/db* and CIRKO mice [63, 69], whereas no changes in β-oxidation enzymes activity and no mitochondrial H_2O_2 generation was detected in *ob/ob* hearts despite increased FA oxidation [69]. Another possible mechanism for increased mitochondrial ROS is inhibition of the ETC, which can trigger superoxide generation through the reverse electron transfer [111]. This inhibition can be caused in part by glucose or hyperglycemia-mediated O-linked β-*N*-acetylglucosamine glycosylation (O-GlcNAcylation) of mitochondrial complex I, which can lead to ROS generation especially in the presence of excess reducing equivalents [81]. Furthermore, hyperglycemia increased H_2O_2 formation in neonatal cardiomyocyte cell line that was dependent on mitochondrial fission [117]. Whether increased mitochondrial ROS formation is indeed responsible for cardiac dysfunction in animals with the MetS is possible but has not been fully investigated (see antioxidant therapy section bellow).

2- Extra-mitochondrial Sources

While mitochondria are considered the major source of cell-damaging ROS in the heart, there are other cellular sources. The three predominant extra-mitochondrial systems that produce ROS mammalian cells are NADPH oxidase (NOX), xanthine oxidase (a form of xanthine oxidoreductase) and uncoupled nitric oxide [118]. Thus, the activity of NOX is enhanced in the hearts of obese Zucker rats, leptin-deficient *ob/ob* mice and high fat-fed rats [103, 119–121]. Interestingly, and confirming the involvement of NOX in ROS generation, NOX inhibition abolished superoxide production in the hearts of these animals [103]. In

addition to NOX, xanthine oxidoreductase activity was shown to be elevated in *ob/ob* hearts whereas nitric oxide synthase level was decreased [122]. All these studies highlight a role for NOX and xanthine oxidoreductase as potential extra-mitochondrial source of ROS but the consequences of inhibiting these enzymes on cardiac function in the MetS have not been extensively investigated. Thus, inhibition of NOX alleviated contractile defects in *ob/ob* mice, in high fat-fed mice subjected to myocardial infarction and in mice with experimental diabetes [120, 123–124]. One additional cardiac ROS-generating system that is relevant in the MetS is the rennin-angiotensin system (RAS). Indeed, RAS is up-regulated by various components of the MetS such as glucose, circulating lipids, obesity and blood pressure [125], and its activation promotes ROS generation by NADPH oxidase and mitochondria [126].

ANTIOXIDANT THERAPIES AND CARDIAC DYSFUNCTION IN THE METS

I- Non Mitochondria-targeted Antioxidants

Systemic therapeutics for the treatment of CVD in the context of the MetS need to address one or several underlying conditions, including metabolic abnormalities (dyslipidemia and hyperglycemia), hypertension, arterosclerosis, and sleep apnea. There has been a substantial interest in using natural antioxidant compounds for the treatment of CVD such as vitamins, flavonoids and polyphenols. More recently, synthetic antioxidants with selective mitochondrial targeting property have been discovered and used to treat abnormalities associated with the MetS (See Table 1).

Vitamins—Vitamin E supplementation in Chinese women for 4 month improved plasma cholesterol levels and markers of oxidative stress [127]. However, unlike smaller trials, investigation of vitamins administration to larger cohorts of patients did not show positive results. A randomized trial using Vitamin E daily did not have significant effects on cardiovascular outcomes in patients enrolled in the Cambridge Heart Antioxidant Study (CHAOS) [128]. A combination of vitamins C and E did not affect metabolic parameters (body weights, hemoglobin Alc, low density lipoprotein or triglycerides) of patients with the MetS or T2D [129]. Furthermore, co-administration of α-lipoic acid and vitamin E to patients with the MetS, failed to improve their metabolic profile [130]. Overall, vitamin supplementation does not appear sufficient to improve preexisting metabolic or cardiovascular complications in humans as reviewed elsewhere [131–132].

Flavonoids and Polyphenols—In contrast to vitamins, flavonoids and polyphenols supplementation has proven to be efficacious in reducing the metabolic abnormalities as well as cardiac dysfunction in patients or animals with the MetS. Thus, resveratrol, which is an antioxidant found in red wine and grape skin/seed, has protective cardiovascular properties [133]. Resveratrol and S17834 (a synthetic flavonoid derivative) prevented LV hypertrophy, diastolic dysfunction, and interstitial fibrosis and reduced levels of oxidative modifications and hyper-insulinemia in high fat high sucrose-fed C57B16 mice [134]. Similarly, resveratrol improved LDL, plasma glucose and insulin, blood pressure, and cardiac function, in Yorkshire mini swine fed a high cholesterol diet [135]. Furthermore, resveratrol supplementation in rats fed 65% sucrose, improved glucose tolerance, plasma insulin and triglyceride levels and enhanced hepatic catalase and superoxide dismutase enzyme activities [136]. In humans, moderate wine consumption may lower the incidence of the MetS and the associated cardiovascular complications, a finding that has been recently reviewed (See review by Liu *et al*. [137]). A recent study in obese humans showed that 30 days of resveratrol supplementation increased metabolic rate, moderately lowered blood pressure, and reduced plasma insulin, glucose and triglyceride levels. This was paralleled by an increase in skeletal muscle mitochondrial function as a result of enhanced AMPK activity

and SIRT1 expression [138]. These beneficial effects of resveratrol are believed to be mediated by AMPK as mice deficient in this metabolic sensor are resistant to the beneficial metabolic effect of resveratrol in high fat-fed mice [139]. Overall, human and animal studies hold a great promise for resveratrol use to treat cardiovascular complications in the MetS [140].

Similar to resveratrol, anthocyanin was shown to reduce oxidative stress *in-vitro* [141] and LDL cholesterol but not blood pressure or other metabolic parameters in dyslipidemic patients [142]. Finally, quercetin reduced systolic blood pressure and plasma oxidized LDL concentration in overweight subjects with high-cardiovascular disease risk [143] reduced blood pressure and improved cardiac function in Wistar rats fed high carbohydrate high fat diet [144]. Other natural supplements such as genistein, triterpenoid, naringenin and curcumin have shown some *in-vitro* activity against the MetS but *in-vivo* studies are required to confirm their benefits on CVD [145].

II- Mitochondria-Targeted Antioxidants

Since mitochondria is considered a substantial source of ROS in the heart of humans and animals with the MetS and mitochondrial dysfunction is believed to participate in the development of CVD under this condition, antioxidant therapies should focus on novel class of compounds with high mitochondrial affinity as the new way to treat CVD in the MetS, a topic that has been recently reviewed by Subramanian *et al* [146]. Among mitochondria-targeted compounds that have been used in animal studies are superoxide dismutase (SOD) mimetics, CoenzymeQ_{10} and its analogues and mitochondria-targeted small peptides.

SOD Mimetics—Pharmacological mimetics of antioxidant enzymes, including MnSOD, were shown to be effective in reducing ROS and restoring mitochondrial function [147]. Treatment of *ob/ob* mice with the SOD mimetic and peroxynitrite scavenger MnTBAP, improved glucose tolerance but cardiac function was not assessed in this study [148]. Furthermore, treatment of L6 myotubes with MnTBAP was able to restore insulin-stimulated GLUT4 translocation after palmitate treatment and in high fat feeding in mice [149]. Whether MnTBAP treatment improves cardiac dysfunction in the MetS is yet to be determined in future studies (See Table 1).

CoenzymeQ_{10} and its Analogs—CoenzymeQ_{10} is a vitamin-like lipid-soluble component of the mitochondrial ETC. Studies in cells showed that exogenous administration of CoenzymeQ_{10} leads to its mitochondrial localization in contrast to vitamin E, as its distribution in cells correlates directly with lipid distribution [150]. A recent study demonstrated that the use of CoenzymeQ_{10} supplementation reduced superoxide generation and ameliorated diastolic dysfunction in *db/db* mice [151]. Furthermore, CoenzymeQ_{10} treatment, in female *db/db* mice, slightly lowered LV mass, systolic blood pressure, and lipid peroxidation [152]. Similarly, addition of CoenzymeQ_{10} to regular medications, reduced diastolic dysfunction in children with cardiomyopathy [153]. However, supplementation with CoenzymeQ_{10} was not sufficient to reduce hypertension in patients with the MetS [154–155].

MitoQ, a triphenylphosphonium-conjugated derivative of Co-enzymeQ, is a mitochondria-targeted antioxidant that efficiently reduces oxidative stress [156] but has no adverse effects on wild-type mice [156–157]. When supplemented in drinking water, MitoQ decreased cardiac dysfunction in rats subjected to I/R [158]. Similarly, MitoQ decreased adiposity, hypercholesterolemia and hypertriglyceridemia in high fat-fed $ApoE^{-/-}$ and $ATM^{+/-}$/$ApoE^{-/-}$ mouse models of the MetS [159]. So far, human studies using this compound have been performed only in the context of Parkinson's disease and chronic hepatitis C [157].

Finally, administration of MitoTempol (another mitochondria-targeted antioxidant) and MitoQ in drinking water improved mitochondrial function and coronary collateral growth after I/R in Zucher obese fatty rats [160].

Mitochondria-targeted Peptides—A mitochondria-targeted synthetic antioxidant peptide SS-31 protected against cardiac I/R injury when given *ex-vivo* and ameliorated hypertensive cardiomyopathy and myocardial oxidative stress induced by Angiotensin-II [161]. In sheep, rabbit, and guinea pig models of I/R, SS-31 analogs moderately reduced infarct size and improved cardiomyocyte survival [162]. Administration of another SS-31 analog at the onset of reperfusion reduced infarct size in diabetes [163–164]. Whereas the use of these small mitochondria-targeted peptides is protective against I/R, their use for the treatment of cardiac dysfunction in the MetS needs further investigations.

Other Semi-natural Products—SkQBerb and SkQPalm (derivatives of natural products) are novel mitochondria-targeted antioxidants that showed potent ROS-scavenging properties in isolated mitochondria and in human cells [165]. Their use in the context of CVD and the MetS has not yet been explored.

III- Gene Transfer Therapy

Despite disappointing results of various oral antioxidant treatment trials, promising findings have been reported using gene delivery of enzymes to improve NO bioavailability and decrease oxidative stress in animal models for cardiovascular diseases. Increased MnSOD expression in diabetic cardiomyocytes led to improved contractility [166]. Furthermore, over-expression of cardiac specific metallothionein (a heavy metal scavenger) in mice reduced ROS levels and improved cardiac and mitochondrial function after long-term high-fat feeding [167]. Finally, enhanced MnSOD or catalase expression normalized contractility in mouse models of type 1 and type 2 diabetes [166, 168]. Whereas these results suggest a protective role of anti-oxidants gene delivery, more work is needed to investigate the signaling pathways involved.

CONCLUSION

Because of the increasing obesity and T2D rates worldwide, there is an urgent need to develop new therapeutic strategies to prevent the CVD associated with these conditions. Therapeutic strategies aimed to reducing systemic abnormalities associated with these conditions such as reducing circulating glucose, cholesterol and triglyceride levels, were unable to reverse cardiovascular complications (ACCORD study) or were abandoned due to failure to reduce the risk of cardiovascular events. These disappointing results indicate that targeted therapies are indeed required to reduce or prevent the development of CVD in the MetS. The use of antioxidant as a therapy for the treatment of CVD in the MetS is to be considered however, care in their use in hearts exhibiting oxidative stress might be useful. Furthermore, caution has to be taken when the rates of FA oxidation are high, because the use of antioxidants in this case might eliminate the beneficial effect of ROS on facilitating FA-induced mitochondrial uncoupling, a process that is required to reduce further ROS generation. Finally, and based on animal studies, antioxidant therapies have proven to be effective only as treatments but not as prevention strategies potentially because of negative effects associated with excessive antioxidant scavenging in non-stressed hearts.

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References

1. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112(17):2735–52. [PubMed: 16157765]
2. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab. 2007 Feb; 92(2):399–404. [PubMed: 17284640]
3. Bugger H, Abel ED. Molecular mechanisms for myocardial mitochondrial dysfunction in the metabolic syndrome. Clin Sci (Lond). 2008; 114(3):195–210. [PubMed: 18184113]
4. Nicolson GL. Metabolic syndrome and mitochondrial function: molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. J Cell Biochem. 2007; 100(6):1352–69. [PubMed: 17243117]
5. Palmieri VO, Grattagliano I, Portincasa P, Palasciano G. Systemic oxidative alterations are associated with visceral adiposity and liver steatosis in patients with metabolic syndrome. J Nutr. 2006; 136(12):3022–6. [PubMed: 17116714]
6. Armutcu F, Ataymen M, Atmaca H, Gurel A. Oxidative stress markers, C-reactive protein and heat shock protein 70 levels in subjects with metabolic syndrome. Clin Chem Lab Med. 2008; 46(6): 785–90. [PubMed: 18601599]
7. Voulgari C, Moyssakis I, Papazafiropoulou A, et al. The impact of metabolic syndrome on left ventricular myocardial performance. Diabetes Metab Res Rev. 2010; 26(2):121–7. [PubMed: 20131336]
8. Chinali M, de Simone G, Roman MJ, et al. Cardiac markers of pre-clinical disease in adolescents with the metabolic syndrome: the strong heart study. J Am Coll Cardiol. 2008; 52(11):932–8. [PubMed: 18772065]
9. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001; 161(7):996–1002. [PubMed: 11295963]
10. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med. 2002; 347(5):305–13. [PubMed: 12151467]
11. Szczepaniak LS, Dobbins RL, Metzger GJ, et al. Myocardial triglycerides and systolic function in humans: *in vivo* evaluation by localized proton spectroscopy and cardiac imaging. Magn Reson Med. 2003; 49(3):417–23. [PubMed: 12594743]
12. Sharma S, Adrogue JV, Golfman L, et al. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. FASEB J. 2004; 18(14):1692–700. [PubMed: 15522914]
13. Kusminski CM, Shetty S, Orci L, Unger RH, Scherer PE. Diabetes and apoptosis: lipotoxicity. Apoptosis. 2009; 14(12):1484–95. [PubMed: 19421860]
14. Karmazyn M, Purdham DM, Rajapurohitam V, Zeidan A. Leptin as a cardiac hypertrophic factor: a potential target for therapeutics. Trends Cardiovasc Med. 2007; 17(6):206–11. [PubMed: 17662916]
15. Zeidan A, Javadov S, Karmazyn M. Essential role of Rho/ROCK-dependent processes and actin dynamics in mediating leptin-induced hypertrophy in rat neonatal ventricular myocytes. Cardiovasc Res. 2006; 72(1):101–11. [PubMed: 16901475]
16. Barouch LA, Berkowitz DE, Harrison RW, O'Donnell CP, Hare JM. Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. Circulation. 2003; 108(6):754–9. [PubMed: 12885755]
17. Mohan V, Deepa R, Pradeepa R, et al. Association of low adiponectin levels with the metabolic syndrome--the Chennai Urban Rural Epidemiology Study (CURES-4). Metabolism. 2005; 54(4): 476–81. [PubMed: 15798954]
18. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA. 2004; 291(14):1730–7. [PubMed: 15082700]

19. Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB. Adiponectin and future coronary heart disease events among men with type 2 diabetes. Diabetes. 2005; 54(2):534–9. [PubMed: 15677512]
20. Shibata R, Ouchi N, Ito M, et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med. 2004; 10(12):1384–9. [PubMed: 15558058]
21. Kim M, Oh JK, Sakata S, et al. Role of resistin in cardiac contractility and hypertrophy. J Mol Cell Cardiol. 2008; 45(2):270–80. [PubMed: 18597775]
22. Takeishi Y, Niizeki T, Arimoto T, et al. Serum resistin is associated with high risk in patients with congestive heart failure--a novel link between metabolic signals and heart failure. Circ J. 2007; 71(4):460–4. [PubMed: 17384443]
23. Zhang MH, Na B, Schiller NB, Whooley MA. Association of resistin with heart failure and mortality in patients with stable coronary heart disease: data from the heart and soul study. J Card Fail. 2011; 17(1):24–30. [PubMed: 21187261]
24. Frankel DS, Vasan RS, D'Agostino RB Sr, et al. Resistin, adiponectin, and risk of heart failure the Framingham offspring study. J Am Coll Cardiol. 2009; 53(9):754–62. [PubMed: 19245965]
25. Chemaly ER, Hadri L, Zhang S, et al. Long-term *in vivo* resistin overexpression induces myocardial dysfunction and remodeling in rats. J Mol Cell Cardiol. 2011; 51(2):144–55. [PubMed: 21549710]
26. Xu A, Wang Y, Xu JY, et al. Adipocyte fatty acid-binding protein is a plasma biomarker closely associated with obesity and metabolic syndrome. Clin Chem. 2006; 52(3):405–13. [PubMed: 16423904]
27. Lamounier-Zepter V, Ehrhart-Bornstein M, Karczewski P, Haase H, Bornstein SR, Morano I. Human adipocytes attenuate cardiomyocyte contraction: characterization of an adipocyte-derived negative inotropic activity. FASEB J. 2006; 20(10):1653–9. [PubMed: 16873888]
28. Lamounier-Zepter V, Look C, Alvarez J, et al. Adipocyte fatty acid-binding protein suppresses cardiomyocyte contraction: a new link between obesity and heart disease. Circ Res. 2009; 105(4): 326–34. [PubMed: 19608978]
29. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol. 1972 Nov 8; 30(6): 595–602. [PubMed: 4263660]
30. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007; 115(25):3213–23. [PubMed: 17592090]
31. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord. 2010 Mar; 11(1):31–9. [PubMed: 20180026]
32. Regan TJ, Lyons MM, Ahmed SS, et al. Evidence for cardiomyopathy in familial diabetes mellitus. J Clin Invest. 1977; 60(4):884–99. [PubMed: 893679]
33. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993; 22(4 Suppl A):6A–13A. [PubMed: 8509564]
34. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241 (19):2035–8. [PubMed: 430798]
35. Hayat SA, Patel B, Khattar RS, Malik RA. Diabetic cardiomyopathy: mechanisms, diagnosis and treatment. Clin Sci (Lond). 2004; 107(6):539–57. [PubMed: 15341511]
36. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr Rev. 2004; 25(4):543–67. [PubMed: 15294881]
37. Carugo S, Giannattasio C, Calchera I, et al. Progression of functional and structural cardiac alterations in young normotensive uncomplicated patients with type I diabetes mellitus. J Hypertens. 2001; 19(9):1675–80. [PubMed: 11564989]
38. Falcao-Pires I, Hamdani N, Borbely A, et al. Diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis through altered myocardial structure and cardiomyocyte stiffness. Circulation. 2011; 124(10):1151–9. [PubMed: 21844073]
39. Avendano GF, Agarwal RK, Bashey RI, et al. Effects of glucose intolerance on myocardial function and collagen-linked glycation. Diabetes. 1999; 48(7):1443–7. [PubMed: 10389851]

40. Ma H, Li SY, Xu P, et al. Advanced glycation endproduct (AGE) accumulation and AGE receptor (RAGE) up-regulation contribute to the onset of diabetic cardiomyopathy. J Cell Mol Med. 2009; 13(8B):1751–64. [PubMed: 19602045]
41. Dobrin JS, Lebeche D. Diabetic cardiomyopathy: signaling defects and therapeutic approaches. Expert Rev Cardiovasc Ther. 2010; 8(3):373–91. [PubMed: 20222816]
42. Tang WH, Cheng WT, Kravtsov GM, et al. Cardiac contractile dysfunction during acute hyperglycemia due to impairment of SERCA by polyol pathway-mediated oxidative stress. Am J Physiol Cell Physiol. 2010; 299(3):C643–53. [PubMed: 20573996]
43. Connelly KA, Kelly DJ, Zhang Y, et al. Functional, structural and molecular aspects of diastolic heart failure in the diabetic (mRen-2)27 rat. Cardiovasc Res. 2007; 76(2):280–91. [PubMed: 17716638]
44. Miklos Z, Kemecsei P, Biro T, et al. Early cardiac dysfunction is rescued by upregulation of SERCA2a pump activity in a rat model of metabolic syndrome. Acta Physiol (Oxf). 2012; 205(3): 381–93. [PubMed: 22289164]
45. Sakata S, Lebeche D, Sakata Y, et al. Mechanical and metabolic rescue in a type II diabetes model of cardiomyopathy by targeted gene transfer. Mol Ther. 2006; 13(5):987–96. [PubMed: 16503203]
46. Xu KY, Zweier JL, Becker LC. Hydroxyl radical inhibits sarcoplasmic reticulum Ca(2+)-ATPase function by direct attack on the ATP binding site. Circ Res. 1997; 80(1):76–81. [PubMed: 8978325]
47. Kantharidis P, Wang B, Carew RM, Lan HY. Diabetes complications: the microRNA perspective. Diabetes. 2011; 60(7):1832–7. [PubMed: 21709278]
48. Feng B, Chen S, George B, Feng Q, Chakrabarti S. miR133a regulates cardiomyocyte hypertrophy in diabetes. Diabetes Metab Res Rev. 2010; 26(1):40–9. [PubMed: 20013939]
49. Hwang YC, Jee JH, Kang M, Rhee EJ, Sung J, Lee MK. Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level. Int J Cardiol. 2011 Mar 9.
50. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA. 2005; 294(3):334–41. [PubMed: 16030278]
51. Belke DD, Betuing S, Tuttle MJ, et al. Insulin signaling coordinately regulates cardiac size, metabolism, and contractile protein isoform expression. J Clin Invest. 2002; 109(5):629–39. [PubMed: 11877471]
52. Hu P, Zhang D, Swenson L, Chakrabarti G, Abel ED, Litwin SE. Minimally invasive aortic banding in mice: effects of altered cardiomyocyte insulin signaling during pressure overload. Am J Physiol Heart Circ Physiol. 2003; 285(3):H1261–9. [PubMed: 12738623]
53. McQueen AP, Zhang D, Hu P, et al. Contractile dysfunction in hypertrophied hearts with deficient insulin receptor signaling: possible role of reduced capillary density. J Mol Cell Cardiol. 2005; 39(6):882–92. [PubMed: 16216265]
54. Sena S, Hu P, Zhang D, et al. Impaired insulin signaling accelerates cardiac mitochondrial dysfunction after myocardial infarction. J Mol Cell Cardiol. 2009; 46(6):910–8. [PubMed: 19249310]
55. Duncan JG. Peroxisome proliferator activated receptor-alpha (PPARalpha) and PPAR gamma coactivator-1 alpha (PGC-1 alpha) regulation of cardiac metabolism in diabetes. Pediatr Cardiol. 2011; 32(3):323–8. [PubMed: 21286700]
56. Buchanan J, Mazumder PK, Hu P, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology. 2005; 146(12):5341–9. [PubMed: 16141388]
57. Sloan C, Tuinei J, Nemetz K, et al. Central leptin signaling is required to normalize myocardial fatty acid oxidation rates in caloric-restricted ob/ob mice. 2011; 60(5):1424–34.
58. Peterson LR, Herrero P, McGill J, et al. Fatty acids and insulin modulate myocardial substrate metabolism in humans with type 1 diabetes. Diabetes. 2008; 57(1):32–40. [PubMed: 17914030]
59. How OJ, Aasum E, Severson DL, Chan WY, Essop MF, Larsen TS. Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. Diabetes. 2006; 55(2):466–73. [PubMed: 16443782]

60. Rijzewijk LJ, van der Meer RW, Lamb HJ, et al. Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. J Am Coll Cardiol. 2009; 54(16): 1524–32. [PubMed: 19815124]
61. Ouwens DM, Diamant M, Fodor M, et al. Cardiac contractile dysfunction in insulin-resistant rats fed a high-fat diet is associated with elevated CD36-mediated fatty acid uptake and esterification. Diabetologia. 2007; 50(9):1938–48. [PubMed: 17639306]
62. Menard SL, Croteau E, Sarrhini O, et al. Abnormal *in vivo* myocardial energy substrate uptake in diet-induced type 2 diabetic cardiomyopathy in rats. Am J Physiol Endocrinol Metab. 2010; 298(5):E1049–57. [PubMed: 20159856]
63. Boudina S, Bugger H, Sena S, et al. Contribution of impaired myocardial insulin signaling to mitochondrial dysfunction and oxidative stress in the heart. Circulation. 2009; 119(9):1272–83. [PubMed: 19237663]
64. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation. 2004; 109(18): 2191–6. [PubMed: 15123530]
65. Neubauer S, Horn M, Cramer M, et al. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation. 1997; 96(7):2190–6. [PubMed: 9337189]
66. Scheuermann-Freestone M, Madsen PL, Manners D, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. Circulation. 2003; 107(24):3040–6. [PubMed: 12810608]
67. Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neufer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. J Am Coll Cardiol. 2009; 54(20):1891–8. [PubMed: 19892241]
68. Kuo TH, Giacomelli F, Wiener J. Oxidative metabolism of Polytron versus Nagarse mitochondria in hearts of genetically diabetic mice. Biochim Biophys Acta. 1985; 806(1):9–15. [PubMed: 3967008]
69. Boudina S, Sena S, Theobald H, et al. Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. Diabetes. 2007; 56(10):2457–66. [PubMed: 17623815]
70. Boudina S, Sena S, O'Neill BT, Tathireddy P, Young ME, Abel ED. Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesitv. Circulation. 2005; 112(17):2686–95. [PubMed: 16246967]
71. Duncan JG, Fong JL, Medeiros DM, Finck BN, Kelly DP. Insulin-resistant heart exhibits a mitochondrial biogenic response driven by the peroxisome proliferator-activated receptor-alpha/PGC-1 alpha gene regulatory pathway. Circulation. 2007; 115(7):909–17. [PubMed: 17261654]
72. Nisoli E, Clementi E, Carruba MO, Moncada S. Defective mitochondrial biogenesis: a hallmark of the high cardiovascular risk in the metabolic syndrome? Circ Res. 2007; 100(6):795–806. [PubMed: 17395885]
73. Ren J, Pulakat L, Whaley-Connell A, Sowers JR. Mitochondrial biogenesis in the metabolic syndrome and cardiovascular disease. J Mol Med (Berl). 2010; 88(10):993–1001. [PubMed: 20725711]
74. Szendroedi J, Phielix E, Roden M. The role of mitochondria in insulin resistance and type 2 diabetes mellitus. Nat Rev Endocrinol. 2012; 8(2):92–103. [PubMed: 21912398]
75. Shen E, Li Y, Shan L, et al. Rac1 is required for cardiomyocyte apoptosis during hyperglycemia. Diabetes. 2009 Oct; 58(10):2386–95. [PubMed: 19592621]
76. Nakamura H, Matoba S, Iwai-Kanai E, et al. p53 promotes cardiac dysfunction in diabetic mellitus caused by excessive mitochondrial respiration-mediated reactive oxygen species generation and lipid accumulation. Circ Heart Fail. 2012; 5(1):106–15. [PubMed: 22075967]
77. Hansford RG, Zorov D. Role of mitochondrial calcium transport in the control of substrate oxidation. Mol Cell Biochem. 1998; 184(1–2):359–69. [PubMed: 9746330]

78. Oliveira PJ, Seica R, Coxito PM, et al. Enhanced permeability transition explains the reduced calcium uptake in cardiac mitochondria from streptozotocin-induced diabetic rats. FEBS Lett. 2003; 554(3):511–4. [PubMed: 14623121]

79. Medikayala S, Piteo B, Zhao X, Edwards JG. Chronically elevated glucose compromises myocardial mitochondrial DNA integrity by alteration of mitochondrial topoisomerase function. Am J Physiol Cell Physiol. 2011; 300(2):C338–48. [PubMed: 21123731]

80. Bugger H, Chen D, Riehle C, et al. Tissue-specific remodeling of the mitochondrial proteome in type 1 diabetic akita mice. Diabetes. 2009; 58(9):1986–97. [PubMed: 19542201]

81. Hu Y, Suarez J, Fricovsky E, et al. Increased enzymatic O-GlcNAcylation of mitochondrial proteins impairs mitochondrial function in cardiac myocytes exposed to high glucose. J Biol Chem. 2009 Jan 2; 284(1):547–55. [PubMed: 19004814]

82. Dabkowski ER, Baseler WA, Williamson CL, et al. Mitochondrial dysfunction in the type 2 diabetic heart is associated with alterations in spatially distinct mitochondrial proteomes. Am J Physiol Heart Circ Physiol. 2010; 299(2):H529–40. [PubMed: 20543078]

83. Essop MF, Chan WA, Hattingh S. Proteomic analysis of mitochondrial proteins in a mouse model of type 2 diabetes. Cardiovasc J Afr. 2011; 22(4):175–8. [PubMed: 20859605]

84. Baseler WA, Dabkowski ER, Williamson CL, et al. Proteomic alterations of distinct mitochondrial subpopulations in the type 1 diabetic heart: contribution of protein import dysfunction. Am J Physiol Regul Integr Comp Physiol. 2011; 300(2):R186–200. [PubMed: 21048079]

85. Makino A, Suarez J, Gawlowski T, et al. Regulation of mitochondrial morphology and function by O-GlcNAcylation in neonatal cardiac myocytes. Am J Physiol Regul Integr Comp Physiol. 2011; 300(6):R1296–302. [PubMed: 21346246]

86. Nakai A, Yamaguchi O, Takeda T, et al. The role of autophagy in cardiomyocytes in the basal state and in response to hemodynamic stress. Nat Med. 2007; 13(5):619–24. [PubMed: 17450150]

87. Terman A, Brunk UT. Autophagy in cardiac myocyte homeostasis, aging, and pathology. Cardiovasc Res. 2005; 68(3):355–65. [PubMed: 16213475]

88. Hua Y, Zhang Y, Ceylan-Isik AF, Wold LE, Nunn JM, Ren J. Chronic Akt activation accentuates aging-induced cardiac hypertrophy and myocardial contractile dysfunction: role of autophagy. Basic Res Cardiol. 2011; 106(6):1173–91. [PubMed: 21901288]

89. Nair S, Ren J. Autophagy and cardiovascular aging: Lesson learned from rapamycin. Cell Cycle. 2012; 11(11):2092–9. [PubMed: 22580468]

90. Han X, Turdi S, Hu N, Guo R, Zhang Y, Ren J. Influence of long-term caloric restriction on myocardial and cardiomyocyte contractile function and autophagy in mice. J Nutr Biochem. 2012 Mar 21.

91. Giricz Z, Mentzer RM Jr, Gottlieb RA. Autophagy, Myocardial Protection and the Metabolic Syndrome. J Cardiovasc Pharmacol. 2012 Apr 2.

92. Sciarretta S, Volpe M, Sadoshima J. Is reactivation of autophagy a possible therapeutic solution for obesity and metabolic syndrome? Autophagy. 2012; 8(8)

93. Xie Z, Lau K, Eby B, et al. Improvement of cardiac functions by chronic metformin treatment is associated with enhanced cardiac autophagy in diabetic OVE26 mice. Diabetes. 2011; 60(6):1770–8. [PubMed: 21562078]

94. Sciarretta S, Zhai P, Shao D, et al. Rheb is a critical regulator of autophagy during myocardial ischemia: pathophysiological implications in obesity and metabolic syndrome. Circulation. 2012; 125(9):1134–46. [PubMed: 22294621]

95. Halliwell B. Biochemistry of oxidative stress. Biochem Soc Trans. 2007; 35(Pt 5):1147–50. [PubMed: 17956298]

96. Huang PL. eNOS, metabolic syndrome and cardiovascular disease. Trends Endocrinol Metab. 2009; 20(6):295–302. [PubMed: 19647446]

97. de Haan JB, Cooper ME. Targeted antioxidant therapies in hyperglycemia-mediated endothelial dysfunction. Front Biosci (Schol Ed). 2011; 3:709–29. [PubMed: 21196407]

98. Ford ES, Mokdad AH, Giles WH, Brown DW. The metabolic syndrome and antioxidant concentrations: findings from the Third National Health and Nutrition Examination Survey. Diabetes. 2003; 52(9):2346–52. [PubMed: 12941775]

99. Meigs JB, Larson MG, Fox CS, Keaney JF Jr, Vasan RS, Benjamin EJ. Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study. Diabetes Care. 2007; 30(10):2529–35. [PubMed: 17586736]
100. Cao J, Sodhi K, Puri N, Monu SR, Rezzani R, Abraham NG. High fat diet enhances cardiac abnormalities in SHR rats: Protective role of heme oxygenase-adiponectin axis. Diabetol Metab Syndr. 2011; 3(1):37. [PubMed: 22196253]
101. Saraiva RM, Minhas KM, Zheng M, Pitz E, Treuer A, Gonzalez D, et al. Reduced neuronal nitric oxide synthase expression contributes to cardiac oxidative stress and nitroso-redox imbalance in ob/ob mice. Nitric Oxide. 2007; 16(3):331–8. [PubMed: 17307368]
102. Ballal K, Wilson CR, Harmancey R, Taegtmeyer H. Obesogenic high fat western diet induces oxidative stress and apoptosis in rat heart. Mol Cell Biochem. 2010; 344(1–2):221–30. [PubMed: 20676734]
103. Serpillon S, Floyd BC, Gupte RS, et al. Superoxide production by NAD(P)H oxidase and mitochondria is increased in genetically obese and hyperglycemic rat heart and aorta before the development of cardiac dysfunction. The role of glucose-6-phosphate dehydrogenase-derived NADPH. Am J Physiol Heart Circ Physiol. 2009; 297(1):H153–62. [PubMed: 19429815]
104. Matsuzawa A, Ichijo H. Stress-responsive protein kinases in redox-regulated apoptosis signaling. Antioxid Redox Signal. 2005; 7(3–4):472–81. [PubMed: 15706095]
105. Erickson JR, Joiner ML, Guan X, et al. A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. Cell. 2008; 133(3):462–74. [PubMed: 18455987]
106. Maejima Y, Kuroda J, Matsushima S, Ago T, Sadoshima J. Regulation of myocardial growth and death by NADPH oxidase. J Mol Cell Cardiol. 2011; 50(3):408–16. [PubMed: 21215757]
107. Ventura-Clapier R, Garnier A, Veksler V. Energy metabolism in heart failure. J Physiol. 2004; 555(Pt 1):1–13. [PubMed: 14660709]
108. Golden TR, Hinerfeld DA, Melov S. Oxidative stress and aging: beyond correlation. Aging Cell. 2002; 1(2):117–23. [PubMed: 12882341]
109. Boveris A. Determination of the production of superoxide radicals and hydrogen peroxide in mitochondria. Methods Enzymol. 1984; 105:429–35. [PubMed: 6328196]
110. Han D, Antunes F, Canali R, Rettori D, Cadenas E. Voltage-dependent anion channels control the release of the superoxide anion from mitochondria to cytosol. J Biol Chem. 2003; 278(8):5557–63. [PubMed: 12482755]
111. St-Pierre J, Buckingham JA, Roebuck SJ, Brand MD. Topology of superoxide production from different sites in the mitochondrial electron transport chain. J Biol Chem. 2002; 277(47):44784–90. [PubMed: 12237311]
112. Starkov AA, Fiskum G, Chinopoulos C, et al. Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species. J Neurosci. 2004; 24(36):7779–88. [PubMed: 15356189]
113. Brand MD. The sites and topology of mitochondrial superoxide production. Exp Gerontol. 2010; 45(7–8):466–72. [PubMed: 20064600]
114. McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem. 1969; 244(22):6049–55. [PubMed: 5389100]
115. Barra D, Schinina ME, Simmaco M, et al. The primary structure of human liver manganese superoxide dismutase. J Biol Chem. 1984; 259(20):12595–601. [PubMed: 6386798]
116. Patenaude A, Ven Murthy MR, Mirault ME. Mitochondrial thioredoxin system: effects of TrxR2 overexpression on redox balance, cell growth, and apoptosis. J Biol Chem. 2004; 279(26):27302–14. [PubMed: 15082714]
117. Yu T, Robotham JL, Yoon Y. Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. Proc Natl Acad Sci U S A. 2006; 103(8):2653–8. [PubMed: 16477035]
118. Dikalov S. Cross talk between mitochondria and NADPH oxidases. Free Radic Biol Med. 2011; 51(7):1289–301. [PubMed: 21777669]
119. Rosen P, Osmers A. Oxidative stress in young Zucker rats with impaired glucose tolerance is diminished by acarbose. Horm Metab Res. 2006; 38(9):575–86. [PubMed: 16981139]

120. Li SY, Yang X, Ceylan-Isik AF, Du M, Sreejayan N, Ren J. Cardiac contractile dysfunction in Lep/Lep obesity is accompanied by NADPH oxidase activation, oxidative modification of sarco(endo)plasmic reticulum Ca2+-ATPase and myosin heavy chain isozyme switch. Diabetologia. 2006; 49(6):1434–46. [PubMed: 16612592]

121. Feillet-Coudray C, Sutra T, Fouret G, et al. Oxidative stress in rats fed a high-fat high-sucrose diet and preventive effect of polyphenols: Involvement of mitochondrial and NAD(P)H oxidase systems. Free Radic Biol Med. 2009; 46(5):624–32. [PubMed: 19135522]

122. Letavic MA, Keith JM, Ly KS, et al. Novel naphthyridines are histamine H3 antagonists and serotonin reuptake transporter inhibitors. Bioorg Med Chem Lett. 2007; 17(9):2566–9. [PubMed: 17307358]

123. Matsushima S, Kinugawa S, Yokota T, et al. Increased myocardial NAD(P)H oxidase-derived superoxide causes the exacerbation of postinfarct heart failure in type 2 diabetes. Am J Physiol Heart Circ Physiol. 2009; 297(1):H409–16. [PubMed: 19465539]

124. Roe ND, Thomas DP, Ren J. Inhibition of NADPH oxidase alleviates experimental diabetes-induced myocardial contractile dysfunction. Diabetes Obes Metab. 2011; 13(5):465–73. [PubMed: 21272185]

125. Putnam K, Shoemaker R, Yiannikouris F, Cassis LA. The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. Am J Physiol Heart Circ Physiol. 2012; 302(6):H1219–30. [PubMed: 22227126]

126. Zhang GX, Lu XM, Kimura S, Nishiyama A. Role of mitochondria in angiotensin II-induced reactive oxygen species and mitogen-activated protein kinase activation. Cardiovasc Res. 2007; 76(2):204–12. [PubMed: 17698051]

127. Wang Q, Sun Y, Ma A, Li Y, Han X, Liang H. Effects of vitamin E on plasma lipid status and oxidative stress in Chinese women with metabolic syndrome. Int J Vitam Nutr Res. 2010; 80(3): 178–87. [PubMed: 21234859]

128. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet. 1996; 347(9004):781–6. [PubMed: 8622332]

129. Lavie CJ, Milani JN. Do antioxidant vitamins ameliorate the beneficial effects of exercise training on insulin sensitivity? J Cardiopulm Rehabil Prev. 2011; 31(4):211–6. [PubMed: 21427602]

130. Manning PJ, Sutherland WH, Williams SM, et al. The effect of lipoic acid and vitamin E therapies in individuals with the metabolic syndrome. Nutr Metab Cardiovasc Dis. 2012 Mar 6.

131. Debreceni B, Debreceni L. Why Do Homocysteine-Lowering B Vitamin and Antioxidant E Vitamin Supplementations Appear To Be Ineffective in the Prevention of Cardiovascular Diseases? Cardiovascular Therapeutics. 2011 no-no.

132. Avignon A, Hokayem M, Bisbal C, Lambert K. Dietary antioxidants: Do they have a role to play in the ongoing fight against abnormal glucose metabolism? Nutrition. 2012; 28(7–8):715–21. [PubMed: 22571840]

133. Wang H, Yang YJ, Qian HY, Zhang Q, Xu H, Li JJ. Resveratrol in cardiovascular disease: what is known from current research? Heart Fail Rev. 2012; 17(3):437–48. [PubMed: 21688187]

134. Qin F, Siwik DA, Luptak I, et al. The Polyphenols Resveratrol and S17834 Prevent the Structural and Functional Sequelae of Diet-Induced Metabolic Heart Disease in Mice / Clinical Perspective. Circulation. 2012; 125(14):1757–64. [PubMed: 22388319]

135. Robich MP, Osipov RM, Chu LM, et al. Resveratrol modifies risk factors for coronary artery disease in swine with metabolic syndrome and myocardial ischemia. Eur J Pharmacol. 2011; 664(1–3):45–53. [PubMed: 21575630]

136. Bagul PK, Middela H, Matapally S, et al. Attenuation of insulin resistance, metabolic syndrome and hepatic oxidative stress by resveratrol in fructose-fed rats. Pharmacol Res. 2012 May 22. (0).

137. Liu L, Wang Y, Lam KS, Xu A. Moderate wine consumption in the prevention of metabolic syndrome and its related medical complications. Endocr Metab Immune Disord Drug Targets. 2008 Jun; 8(2):89–98. [PubMed: 18537695]

138. Timmers S, Konings E, Bilet L, et al. Calorie Restriction-like Effects of 30 Days of Resveratrol Supplementation on Energy Metabolism and Metabolic Profile in Obese Humans. Cell Metabolism. 2011; 14(5):612–22. [PubMed: 22055504]

139. Um JH, Park SJ, Kang H, Yang S, Foretz M, McBurney MW, et al. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. Diabetes. 2010; 59(3): 554–63. [PubMed: 19934007]

140. Penumathsa SV, Maulik N. Resveratrol: a promising agent in promoting cardioprotection against coronary heart disease. Can J Physiol Pharmacol. 2009; 87(4):275–86. [PubMed: 19370081]

141. Guo H, Ling W, Wang Q, Liu C, Hu Y, Xia M. Cyanidin 3-glucoside protects 3T3-L1 adipocytes against H2O2- or TNF-alpha-induced insulin resistance by inhibiting c-Jun NH2-terminal kinase activation. Biochem Pharmacol. 2008; 75(6):1393–401. [PubMed: 18179781]

142. Qin Y, Xia M, Ma J, et al. Anthocyanin supplementation improves serum LDL- and HDL-cholesterol concentrations associated with the inhibition of cholesteryl ester transfer protein in dyslipidemic subjects. The American Journal of Clinical Nutrition. 2009; 90(3):485–92. [PubMed: 19640950]

143. Egert S, Bosy-Westphal A, Seiberl J, et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. The British journal of nutrition. 2009; 102(7):1065–74. [PubMed: 19402938]

144. Panchal SK, Poudyal H, Brown L. Quercetin Ameliorates Cardiovascular, Hepatic, and Metabolic Changes in Diet-Induced Metabolic Syndrome in Rats. J Nutrition. 2012; 142(6):1026–32. [PubMed: 22535755]

145. Xia X, Weng J. Targeting metabolic syndrome: candidate natural agents. J Diabetes. 2010; 2(4): 243–9. [PubMed: 20923500]

146. Subramanian S, Kalyanaraman B, Migrino RQ. Mitochondrially targeted antioxidants for the treatment of cardiovascular diseases. Recent Pat Cardiovasc Drug Discov. 2010; 5(1):54–65. [PubMed: 19807685]

147. Ramos-Marquez ME, Siller-Lopez F. Current antioxidant molecular therapies for oxidative stress-related ailments. Current gene therapy. 2008; 8(4):256–63. [PubMed: 18691021]

148. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature. 2006; 440(7086):944–8. [PubMed: 16612386]

149. Hoehn KL, Salmon AB, Hohnen-Behrens C, et al. Insulin resistance is a cellular antioxidant defense mechanism. Proc Natl Acad Sci U S A. 2009; 106(42):17787–92. [PubMed: 19805130]

150. Saito Y, Fukuhara A, Nishio K, et al. Characterization of cellular uptake and distribution of coenzyme Q10 and vitamin E in PC12 cells. The Journal of Nutritional Biochemistry. 2009; 20(5):350–7. [PubMed: 18602819]

151. Huynh K, Kiriazis H, Du XJ, et al. Coenzyme Q10 attenuates diastolic dysfunction, cardiomyocyte hypertrophy and cardiac fibrosis in the db/db mouse model of type 2 diabetes. Diabetologia. 2012; 55(5):1544–53. [PubMed: 22374176]

152. Huynh K, Kiriazis H, Du XJ, et al. Coenzyme Q< sub> 10< /sub> attenuates diastolic dysfunction, cardiomyocyte hypertrophy and cardiac fibrosis in the < i> db/db mouse model of type 2 diabetes. Diabetologia. 2012; 55(5):1544–53. [PubMed: 22374176]

153. Kocharian A, Shabanian R, Rafiei-Khorgami M, Kiani A, Heidari-Bateni G. Coenzyme Q10 improves diastolic function in children with idiopathic dilated cardiomyopathy. Cardiology in the Young. 2009; 19(05):501–6. [PubMed: 19703336]

154. Young JM, Florkowski CM, Molyneux SL, et al. A Randomized, Double-Blind, Placebo-Controlled Crossover Study of Coenzyme Q10 Therapy in Hypertensive Patients With the Metabolic Syndrome. Am J Hypertens. 2012; 25(2):261–70. [PubMed: 22113168]

155. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev. 2008; (2):CD007176. [PubMed: 18425980]

156. Rodriguez-Cuenca S, Cochemé HM, Logan A, et al. Consequences of long-term oral administration of the mitochondria-targeted antioxidant MitoQ to wild-type mice. Free Radical Biology and Medicine. 2010; 48(1):161–72. [PubMed: 19854266]

157. Smith RA, Murphy MP. Mitochondria-targeted antioxidants as therapies. Discov Med. 2011; 11(57):106–14. [PubMed: 21356165]

158. Adlam VJ, Harrison JC, Porteous CM, et al. Targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury. FASEB J. 2005; 19(9):1088–95. [PubMed: 15985532]

159. Mercer JR, Yu E, Figg N, et al. The mitochondria-targeted antioxidant MitoQ decreases features of the metabolic syndrome in ATM+/−/ApoE−/− mice. Free Radic Biol Med. 2012; 52(5):841–9. [PubMed: 22210379]

160. Pung YF, Rocic P, Murphy MP, et al. Resolution of Mitochondrial Oxidative Stress Rescues Coronary Collateral Growth in Zucker Obese Fatty Rats. Arteriosclerosis, Thrombosis, and Vascular Biology. 2012; 32(2):325–34.

161. Dai D-F, Chen T, Szeto H, et al. Mitochondrial Targeted Antioxidant Peptide Ameliorates Hypertensive Cardiomyopathy. J Am College Cardiol. 2011; 58(1):73–82.

162. Kloner RA, Hale SL, Dai W, et al. Reduction of Ischemia/Reperfusion Injury With Bendavia, a Mitochondria-Targeting Cytoprotective Peptide. J Am Heart Association. 2012; 1(3)

163. Chen M, Liu B, Gao Q, Zhuo Y, Ge J. Mitochondria-Targeted Peptide MTP-131 Alleviates Mitochondrial Dysfunction and Oxidative Damage in Human Trabecular Meshwork Cells. Investigative Ophthalmol Visual Sci. 2011; 52(10):7027–37.

164. Sloan RC, Moukdar F, Frasier CR, et al. Mitochondrial permeability transition in the diabetic heart: Contributions of thiol redox state and mitochondrial calcium to augmented reperfusion injury. J Mol Cellular Cardiol. 2012; 52(5):1009–18. [PubMed: 22406429]

165. Lyamzaev K, Pustovidko A, Simonyan R, et al. Novel Mitochondria-Targeted Antioxidants: Plastoquinone Conjugated with Cationic Plant Alkaloids Berberine and Palmatine. Pharm Res. 2011; 28(11):2883–95. [PubMed: 21671134]

166. Shen X, Zheng S, Metreveli NS, Epstein PN. Protection of cardiac mitochondria by overexpression of MnSOD reduces diabetic cardiomyopathy. Diabetes. 2006; 55(3):798–805. [PubMed: 16505246]

167. Dong F, Li Q, Sreejayan N, Nunn JM, Ren J. Metallothionein Prevents High-Fat Diet–Induced Cardiac Contractile Dysfunction. Diabetes 2007 September. 2007; 56(9):2201–12.

168. Ye G, Metreveli NS, Donthi RV, et al. Catalase protects cardiomyocyte function in models of type 1 and type 2 diabetes. Diabetes. 2004; 53(5):1336–43. [PubMed: 15111504]

169. Bruno RM, Daghini E, Ghiadoni L, et al. Effect of acute administration of vitamin C on muscle sympathetic activity, cardiac sympathovagal balance, and baroreflex sensitivity in hypertensive patients. Am J Clin Nutr. 2012 Jun 13.

170. Feng B, Chen S, Chiu J, George B, Chakrabarti S. Regulation of cardiomyocyte hypertrophy in diabetes at the transcriptional level. American journal of physiology Endocrinology and metabolism. 2008; 294(6):E1119–26. [Research Support, Non-U. S Gov't]. [PubMed: 18413674]

171. Hardeland R. Antioxidative protection by melatonin: multiplicity of mechanisms from radical detoxification to radical avoidance. Endocrine. 2005; 27(2):119–30. [PubMed: 16217125]

172. Hardeland R, Pandi-Perumal SR. Melatonin, a potent agent in antioxidative defense: actions as a natural food constituent, gastrointestinal factor, drug and prodrug. Nutr Metab (Lond). 2005; 2:22. [PubMed: 16153306]

173. Reiter RJ, Manchester LC, Tan DX. Neurotoxins: free radical mechanisms and melatonin protection. Curr Neuropharmacol. 2010; 8(3):194–210. [PubMed: 21358970]

174. Poeggeler B, Saarela S, Reiter RJ, Tan DX, Chen LD, Manchester LC, et al. Melatonin--a highly potent endogenous radical scavenger and electron donor: new aspects of the oxidation chemistry, of this indole accessed *in vitro*. Ann N Y Acad Sci. 1994; 738:419–20. [PubMed: 7832450]

175. Nduhirabandi F, du Toit EF, Lochner A. Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? Acta Physiol (Oxf). 2012; 205(2):209–23. [PubMed: 22226301]

176. Kolar F, Jezkova J, Balkova P, et al. Role of oxidative stress in PKC-delta upregulation and cardioprotection induced by chronic intermittent hypoxia. Am J Physiol Heart Circ Physiol. 2007; 292(1):H224–30. [PubMed: 16936002]

177. Tsujita K, Shimomura H, Kawano H, et al. Effects of edaravone on reperfusion injury in patients with acute myocardial infarction. Am J Cardiol. 2004; 94(4):481–4. [PubMed: 15325934]

178. Kikuchi K, Uchikado H, Miyagi N, et al. Beyond neurological disease: new targets for edaravone (Review). International journal of molecular medicine. 2011; 28(6):899–906. [PubMed: 21922128]

179. Anderson EJ, Lustig ME, Boyle KE, et al. Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. J Clin Invest. 2009; 119(3):573–81. [PubMed: 19188683]

180. Zhao K, Zhao G-M, Wu D, et al. Cell-permeable Peptide Antioxidants Targeted to Inner Mitochondrial Membrane inhibit Mitochondrial Swelling, Oxidative Cell Death, and Reperfusion Injury. J Biological Chem. 2004; 279(33):34682–90.

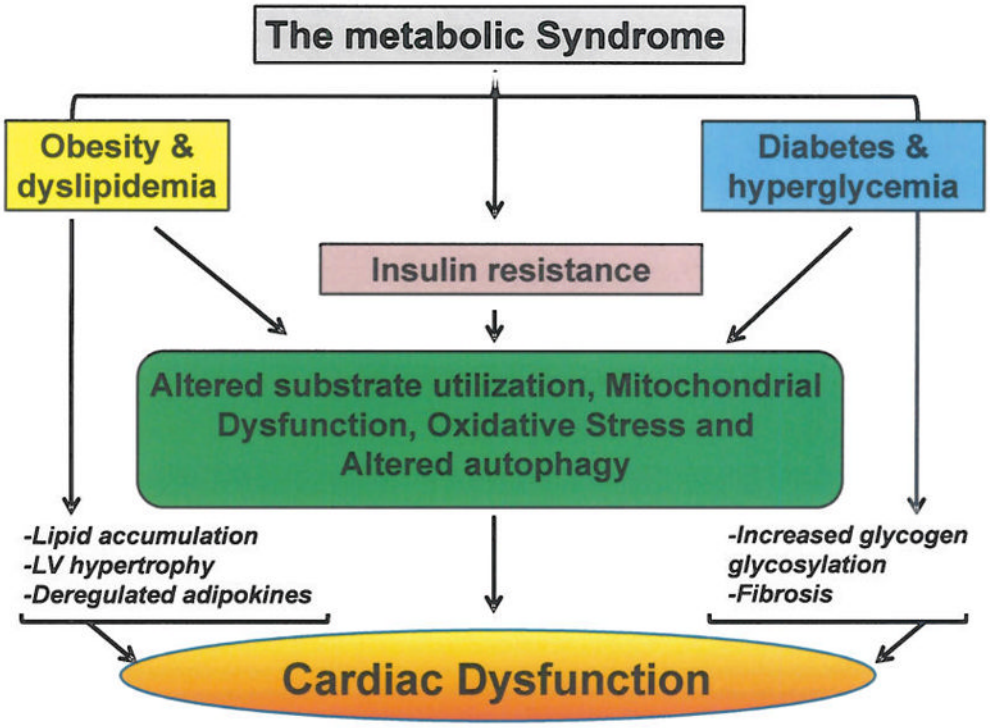

Fig. 1. Mechanisms for altered cardiac function in the metabolic syndrome

Common and distinct mechanisms responsible for cardiac dysfunction are highlighted for three important components of the metabolic syndrome; Obesity and dyslipidemia, diabetes and hyperglycemia and insulin resistance.

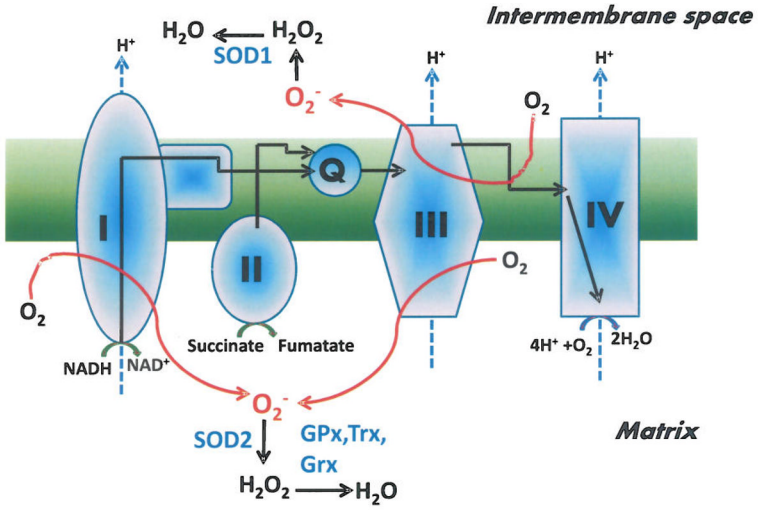

Fig. 2. Major sites for mitochondrial superoxide (O_2^-) generation and its detoxification

Black arrows indicate electron flow, blue hatched arrows indicate proton flow and red arrows indicate superoxide production. SOD1 and SOD2: superoxide dismutase 1 and 2; GPx: glutathione peroxidase; Trx: thioredoxin and Grx: glutaredoxin. (The color version of the figure is available in the electronic copy of the article).

Table 1

Human and animals studies using non mitochondria-targeted or mitochondria-targeted antioxidants for the treatment of cardiovascular disease in the metabolic syndrome Table 1. Human and animals studies using non mitochondria-targeted or mitochondria-targeted antioxidants for the treatment of cardiovascular disease in the metabolic syndrome

Class of Antioxidants	Name of Antioxidants	Mode of Action	Effect	Animal/*In Vitro* Studies	Human Studies
Non-mitochondria-targeted antioxidants					
Vitamins	Vitamin C (L-ascorbic acid)	Suppression of adrenergic activity	Reduction of blood pressure		Reduction of blood pressure in non-MetS patients [169]
	Vitamin E		No effect		CHAOS trial [128]
Natural compounds	$CoenzymeQ_{10}$	Vitamin-like lipid-soluble component of mitochondrial electron transport chain	Slight reduction of LV mass and systolic blood pressure	Female *db/db* mice [152]	
			Reduction of diastolic dysfunction		Children with cardiomyopathy [153]
			No effect on hypertension		Patients with the MetS [154–155]
	Resveratrol	Increases expression of SIRT1 [138]. Increases GLUT1, IRS1 expression, AMPK and mTOR phosphorylation, reduces RBP4 and PPAR gamma expression [135].	Prevention of LV hypertrophy, diastolic dysfunction, interstitial fibrosis	HFHS-fed C57B16 mice [134].	
			Improvement of blood pressure, and cardiac function	Yorkshire miniswine [135].	
			Moderate reduction of blood pressure		Obese humans [138]
	Anthocyanin	Nonspecific/Unknown	Reduces oxidative stress	*In vitro* [141]	
			No reduction of blood pressure		Dyslipedemic patients [142]
	Curcumin	p300 blocker	Regulation of cardiac hypertrophy	Rat neonatal cardiomyocytes cultured in high-glucose medium and rats with STZ-induced diabetes [170]	
	Melatonin	Scavenges HO^-, O_2^-, and NO) capable of crossing cell membranes and the blood–brain barrier [171–175]	Reduction of infarct size after IR diet and whole-body metabolic abnormalities	Wistar rats on a high-calorie diet	
	Allopurinol	Xantine oxidase inhibitor			

Class of Antioxidants	Name of Antioxidants	Mode of Action	Effect	Animal/*In Vitro* Studies	Human Studies
	N-acetylcysteine		Reduction of oxidative stress but compromised cardioprotection	Rats [176].	
Synthetic compounds	Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one)	Non-specific ROS scavenger	Significant improvement of clinical outcomes		Patients with AMI given during, given during stenting of stenotic arteries [177–178]
Derivatives of natural products	SkQBerb, SkQ-Palm	Mitochondria-targeted derivatives of natural products	Potent ROS-scavenging	Isolated mitochondria and human cells [165]	
	S17834	Synthetic analog of resveratrol			
Mitochondria targeted antioxidants					
	Mn (III) tetrakis 4-benzoic acid porphyrin (MnTBAP)		Improvement of glucose tolerance	Ob/ob mice [148]	
			Prevention of cardiac hypertrophy	UCP-DTA mice (unpublished data)	
	MitoTempo and MitoQuinone		Improvement of mitochondrial function and coronary collateral growth after ischemia injury	Zucher obese fatty rats [160]	
Mitochondria-targeted synthetic antioxidant peptide	SS-31	Targeting to inner mitochondrial membrane	Prevention of cardiac ischemia/reperfusion injury	HF-fed rats [179].	
			Prevention of mitochondrial depolarization	Immortalized cell lines [180]	
	Bendavia	Analog of SS-31	Moderate reduction of infarct size and improved cardiomyocyte survival	Sheep, rabbit, and guinea pig models of ischemia/ reperfusion injury [162]	
			Scavenging of H_2O_2	Immortalized cell lines [163]	

List of non- standard abbreviations and acronyms

CPT-1: Carnitine palmitoyl transferase 1

FA: Fatty acid

AMPK: AMP-activated protein kinase

OS: Oxidative stress

GSH: Reduced glutathione

GSSG: Oxidized glutathione

ETC: Electron transport chain

NADPH: Nicotinamide adenine dinucleotide phosphate-oxidase

SIRT-1: Sirtuin 1

LDL: Low density lipoprotein

JNK: Jun N-terminal kinase

ASK-1: apoptosis signal-regulated kinase 1