Review article

Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies☆

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Abstract

Increased body weight and metabolic disorder including insulin resistance, type 2 diabetes and cardiovascular complications together constitute metabolic syndrome. The pathogenesis of metabolic syndrome involves multitude of factors. A number of studies however indicate, with some conformity, that oxidative stress along with chronic inflammatory condition pave the way for the development of metabolic diseases. Oxidative stress, a state of lost balance between the oxidative and anti-oxidative systems of the cells and tissues, results in the over production of oxidative free radicals and reactive oxygen species (ROS). Excessive ROS generated could attack the cellular proteins, lipids and nucleic acids leading to cellular dysfunction including loss of energy metabolism, altered cell signalling and cell cycle control, genetic mutations, altered cellular transport mechanisms and overall decreased biological activity, immune activation and inflammation. In addition, nutritional stress such as that caused by high fat high carbohydrate diet also promotes oxidative stress as evident by increased lipid per-oxidation products, protein carbonylation, and decreased antioxidant system and reduced glutathione (GSH) levels. These changes lead to initiation of pathogenic milieu and development of several chronic diseases. Studies suggest that in obese person oxidative stress and chronic inflammation are the important underlying factors that lead to development of pathologies such as carcinogenesis, obesity, diabetes, and cardiovascular diseases through altered cellular and nuclear mechanisms, including impaired DNA damage repair and cell cycle regulation. Here we discuss the aspects of metabolic disorders-induced oxidative stress in major pathological conditions and strategies for their prevention and therapy.

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Keywords:
Oxidative stress
Antioxidant
Metabolic disorders
Inflammation
Diabetes
Cardiovascular diseases
Insulin resistance
Carcinogenesis
Phytochemicals

ARTICLE INFO

Article history:
Received 20 November 2015
Received in revised form 15 January 2016
Accepted 2 February 2016
Available online 3 February 2016

Keywords:
Oxidative stress
Antioxidant
Metabolic disorders
Inflammation
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http://dx.doi.org/10.1016/j.lfs.2016.02.002
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1. Introduction

Disruption of normal metabolic processes resulting in energy and redox imbalance sets the seed of many pathophysiological conditions in body which are collectively called metabolic disorders. The key hallmarks of metabolic disorder include risk factors such as dyslipidaemia, leptin resistance, reduced adiponectin, insulin refractoriness, defective insulin secretion, glucose intolerance which collectively referred to as metabolic syndrome [1]. According to National heart, lung and blood institute an individual must have at least three risk factors to be diagnosed with metabolic syndrome [2]. These risk factors contribute to cellular dysfunction and redox imbalance that contribute towards progression of pro-oxidative environment leading to damaged biomolecules, which are highly reactive in nature and can promote cell and tissue dysfunction leading to metabolic diseases. A clear correlation has emerged between oxidative stress and metabolic disorders which can be helpful in the identification of novel biomarkers, molecular targets, and effective drug development for prevention and therapy of these diseases.

Metabolic disorder, emanating from elevated body weight and obesity, has reached epidemic proportions in industrialized countries. According to World Health Organisation (WHO) in 2014, more than 1.9 billion adults, which included 18 years and older, were overweight. Of these more than 600 million were obese [3]. According to a systematic analysis for the Global Burden of disease study in 2013, the USA led the list of countries with maximum obese persons followed by China and India, respectively [4].

The prevailing oxidative and inflammatory conditions constitute major risk factors for the development of a number of pathologies such as tumour development, diabetes and cardiovascular complications. Obese people have relatively enhanced risk of developing colon cancer, gastric cardia, oesophageal adenocarcinoma and cholangiocarcinoma [5], whereas diabetes is reported to predict mortality from cancer of the colon, pancreas, female breast, male liver and bladder [6]. Further, a high BMI could lead to increased risk of developing non-Hodgkins lymphoma and multiple myeloma in gender independent manner [7]. Although a clear mechanism is not available, however, increased oxidative stress in obesity and metabolic syndrome has been linked with DNA damage and subsequent malignancies [8]. A positive correlation between serum 8-hydroxy 2′-deoxy-guanosine (8-OHdG) and increased body mass index has been shown which suggests that oxidative DNA damage may be caused due to obesity condition [9]. DNA damage can alter regulation of cell cycle along with other cellular process including transcription, signal transduction pathways, replication mismatch, DNA damage repair and resultant genomic instability, which may eventually lead to tumorigenesis [10]. Furthermore, reactive oxygen species (ROS) generated during metabolic disorder can cause increased inflammatory condition in body by upregulating redox signalling pathways, altered gene expression of inflammatory cytokines, chemokines and growth factors resulting in the development of pathologies such as insulin resistance, diabetes and cardiovascular damage [11, 12]. A positive correlation has been established between presence of oxidative stress and increased low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) in the animal models. Several mechanisms have been proposed that elevate the oxidative stress in metabolic disorder. One of these mechanisms is dysfunctional high-density lipoprotein (HDL) enabled antioxidant mechanism which may result from decreased HDL levels in metabolic disorders [13]. The subfraction of small HDL particle are known to play protective role but have been found with low antioxidant activity in metabolic syndrome [12]. The anti-oxidant activity of dense HDL sub-fractions has been found impaired and associated with elevated oxidative stress and insulin resistance in metabolic syndrome. Presence of oxidative stress markers in plasma correlates inversely with low levels of HDL while lipid peroxidation products correlate with low HDL in metabolic syndrome [14, 15]. Oxidative process may modify LDL into oxidized-LDL (oxLDL) due to prevalent oxidative condition during metabolic disorder such as glycoxidation, ROS, reactive nitrogen species (RNS), and activation of various oxidases and oxygenases along with decreased activity of cellular antioxidant system. Further, LDL oxidation may also become highly likely due to changes in the distribution of smaller and denser LDL particles. Studies have also shown increased levels of oxLDL in the blood circulation in patients with metabolic syndrome, which indicates increased risk for atherosclerosis and myocardial infarction as well as increased oxidative stress in these patients [16]. Furthermore, increased lipid peroxidation, carbonylation of cellular proteins and NADPH oxidase activity as well as decreased levels of GSH can occur in metabolic syndrome leading to enhanced ROS formation [17]. In fact, in metabolic syndrome patients, elevated levels of oxLDL correlate well with low HDL and oxidative stress, and pose increased risk for developing pathological conditions [18].

Mitochondria are also an important source of ROS. The respiratory circuit in mitochondria comprising of the four complexes which work as electron transport chain (ETC) can become dysfunction resulting in leakage. According to an estimate up to 2% oxygen consumed can be diverted to the production of ROS formation by mitochondria, especially at complexes I and III [19]. High energy diet, which is one of the risk factors for metabolic disorders, could lead to increased metabolic load of the mitochondria resulting in over active ETC that can form excessive ROS as by-products. The ROS produced in the mitochondria also contribute to mitochondrial damage which affect the cellular redox signalling on the one hand while on the other hand they cause a range on pathologies that comprise metabolic disorders [20] indicating that mitochondria can be an important target in such pathologies.

The secretion of 8-epi-prostaglandin E2 (8-epi-PGE2) in urine of people with high BMI indicates strong association of metabolic disorder with systemic oxidative stress [21]. Further, generation of adipocytokines such as tumour necrosis factor-alpha (TNF-α), free fatty acids, angiotensin and leukotrienes can also be linked with oxidative stress and inflammatory condition [22, 23]. The production of free radicals during metabolic disorder can also be attributed to redox imbalance and decreased potency of free radical scavenging system. Cu-Zn superoxide dismutase (SOD) is downregulated along with other antioxidant system in body such as catalase and glutathione peroxidase (GPx) [21]. A number of studies have also demonstrated strong correlation between NADPH oxidase (NOX) activity and increased oxidative stress in metabolic syndrome [17]. Further, animal models of obesity, both diet-induced and genetic, have shown overexpression of NOX subunits e.g. high fat diet-fed rats showed increased expression of NOX2 and p47phox. Similarly, NOX2, p22phox, p47phox and p67phox subunits are up-regulated in the genetic model of obese mouse had NOX subunits overexpressed in heart tissue [17]. Furthermore, systemic up-regulation of NOX in diet-induced obesity in rats has been linked with adiponectin [24]. Increased activity of NOX in metabolic syndrome leads to excessive production of superoxide ions (•O2−) in obese, which may react with nitric oxide (NO) and form RNS such as peroxynitrite, nitroxy anion, nitrosonium cation, nitrogen oxides and s-nitrosothiols [25]. These species have the ability
to post-translationally change the biomolecular targets such as lipids, proteins, DNA and low molecular weight antioxidants. Further, peroxynitrite may react with other ROS and form an array of different types of RNS and cause nitrosative stress resulting in cellular and organ damage. Consequently, the altered NO bioactivity may lead to the development of endothelial dysfunction and cardiovascular complications in obese [26]. Superoxide anions may also cause oxidative changes to cellular proteins by nitrosylation of tyrosine residues, an important marker of cardiovascular problem, and render them dysfunctional [27]. The mechanisms of ROS and RNS formation during metabolic disorder and their cellular impact have been summarised in Fig. 1.

3. Oxidative stress in metabolic disorder leading to Carcinogenesis

Obesity and metabolic disorder have been identified as a major risk factor associated with cancer. Individuals with high BMI are at risk of developing several types of cancer including endometrial, colorectal, and ovarian and breast cancers [28–30]. The incidence of cancer due to obesity is estimated to be approximately 20% of all causes of cancers [30]. The development of cancer in obese population is associated with the redox alteration caused by adipokines such as leptins, adiponectin, vascular endothelial growth factor (VEGF), TNF-α and interleukin (IL)-6 [31]. Several studies have shown that obesity enhances oxidative stress by increasing the concentration of ROS, which is one of the major contributor to cancer development [11, 32]. The persistent oxidative stress in cancer cells is due to several factors including activation of oncogenes (Ras2, c-Myc, and Bcr-Abl), inactivation of antioxidant enzymes, inflammation, activation of NOX system as well as by-products of cellular metabolism [33, 34]. Cancer growth and progression has been associated with the disrupted redox balance that impacts several signalling pathways associated with cell proliferation, apoptosis, invasiveness, drug-resistance and energy metabolism [33–35]. Inhibition of adenosine nucleotide translocator (ANT) by intracellular triglycerides leads to the accumulation of ATP within mitochondria and that lowers the oxidative phosphorylation due to decreased levels of ADP. This uncoupling effect results in the leakage of electrons and partial reduction of molecular oxygen in form of superoxide ions [36]. The accumulated level of ROS may contribute to tumour development either by acting as signalling molecule or promoting the mutation of genomic DNA. ROS can also promote tumour growth by activating redox sensitive kinases such as mitogen activated protein kinase (MAPK), extracellular-signal regulated kinases (ERKs), by phosphorylation, or by increasing the expression of cyclin D1 and activation of c-JUN which are instrumental in growth and survival of cancer cells [37, 38].

One of the main mechanisms by which oxidative stress manifests its damaging effects is by causing genomic instability. ROS are known to induce DNA damage by causing base/nucleotide damages as well as DNA strand breaks. The species of 8-hydroxylated guanine such as 8-oxoguanine (8-oxoG) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG), products of oxidized guanine lesions, are primarily induced by ROS which has been shown to play important role in tumour development [9, 39]. These modified guanines can pair with both adenine and cytosine bases and therefore can cause transversion mutations such as G:C to T:A (Fig. 2). The increase of the mutagenic base 8-oxo-dG may enhance the mutational rate of cells and/or interfere with DNA repair mechanism which eventually characterizes tumour development [40]. Interestingly, tumours under oxidative stress have been shown to exhibit up to 10-fold increase in 8-oxoG levels compared to neighbouring normal cells [41].

Genome integrity can also be altered by epigenetic changes. The most important and widely studied epigenetic modification is DNA methylation at cytosine residues. The reaction is catalysed by DNA methyltransferases, which uses S-adenosyl methionine (SAM) as the methyl group donor leading to formation of 5-methyl cytosine [42]. Several diabetes-related genes such as IL2RA, PPARC1A, GLP1R, PDX-1 and CTGF are regulated by DNA methylation [43–46]. In recent years, a number of studies have shown that obesity can alter DNA methylation, however the mechanistic details are still sketchy.

Besides DNA modification, histone modifications are also known to play critical role in genome maintenance and carcinogenesis [47, 48]. Histone methylation and acetylation, catalysed by histone methyl transferases and histone acetyl transferases enzymes, respectively, are primary modulators of gene expression. Role of ROS in histone modification and subsequent effect on cell survival has been demonstrated [49]. Another study has shown a novel nucleophilic mechanism of ROS-dependent epigenetic changes in cancer cells where enhanced DNA methylation caused the silencing of tumour suppressor and antioxidant genes and enhanced the proliferation of cancer cells under oxidative stress conditions [50].

The tumour suppressor protein p53, considered the guardian of the genome, has been shown to over express in adipocytes of ob/ob mice and negatively regulate fat accumulation in adipocytes by transcriptional regulation of lipogenic enzymes [51]. Further, p53 overexpressing

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**Fig. 1.** Schematic diagram showing sources of ROS/RNS in metabolic disorder leading to macro-biomolecular damage and subsequently to the various related diseases. Enzymes in green boxes show antioxidative system in the cells. Abbreviations have been explained in text.
transgenic mice showed decreased body mass and reduced adipose deposition [52]. This negative correlation between p53 expression and adipogenesis may be linked with altered metabolism suitable to develop cancer e.g. lack of p53 may lead to excessive fat accumulation leading to obesity and subsequently development of cancer. The p53 protein has been shown to regulate oxidative phosphorylation as well as glycolysis, which may be related to its ability to suppress tumorigenesis [53]. It has been observed that p53-deficient cells metabolism shifts from oxidative phosphorylation towards glycolysis, a hallmark of cancer cells [54]. Such alteration may serve dual purpose of increasing the availability of acetyl-CoA for fatty acid synthesis which is required for fast dividing cancer cells and also contribute to the accumulation of fat leading to obesity. However, this correlation merits detailed investigation.

4. Oxidative stress in metabolic disorder leading to obesity, diabetes and cardiovascular diseases

A balanced metabolic system and cellular homeostasis are fundamental requirements for normal functioning of cells and maintaining fundamental attributes of life and health. Any dysregulation in the metabolism and nutrient sensing mechanism can lead to a cluster of metabolic disorders including obesity, type 2 diabetes and cardiovascular diseases. Diabetes and obesity are closely inter-related and frequently occur together in patients and result from poor metabolic conditions. Together, they are described as ‘diabesity’ and marked by concomitant increase in morbidity and mortality due to cardiovascular diseases (CVD) [55]. Often both, diabetes and obesity, cause cellular dysfunction which is mainly associated with redox imbalance and an environment of oxidative stress. In such case where these two conditions coexist, it becomes difficult to understand which one activates which molecular pathway. Even though an overlap of the pathways occurs some common nodes in terms of mediators of oxidative stress also exist. Hence, understanding the mechanisms involved in the activation of these pathways and nodes could be helpful in unfolding the process how metabolic disorder leads to conditions such as obesity, diabetes and cardiovascular complications.

4.1. Oxidative stress in metabolic disorder leading to obesity

Oxidative stress is a dual sword, it can be the trigger as well as the outcome of obesity. The outcome of a number of studies including epidemiological, animal and clinical studies suggest that obesity can be associated with redox alteration [56–58]. Various factors including high-fat high-carbohydrate diet and continuous hyper nutrition can cause increased oxidative stress through activation of intracellular pathways such as NOX, oxidative phosphorylation in mitochondria, glycoxidation, protein kinase C (PKC) and polyol pathway [59–62]. Indeed, evidences from in vitro and in vivo studies suggest that oxidative stress can cause obesity through proliferation of pre-adipocytes and increased size of differentiated adipocytes [63, 65]. Increased adipose tissue mass develops when terminally differentiated pre-adipocytes re-enter the cell cycle and undergoes proliferation, a process called adipogenesis. The two-step adipogenesis includes the proliferation of pre-adipocytes and their differentiation into mature adipocytes [65]. ROS have been shown to be involved in both of these events. Murine 3T3-L1 cells and human pre-adipocytes when treated with H2O2 resulted in adipogenic differentiation in the absence of insulin [66]. Further, ROS generated by NOX4 as well as mitochondria have been shown to induce adipocyte differentiation in adipose-derived stem cells [64, 67]. All such evidences clearly indicate that ROS-induced proliferative potential in pre-adipocytes plays important role in the development of metabolic disorders, which generate more ROS by various mechanisms including chronic adipocyte inflammation, fatty acid oxidation, over consumption of oxygen, accumulation of cellular damage, diet and mitochondrial activity [65–69]. Abnormal generation of ROS induces cellular dysregulation in many other tissue and promotes obesity.

Increased cell cycle proliferation markers such as cyclin D1 and cyclin E are found to be increased during adipogenesis [70]. In vitro modulation of cellular redox conditions by glutathione depletion induces rapid dephosphorylation of retinoblastoma protein (pRb), which in turn activates the transcription factor E2F [71], a critical regulator of the expression of cell proliferation genes, particularly those involved in progression through G1 and S-phase of cell cycle [72]. E2F also regulates 3T3-L1 adipocyte differentiation in growth-arrested and post-confluent pre-adipocytes by forcing them to re-enter the cell cycle prior to terminal differentiation [73]. Subsequent to the clonal expansion of adipocytes, cyclin dependent kinase inhibitor p21 and p27 are overexpressed in the cells which arrest the proliferation and facilitate the differentiation [73]. ROS also regulate adipocyte differentiation in human mesenchymal stem cells (hMSCs) by activating peroxisome proliferator-activated receptor gamma (PPARγ), a downstream target of E2F [74]. The antioxidant N-acetyl-L-cysteine (NAC), a well-known ROS quencher, significantly inhibits adipocyte differentiation. These evidences confirm the role of ROS-mediated oxidative stress signals in inducing adipogenesis by regulating the cell cycle that promotes obesity.

Thus, obesity and oxidative stress appear to be connected to each other through mutual sustenance mechanisms. Obesity can cause systemic oxidative stress through NOX activation and ER stress in adipocytes besides creating a sustained chronic inflammatory condition through excessive ROS generation subsequent to high-fat high-carbohydrate diet and suppressed antioxidative system [75–77]. In fact, obesity appears to harbour both oxidative stress and inflammation even though it is difficult to precisely trace which one precedes the other [76]. The redox sensitive transcription factors such as NF-kB and activator protein (AP)-1 get activated by the ROS and transcribes several proinflammatory cytokines, which may further increase the overproduction of ROS [78]. It leads to a cyclical event which churns out many diseases such as insulin resistance, type 2 diabetes, atherosclerosis and cancer that collectively referred to as metabolic syndrome [79].
4.2. Oxidative stress in metabolic disorder leading to diabetes

Diabetes is a group of a number of diseases which include increased blood glucose and diminished insulin sensitivity leading to the development of diabetic complications such as nephropathy, retinopathy, neuropathy, micro- or macro-vascular injuries. In most of the obese people diabetes develops due to insulin resistance and subsequent hyperinsulinaemia as a compensatory mechanism. Oxidative stress has been linked with the development of insulin resistance and subsequent disruption of insulin signalling and adipocytokines [80]. Increased ROS production in the liver and adipose tissue of high fat diet-fed mice has been linked with insulin resistance [81] which was reversed by the use of antioxidants [82]. Strong correlation between obesity and insulin resistance could be through the mediator of oxidative stress derived from adipocytes including leptins and free fatty acids (FFA) [83, 84]. The elevated levels of FFA can cause mitochondrial dysfunction by activating uncouplers of oxidative phosphorylation in mitochondria [85]. In the disruptive metabolic state that results from high energy diet leading to increased glucose, free fatty acid and insulin levels, there is further increase in ROS production through dysfunctional mitochondria as discussed above. Insulin resistance can cause incessant variations in compensatory responses of insulin secretion which results in impaired glucose tolerance. This can cause insulin activity inhibition and secretion to accelerate the onset of type 2 diabetes.

In pre-diabetic condition, excessive insulin secretion leads to beta-cells death which is also augmented due to prevailing redox imbalance as pancreatic β-cells lack major antioxidants against oxidative stress [86]. This results in ROS-induced β-cell dysfunction, defective proliferation and growth, leading to type-2 diabetes [87, 88]. The altered secretion of adipokines in obesity also leads to beta-cell loss [89].

Excessive ROS generated in obese also induce proliferative arrest of pancreatic beta (β)-cells resulting in diabetes. Besides having short cell cycle duration, most of the β-cells do not have the ability to re-enter the cell cycle. ROS plays an important role in dysregulation of pancreatic β-cell proliferation by altering the cell cycle regulators and thus contribute to the development and progression of diabetes [90] (Fig. 3). Genomic analysis of insulin resistant cellular models showed that increased ROS causes insulin resistance while ROS scavengers prevent it. Also, it showed 2- to 5-fold decrease in the proteins responsible for G0/G1 switch that is believed to regulate quiescent cell transition into the proliferative cycle [91]. This is directly associated with decreased CDK1 and cyclin B1 mRNA levels in these cells, which are responsible for G1/S and G2/M transitions, respectively [91]. Other proteins associated with defective β-cell proliferation are CDK4, cyclin D1 and cyclin D2, which are important for G1/S progression. Adenovirus expression of CDK4 and cyclin D1 resulted in enhanced pRb phosphorylation and increased proliferation of β-cells [92]. On the other hand, CDK4 knockout mice, fertile but smaller in size, developed insulin-deficient diabetes due to the reduction in β-cell mass. Mice expressing mutant CDK4 displayed pancreatic hyperplasia due to non-binding of the cell-cycle inhibitor P16INK4a (G1 arrest) leading to abnormal proliferation of β-cells [93]. These data indicate that alteration in the levels of cell cycle components could affect the maintenance of β-cell mass in basal states as well as their adaptation to pathological states resulting in diabetes [94]. Thus, ROS induce the pathogenesis of metabolic disorders by regulating the cell cycle machinery.

Diabetes also involves changes in cell cycle regulation during altered redox state in body. The primary source of oxidative stress during diabetes is hyperglycaemia and glucotoxicity [95, 96]. Diabetes-induced ROS are known to cause overexpression of CDK inhibitor p27, whereas cyclin D1 and D2 were repressed [97, 98]. Additionally, diabetes-induced inflammation and elevated ROS are also known to induce FOXO transcription factors, which in turn alter the expression of certain proteins important for cell cycle regulation, especially those involved in G1/S transition [99, 100].

4.3. Oxidative stress in metabolic disorder leading to associated cardiovascular diseases

Cardiovascular diseases, major health issue across the world, are also associated with metabolic disorder as it is frequently a consequence of dyslipidaemia and diabetes. Metabolic disorder contributes majorly towards progression of pro-oxidative environment [56]. Increased cardiac lipid accumulation and altered substrate metabolism in obesity is known to alter the hemodynamic load and cause cardiovascular complications. For example decreased systolic function has been shown to be
associated with enhanced myocardial triacylglycerol deposition and concentric left ventricular hypertrophy [101]. Further, various chemical mediators including plasminogen activator inhibitor-1 (PAI-1), cholesteryl ester transport protein, retinal binding protein, acylation stimulating protein, lipoprotein lipase, oestrogen and insulin growth factor-1 (IGF-1) are also implicated in cardiovascular abnormalities. In addition, adipocyte-derived factors and adipokines such as leptin, adiponectin, resistin and fatty acid binding protein 4 (FABP4) can directly affect cardiac structure and function [102].

Adiponectin, a white and brown adipose tissue-derived cytokine, plays a central role in metabolic disorders leading to cardiac failure [103]. Levels of Adiponectin are inversely correlated with BMI in adults such that people with obesity and/or diabetes have low levels of adiponectin which contribute to higher LDL and lower HDL levels. In obesity, similar correlation exist between adiponectin and inflammatory cytokines such as TNF-α and IL-6, which also contribute to higher LDL levels and lower HDL levels. Inflammatory conditions also persist during insulin resistance and Type-2 diabetes which increases the C-reactive protein (CRP) and ROS levels and trigger endothelial dysfunction, a well-established response to cardiovascular risk factors. These changes increase the levels of ICAM-1 and VCAM-1 that further bind LDL molecules to the blood vessel walls leading to increased monocytes chemoattraction and elevate the risk of CVD [104]. Low levels of adiponectin also promote left ventricular hypertrophy especially in patients with diabetes and obesity [105]. Cardiac hypertrophy occurs as a compensatory response to the stress where cardiac myocytes get enlarged in order to increase their work output. This results in increased protein synthesis, addition of sarcomeres, activation of early response genes, such as c-jun, c-fos and c-myc and re-expression of the foetal genes such as atrial natriuretic factor (ANF), beta-myosin heavy chain (β-MHC), skeletal alpha actin and GATA-1 [106, 107].

In hypertrophic conditions various signalling pathways such as tyrosine kinase Src, GTP-binding protein Ras, PKC, MAPKs, ERK and phosphoinositol 3-kinase (PI3K) are activated. These changes initially help to combat the increased workload, however, prolonged hypertrophy leads to cardiac cell death and ultimately to heart failure [108]. Thus, a close relationship between adiponectin in diabetes and obesity is well documented risk marker of CVDs (Fig. 4).

Metabolic disorder can also induce endoplasmic reticulum stress, which may disturb the equilibrium of free radical productions and antioxidant capability leading to cardiac stress. Glycotoxic stress has been suggested to be the unifying link between various molecular disorders [109]. Diabetes and obesity increase glycotoxic stress leading to altered enzymatic activities, altered binding of ligands to their receptors and modified protein functionality and immunogenicity. Hyperglycaemia-induced oxidative stress results in accumulation of advanced glycation end products (AGEs), which further cause cellular damage [110]. The AGEs are formed by a non-enzymatic reaction between amino groups of proteins, lipids and nucleic acids and reducing sugars contribute to the aging of macromolecules, leading to the pathological conditions. AGEs can also act directly to induce cross-linking of proteins such as collagen to promote vascular stiffness and thus alter extracellular matrix, vascular structure and function [111].

Fig. 4. Schematic representation of mechanism of association of metabolic disorder with obesity, diabetes and cardiovascular diseases. Oxidative stress, decreased adiponectin, increased inflammatory markers and insulin refractoriness characterize metabolic syndrome. Diabetes and obesity trigger the hypertrophic responses by activation of early response genes, such as c-jun, c-fos and c-myc and re-expression of the foetal genes such as atrial natriuretic factor (ANF), beta-myosin heavy chain (β-MHC), and GATA-1. Insulin resistance contributes to overproduction of ROS, pro-inflammatory cytokines (TNF-α, IL-6), subsequent endothelial dysfunction and increased levels of ICAM-1 and VCAM-1, which further lead to cardiovascular diseases, including cardiac hypertrophy. Several other signalling pathways such as GTP-binding protein Ras, MAPK, ERKs are also involved in hypertrophic condition. Prolonged hypertrophy leads to activation of various apoptotic pathways inducing cardiac cell death which eventually lead to cardiac failure.
High glucose induces activity of endothelial nitric oxide synthase (eNOS) and NOX leading to over production of NO and ROS, respectively which may cause nitrosative stress-mediated vascular endothelial cell dysfunction [112]. NO is believed to be a major player in endothelial dysfunction that influences vascular homeostasis and contributes towards development of vascular complications such as atherosclerosis [113]. Further, highly reactive molecules ROS and RNS have been identified as major mediators of endothelial dysfunction in diabetes leading to abnormal cardiovascular events [114]. Also, high glucose-induced oxidative stress promotes inflammatory condition by modulating the expression of various cytokines such as TNF-α, IL-6, IL-1β, and IL-18 which further act as autocrine/paracrine agonists and trigger hypertrophy-mediated myocardial remodelling leading to cardiovascular diseases [115, 116], which establishes the fact that there is a close association between metabolic disorders and oxidative stress which instigates mechanisms of cardiac insult. Functional significance of the oxidative modifications during metabolic disorder is availability of a number of potential biological markers of CVDs including lipid peroxidation products, oxidative protein modification products, enzymatic biomarkers, oxLDL, phospholipids and changes in genetic expression of ROS-sensitive genes [117].

Abnormal increase in ROS also promotes vascular smooth muscle cells (VSMCs) proliferation resulting in cardiovascular diseases [118]. The association between ROS and cardiovascular pathologies such as atherosclerosis is well documented and summarised in Fig. 5. Studies have demonstrated that ROS induces mutagenic signals and proliferation of VSMCs. For example, H2O2 exposure stimulated growth, DNA synthesis and the expression of proto-oncogenes c-Myc and c-Fos in VSMCs [119, 120]. The ROS-induced increase in the proliferation of VSMCs also correlated with the activation of MAPK through ERK activation [121] and cyclin D1 up regulation [122]. ROS-induced cell cycle entry is mostly regulated by cell cycle regulatory protein cyclin D1, which plays a primary role in allowing G0 phase cells to enter into G1 phase [123]. Further, redox factor-1 (Ref-1/APE), a DNA base excision repair and redox regulation enzyme, has been implicated in regulation of platelet-derived growth factor (PDGF)-stimulated cell cycle progression from G0/G1 phase to S phase in VSMCs [124].

Ezetimibe, a lipid lowering agent, abrogated VSMCs proliferation by abolishing cyclin D1, CDK2, pRb, and E2F protein expressions and caused cell cycle arrest at the G0/G1 phase. Ezetimibe also abolished increase in phospho-ERK1/2 and nuclear accumulation of ERK1/2, which repressed MAPK Pathway in VSMCs halting its growth [125]. Similarly, scoparone, a hypolipidaemic and an antioxidant drug molecule, abrogated VSMCs proliferation by decreasing the expression of cyclin D1 via inhibiting the activity of transcription factor STAT3 [126]. Further, treatment of VSMCs with butyrate, a histone deacetylase inhibitor, up-regulated glutathione peroxidase, a family of antioxidant enzymes, and arrested its proliferation [127]. These studies clearly indicate important roles for ROS in dysregulation of cell cycle in VSMCs and development of cardiovascular diseases, and further establish that strong relationship between the metabolic disorder-induced oxidative stress and incidence as well as severity of CVD is a possible unifying factor in the progression of CVD.

5. Therapeutic strategies to overcome oxidative stress induced metabolic abnormalities

The best strategies to get rid of unhealthy oxidative stress are to restore the body’s redox balance. The goal may include to restore healthy BMI by physical activity and consuming low-fat low-carbohydrate diet containing a plenty of antioxidants. A clinical study has shown that cardiovascular risk associated with obesity can be improved through weight reduction which subsequently decreases markers of oxidative stress and increased antioxidant system [128]. The diet regimen containing natural fruits, green vegetables, whole grains, legumes, fish, olive oil, and probiotics which are rich in monounsaturated fatty acids (MUFA) and Ω-3 polyunsaturated fatty acids (Ω-3 PUFA), vitamin C, vitamin E and phytochemicals, help in good weight management and decrease the chances of developing metabolic diseases [129–131] through a number of potential mechanisms including cell signalling, altered gene expression, and decreased oxidative stress, inflammatory molecules and lipid accumulation [132, 133]. However, in human clinical studies use of purified individual nutritional molecule has not been successful and failed to reverse obesity or related pathologies [134, 135]. Therefore, treatment with multiple natural product combinations may result in a synergistic activity which may increase their bioavailability and act on multiple molecular targets, may offer advantages over pure chemical formulation [136]. Physical activity and exercise improve antioxidant system of the body which helps manage the oxidative stress by scavenging harmful free radicals and modifies cell-signalling pathways which activate detoxification enzymes, ameliorate inflammation, preserve normal cell cycle, inhibit proliferation, induce apoptosis and inhibit tumour invasion and angiogenesis [137, 138].

Fig. 5. ROS-induced abnormal cell cycle initiation and proliferation of adipocytes and VSMCs results in obesity and cardiovascular diseases, respectively. ROS-induced mitogenic activation of cyclin D allows the resting adipocytes and VSMCs to enter into the cell cycle. In addition, ROS also regulates cyclins E and A, and transcription factors E2F and c-Myc which promote the cell cycle initiated cells to progress through the complete cell cycle smoothly until it divides. Dysregulated activation of adipocytes or VSMCs by ROS modulates the cell cycle regulatory proteins that result in the development of obesity or cardiovascular diseases, respectively.
Oxidative and anti-oxidative regimes may successfully suppress carcinogenesis. Cancer cells seem to depend more on the redox buffering system for the maintenance of redox homeostasis as compared to normal cells. This has been exploited to target cancer cells via further increasing the cellular ROS level and oxidative stress to intolerable level resulting in their death [139]. Grape seed extract has been shown to target mitochondrial electron transport chain complex III, inhibit the glycolytic and oxidative phosphorylation rate, and induce strong oxidative and metabolic stress in head and neck squamous cancer cells leading to autophagy and apoptotic death [140]. Similarly, novel combination strategies have been adopted that include targeting glycolysis (via targeting PKM2 or pyruvate dehydrogenase kinase) and promoting oxidative phosphorylation, resulting in higher oxidative stress in cancer cells [141]. Rysman et al. [142] showed that targeting the de novo lipogenesis in prostate cancer cells by soraphen A (an inhibitor of acetyl CoA carboxylase) can result in an increased level of polyunsaturated fatty acids, strong oxidative stress, and cancer cells could be further sensitized to chemotherapeutic drugs [142]. Overall, oxidative stress is an integral component of carcinogenesis as well as cancer cell metabolism, and offers unique therapeutic opportunities. The prevention strategy in obesity-associated colon cancer has been suggested to use phytochemicals such as green tea component epigallocatechin-3 gallate and curcumin component curcumin, which have been demonstrated to decrease obesity-associated polyph complex formation in animal models by inhibiting PFK/Akt and MAPK signal pathways [143].

A series of epidemiological studies have also shown a decrease in cancer incidence among metformin-treated diabetic patients [144–146]. Metformin activates AMPK (AMP-activated protein kinase) pathway, a major sensor of cellular energy status that inhibits mTOR-mediated biosynthesis [147]. A recent study suggested that use of metformin in pancreatic cancer stem cells (CSCs) which are dependent upon oxidative metabolism and limited metabolic plasticity can cause mitochondrial inhibition leading to energy crisis and induction of apoptosis of CSCs [148]. Metformin is now being tested both in the laboratories and clinic for its effectiveness against several cancers including pancreatic cancer, breast cancer, prostate cancer, head and neck cancer [149–151].

The current strategies designed for therapeutics are to target either metabolic diseases or associated abnormalities. It is therefore imperative that targeting a common node such as redox imbalance between these multifactorial disorders could be beneficial in developing strategies for novel therapeutics. Based on animal studies, anti-oxidative therapies have been found effective in treatment [152, 153]. Besides assisting in treatment of such disorders, it is important to develop therapeutics which could prevent the progression of disease as such or at least block the progression from one clinical stage to the other. It is however a tough challenge to design such a therapeutic intervention with the meagre mechanistic information available that can link such disorders. Additionally, it becomes difficult to control events of adverse effects and toxicity which further delays the progress in this field.

To take into account the increasing population of obese, diabetic and heart patients, there is an urgent need to develop safer and less toxic therapy for long-term relief. Considering the disadvantages associated with synthetic drugs, plant-based therapies are found to be less toxic and their marked effects in the prevention of oxidative stress have been well documented [152–154]. Recently, there is a growing interest in identifying natural source of antioxidants that have therapeutic role in global healthcare and in this context, anti-oxidant natural substances including herbal medicines may prevent these metabolic disorders. Herbal formulations have taken preference due to low cost and lesser side effects and also contain free radical-scavenging and reducing potential that protect cells against oxidative stress-induced anomalies and have multiple biological effects under varied stress conditions [155]. Plants contain bioactive compounds known as phytochemicals that work along with essential nutrients and dietary fibre to protect against diseases [156]. Such treatments help maintain glycaemic control, assist in healthy weight loss and improve insulin action, and therefore may be beneficial in metabolic syndrome associated pathologies and exert a positive effect on human health.

6. Conclusion and future prospects

Life-style and diet-related chronic non-communicable diseases have already become a major burden on global health care. A multi-pronged strategy of dealing with this epidemic must be rapidly evolved and implemented to stem the rising tide of diseases of metabolic syndrome. Along with advocating the adoption of healthy life style, a massive influx of funding for research in the area of metabolic syndrome is the need of the hour. Since oxidative stress has emerged as a central player in chronic metabolic diseases such as diabetes, obesity, cancer and CVDs, it is imperative to explore the mechanisms that disrupt the normal equilibrium between oxidative and anti-oxidative processes. As discussed above excessive release of ROS and RNS (from endogenous as well as exogenous sources) leads to oxidation of all important macromolecules of life including lipid, proteins and nucleic acids. The persistent oxidative stress-induced DNA damage may not only lead to genomic instability but also activate transcription factors and induce expression of proto-oncogenes. It has further been shown that insulin’s pro-tumorigenic potential is exhibited by excess generation of ROS, subsequently leading to DNA damage, genomic instability and consequently carcinogenesis. Further, the damaged macro-biomolecules disrupt the normal cellular physiology leading to metabolic disorders-related diseases. In order to prevent the development of or to clinically intervene in these health anomalies novel therapeutic strategies are being investigated including the use of plant-based natural anti-oxidative medicines.

One of the emerging areas of research is the effect of oxidative stress and chronic inflammation on stem cells. The effect of ROS on stem cells is especially significant as it may disturb their ability to self-renew and replenish various types of body cells for the life span of the organism. It has been demonstrated that ROS production in cancer stem cells is dysregulated, which may present a therapeutic opportunity as the cancer stem cells are the most problematic to deal with in the current cancer therapy regimes and are responsible for relapse in many cases. In light of catastrophic consequences of oxidative stress and chronic inflammation in metabolic syndrome, it is imperative to identify molecular targets that may help re-establish the oxidative balance for a better health. Future research should focus to understand the disease mechanisms and to detect common targets to prevent or treat oxidative stress-induced pathologies in people with metabolic disorders.

Conflict of interest

All the authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgements

Award of Ramanujan Fellowship from Department of Science and Technology (DST), Government of India SR/S2/RJN-102/2012 (UCSY); fund support from Department of Biotechnology (DBT), Government of India BT/PR9378/17/766/2011 (VR) and Abraham A. Mitchell Cancer Research Scholar Endowment Grant (KP) are acknowledged. Assistance of Drs. Chinnadurai Mani and Neha Atale for assisting with preparation of the manuscript is also acknowledged.

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