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Review article

Oxidative stress and metabolic disorders: Pathogenesis and therapeutic strategies☆

Vibha Rani [a], Gagan Deep [b], Rakesh K. Singh [c], Komaraiah Palle [d], Umesh C.S. Yadav [e,*]

[a] Department of Biotechnology, JayPee Institute of Information Technology, A-10, Sector-62, Noida 201 307, UP, India
[b] Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Denver, 12850 E. Montview Blvd, Aurora, CO 80045, USA
[c] Translational Science Laboratory, College of Medicine, Florida State University, 1115 West Call St., Tallahassee, FL 32306-4300, USA
[d] Department of Oncologic Sciences, USA Mitchell Cancer Institute, 1660 Spring Hill Avenue, Mobile, AL 36604, USA
[e] Metabolic Disorder & Inflammatory Pathologies Laboratory, School of Life Sciences, Central University of Gujarat, Gandhinagar 382030, India

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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 peroxidation 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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☆ All authors contributed equally to the manuscript.

* Corresponding author at: Metabolic Disorder & Inflammatory Pathologies Laboratory, School of Life Sciences, Central University of Gujarat, Sector-30, Gandhinagar 382030, Gujarat, India.
E-mail addresses: vibha.rani@jiit.ac.in (V. Rani), Gagan.Deep@ucdenver.edu (G. Deep), rakesh.singh@med.fsu.edu (R.K. Singh), kpalle@health.southalabama.edu (K. Palle), umeshyadav@cug.ac.in (U.C.S. Yadav).

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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]. Furthermore, 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].

The preceding evidences suggest that metabolic disorder and obesity have myriads of effect on cellular physiology and affect the body negatively leading to development of pathological conditions. Since ROS and oxidative stress have been implicated in several cellular signalling and pathological conditions, in the present review we have particularly focused on how metabolic disorder creates redox imbalance that lead to complications such as carcinogenesis, diabetes, and cardiovascular diseases and how understanding the mechanisms may be helpful in developing potential preventive and therapeutic strategies.

2. Oxidative stress in metabolic disorders

Oxidative stress is mainly defined as a disparity in the production and degradation of ROS. Available evidences indicate that elevated systemic oxidative stress is closely associated with metabolic syndrome [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 sub-fraction 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 factor 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-epiprostaglandin F_2a 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 ($\bullet O_2^-$) in obese, which may react with nitric oxide (NO) and form RNS such as peroxynitrite, nitroxyl anion, nitrosonium cation, nitrogen oxides and s-nitrosothiols [25]. These species have the ability

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