ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 1, 2016

ISSN - 0974-2441

Review Article

HIGH-FAT DIET-INDUCED OXIDATIVE STRESS AND ITS IMPACT ON METABOLIC SYNDROME: A REVIEW

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Received: 12 September 2015, Revised and Accepted: 25 November 2015

ABSTRACT

Environmental factors such as high saturated fat content in a diet affect pro- and antioxidative balances in metabolic tissues. High-dietary fat intake promotes the development of obesity and metabolic disorders in humans and rodents as a result of disproportion between energy intake and energy expenditure. The dreaded events of high-fat diet (HFD) are obesity, hypertension, cardiovascular and cerebrovascular anarchy, Type II diabetes, infertility, and even cancer. HFD - induced systemic oxidative stress insults an imbalance between oxidants derivatives production and antioxidants defenses. Reactive oxygen species are mostly reasoned to be detrimental for health. Many evidences regarding HFD - elicited oxidative stress gathered over the past few years based on established correlations of biomarkers or end-products of free-radical-mediated oxidative stress. The hypothesis that oxidative stress plays a prodigious role in the development of metabolic disorders, especially insulin resistance, hyperlipidemia, cardiovascular disease or hepatic steatosis, and steatohepatitis. In this review, we elucidated the mechanistic links between HFD - induced oxidative stress and its impact on metabolic complications development.

Keywords: Adenosine monophosphate-activated protein kinase, Complications, High-fat diet, Metabolic syndrome, Oxidative stress.

INTRODUCTION

High-fat diet (HFD) is a most important risk factor for a plethora of severe ailments, including obesity, dyslipidemia, cardiovascular disease, Type II diabetes, non-alcoholic fatty liver, non-alcoholic steatohepatitis (NASH), and cancer [1-3]. The increased occurrence of obesity and obesity-associated impediment continues to be a global health issue. Multifactorial reasons, such as high-fat, caloric-dense diets, sedentary lifestyles, increased urbanization, and psychosocial hassles, are the most frequent contributing factors for the inception of metabolic syndrome (MetS) [4]. The prevalence of MetS raises with the use of high saturated fat as an imminent component of many food stuffs and increases morbidity in obese youngsters [5]. The mechanisms for increased oxidative stress in the MetS are not completely understood but include increased fatty acid oxidation, mitochondrial dysfunction, and augmented NADPH oxidase activity. Most studies so far focus on relating abnormal gene expression in the liver and adipose tissues to HFD, accompanied by augmented expression of NADPH oxidase and decreased expression of antioxidative enzymes [6,7]. HFD provoked dyslipidemia which is linked to oxidative stress, an accumulation of several transition metals as well as increased free radicals [8]. Fat accumulation associated with systemic oxidative stress in humans and mice through increased production of reactive oxygen species (ROS) accompanied by enhanced expression of NADPH oxidase and reduced expression of antioxidative enzymes [7,9]. HFD increases NADPH oxidase activation, oxidative stress, and lipid peroxidation caused deregulated production of redox-sensitive transcription factor-nuclear factor kappa beta (NF-κB), adipocytokines (fat-derived hormones), including adiponectin, plasminogen activator inhibitor-1, IL-6, and monocyte chemotactic protein-1 (MCP-1), and other inflammatory cytokines form different metabolic tissues [9,10].

In this review, we will represent mechanistic relations linking to oxidative stress generated by high saturated fat in the context of deregulation of different body parameters associated with fat metabolism and its impact on metabolic complications development. We will particularly focus on how HFD associated with oxidative stress, obesity, deregulation of adenosine monophosphate-activated protein kinase (AMPK) activity, pathophysiological and biochemical changes in the gut, liver, heart, and blood vessels which ultimately lead to the progression of MetS.

HFD - INDUCED OXIDATIVE STRESS, A KEY FACTOR FOR PATHOPHYSIOLOGICAL CHANGES IN MetS

HFD increases the amount of chylomicrons in the intestine. The later upon entry into the circulation leads to generate free fatty acid (FFA) that is taken up by the liver. These hepatic FFAs either enter mitochondria for β oxidation or esterified to form triglycerides (TG). These TGs are either accumulated in the hepatocytes as tiny droplets or produces very low-density lipoprotein (VLDL) which in turn converts into LDL [11]. Too much LDL burden in the blood due to its excessive generation as well as due to lack of LDL-receptor in hepatocytes forms oxidized-LDL (Ox-LDL) those are engulfed by macrophages to become foam cells. They accumulate in the arterial endothelium and forms plaque. It ultimately leads to circulatory and cardiovascular disorders such as atherosclerosis, hypertension, thromboembolism, heart block, etc. [12-14]. FFA generated from fat digestion and metabolism either enter mitochondria for oxidation or are esterified into TG [11]. The mitochondrial β-oxidation of FFAs is associated with the conversion of oxidized cofactors (NAD^+ and FAD) into reduced cofactors NADH and $FADH_2$, which in turn gets reoxidized and back into NAD^+ and FAD by a mitochondrial respiratory chain. During their reoxidation, NADH and $FADH_2$ transfer their electrons to the first complexes of the respiratory chain. Most of these electrons migrate up to cytochrome-c oxidase, where they safely combine with oxygen and protons to form water; but a fraction of these electrons directly reacts with oxygen to form the superoxide anion radical and other ROS. Hence, excess intake of fat-rich diets increases mitochondrial β oxidation of FFAs. It leads to an excess electron flow using cytochrome-c oxidase and thereby enhances the production of ROS. Moreover, mitochondria are the most important cellular source of ROS, which oxidize the unsaturated lipids of fat deposits to cause lipid peroxidation. These intermediates react with oxygen to form more and more superoxide anion and other ROS [15,16]. Lipid peroxidation and ROS can consume antioxidant enzymes and vitamins as well [15]. Depletion of these protective substances may hamper

ROS inactivation and increase lipid peroxidation and ROS-mediated damage [7]. This HFD - induced ROS directed pro-inflammatory state may activate one of the major transcription factor linked with inflammation, NF-κB. Moreover, either this HFD triggers ROS or NF-κB induces the expression of NF-κB-dependent pro-inflammatory agents namely, inducible nitric oxide synthase (iNOS), tumor necrosis factor (TNF-α) interferon γ (IFN-γ) [17]. This cause overproduction of nitric oxide (NO) by activated iNOS; in turn increased generation of reactive nitrogen species (RNS) is imminent due to the interaction between superoxides and NO [2,18]. All these interlinked events may explain the reasons for the development of multiple risk factors and chronic disorders on high-fat consumption, systemic oxidative stress, and MetS.

HFD – INDUCED ROS PRODUCTION IN ADIPOSE TISSUE AND PROGRESSION OF MetS

Studies showed that elevated ROS is produced from hypertrophoid adipocytes from HFD. Fat mass expansion occurs via two processes concomitantly occurring during white adipose tissue expansion including hypertrophy (increasing size of fat cells) and hyperplasia (more numbers of fat cells linked to differentiation of adipocyte precursors) [19,20]. Many studies have established a close association between ROS and adipogenesis. Fat accumulation parallels ROS production, as established by increased ROS production during adipocyte 3T3-L1 alteration [21]. Leptin, a white adipose tissue-derived hormone, has been shown to increase the generation of ROS in endothelial cells [22,23]. NF-κB is also activated by leptin in an oxidant-dependent manner. This effect is linked with an enhanced expression of MCP1, which promotes atherosclerosis by supporting the relocation of inflammatory cells [19,22]. Stimulation of ROS by leptin occurs via protein kinase C-dependent activation of NAD(P)H oxidase in vascular smooth muscle cells [24]. In addition, leptin, at concentrations related to those found in the plasma of diabetic patients, stimulates the release of active macrophage lipoprotein lipase through an oxidative stress-dependent pathway signifying a proatherogenic effect of leptin on macrophages in diabetes [25]. Exposition of adipocytes to high ROS levels restrain adiponectin expression and secretion [9,26], an adipokine which exhibits insulin-sensitizing, antiatherogenic, and anti-inflammatory properties [27]. Therefore, human serum adiponectin levels have been inversely allied with systemic oxidative stress [9,28].

HFD – EVOKED PATHOPHYSIOLOGICAL CHANGES OF THE GUT IN MetS

Low-grade inflammation with high-fat and obese patients corresponds with augmented plasma levels of C-reactive protein, TNF-α, IL-6, MCP-1, IL-8, osteopontin, and leptin [20]. Spagnuolo *et al*. suggested a significant positive correlation between body mass index and C-reactive protein which may lead to obesity-associated complications [29]. Obesity and diabetes modify the glucose-stimulated gut to hypothalamic NO signaling pathway. The disturbed enteric glucose detection is linked with a significant increase in inflammatory, oxidative/NO, and endoplasmic reticulum (ER) stress gene expression [30,31]. Signaling mechanisms reported to promote inflammation have been established to be started and mediated by luminal lipid and gut microbiota [32,33]. These observations suggested the significance of preserving gut function, and a greater understanding of the pathological condition of the gut may be helpful in finding new approach to treat and to avert obesity and associated disorders [30]. Lee assessed that main factor that contributes to the development of obesity is high-fat consumption. Lipid absorption begins from the gastrointestinal tract/gut on the basis of feedback mechanisms to regulate glucose and lipid metabolisms. Lipid-sensing pathways are impaired in HFD - induced insulin resistance, ensuing in hyperglycemia. In addition, lipid in the duodenum activates mucosal mast cells, leading to the disruption of the intestinal tight junction. Lipopolysaccharide which is co-transited with postprandial fat consumed with diet promotes the release of cytokines and may be linked with the development of metabolic syndrome. HFD also modifies microbiota composition and increases fat storage. Though the gut is protected by the immune system and contains a high level of antioxidants, obesity developed most likely when this protective mechanism is compromised by the presence of too much fat [6].

HFD - INDUCED OXIDATIVE STRESS AND CARDIOVASCULAR DYSFUNCTION IN MetS

The MetS increase the risk for cardiovascular disease and Type II diabetes. Each factor of the MetS causes cardiac dysfunction, and their combination carries additional risk. The etiology of cardiovascular diseases in patients with MetS may involve coronary atherosclerosis, left ventricular hypertrophy, arterial hypertension, diastolic dysfunction, endothelial dysfunction, coronary micro-vascular disease, and autonomic deregulation. One common characteristic of cardiovascular disease in the MetS is increased oxidative stress in the heart [34,35]. In reality, patients with the MetS have elevated systemic oxidative damage as a result of ROS production and decreased antioxidant defense [36,37]. HFD evoked magnified ROS production and the decrease in antioxidant capacity leads to a variety of anomalies such as endothelial dysfunction that is characterized by a reduction in the bioavailability of vasodilators, mostly NO, and an increase in endothelium-derived contractile factors, promoting atherosclerotic disease [38]. The mechanisms for increased cardiac oxidative stress in the MetS are not completely unstated but include augmented fatty acid oxidation, mitochondrial dysfunction, and an increased NADPH oxidase activity [38]. Ilkun and Boudina evaluated the mechanisms underlying cardiac pathology in the MetS are complex and might include lipid accumulation, altered calcium homeostasis, increased fibrosis and stiffness, abnormal autophagy, mitochondrial dysfunction, and increased oxidative stress. Mitochondrial and extra-mitochondrial sources of reactive oxygen species and reduced antioxidant defense mechanisms characterize the myocardium of animals and humans with MetS [38].

HFD - INDUCED OXIDATIVE STRESS IN THE PROGRESSION OF NON-ALCOHOLIC FATTY LIVER (NAFL) AND NASH IN MetS

NAFL is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning degeneration of the hepatocytes. NASH is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. [39]. High-fat induced weight gain promotes hepatic oxidative stress, triggers the redox-sensitive transcription factor such as NF-κB, some inflammatory processes, prevalence of hepatic steatosis, and other liver lesions called steatohepatitis [40-46]. Another redox-sensitive transcription factor, i.e., nuclear factor E2-related factor 2 (Nrf2) up-regulates a battery of antioxidative genes and cytoprotective enzymes that constitute the cellular response to oxidative stress; however, the chronic stress factors are liable for the diminished function of Nrf2 [47]. Indeed, chronic fat ingestion (inflammation) plays a role in the development of insulin resistance and other obesity-related features commonly recognized as MetS in both developed and developing countries [48-50]. Hepatic TG accumulation is an etiological factor for NAFLD or is associated with steatohepatitis [51]. NASH develops via the "two-hit" model [52]. Insulin resistance shows to be the "first-hit" which provokes fat accumulation in hepatocytes along with diminution in the insulin signaling pathway activity [53]. "Second-hit" includes HFD, obesity, diabetes, hyperlipidemia, oxidative stress along with hepatocyte apoptosis which is supposed to play a fundamental role in the pathogenesis of NAFLD [54]. HFD inhibits the metabolic phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway which may lead to activation of the mitochondria-dependent apoptosis [55]. Apoptosis in HFD - induced NASH activates c-Jun NH2-terminal kinase (JNK) and elevates proapoptotic Bax. In addition, oxidative stress and its associated JNK activation, as well as an imbalance of pro and anti-apoptotic proteins in the Bcl-2 family, contribute to high hepatocyte apoptosis which plays an important role in the pathogenesis of NASH [56]. NAFLD encompasses a large spectrum of conditions ranging from fatty liver to NASH, which can develop cirrhosis and cancer [39]. Study reports revealed the association between the levels of lipid oxidation products and disease

state. However, often neither oxidative stress nor ROS has been characterized, despite oxidative stress is mediated by multiple active species by different mechanisms and the same lipid oxidation products are produced by different active species [40,57].

HFD - INDUCED OXIDATIVE STRESS AND AMPK ACTIVITY IN MetS

The AMPK system is a key player in regulating energy homeostasis at both the cellular and whole-body levels, placing it at center stage in studies of obesity, diabetes, and the MetS [58]. AMPK comprised of a heterotrimeric complex including a catalytic α subunit and regulatory β and γ units. There are two isoforms of α (α1and α2) and β (β1 and β2) and three γ subunits (γ1-3) which are differently expressed in mammalian tissue [58]. AMPK activation can induce ATP (adenosine triphosphate) generation through pathways such as glycolysis and β-oxidation. On the contrary, ATP-consuming pathways, including fatty acid and cholesterol syntheses, and gluconeogenesis, are suppressed by AMPK activation [59]. HFD substantially decreased the activities of both isoforms of AMPK in white adipose tissue, heart, and liver. These decreases in AMPK activity happens in the absence of reduced AMPK transcription, systemic inflammation, hyperglycemia, or high levels of FFA. The HFD - induced decrease in AMPK activity was associated with systemic insulin resistance and hyperleptinemia [60]. Due to the vital role of AMPK in modulating these aspects of energy balance, it is not surprising that modifications in AMPK have been concerned in the commencement of obesity and MetS [61-63]. There are several studies indicating that the activation of AMPK represses the oxidative stress triggered by different insults such as fatty acids and hyperglycemia [64-67]. Xie *et al*. observed that AMPK signaling induced the expression of mitochondrial uncoupling protein-2 (UCP-2) and accordingly reduced the production of superoxide radicals in hyperglycemic endothelial cells. It is known that UCP-2 is able to inhibit the mitochondrial ROS production [66]. Wang *et al.* demonstrated using different techniques that AMPKα2 is the physiological suppressor of the ROS produced through NAD(P)H oxidase. These results support the mechanism whereby AMPK inhibits the NF-κB signaling and thus down-regulates the expression of several NAD(P)H oxidase subunits and thus lessens oxidative stress [64]. Li *et al.* revealed that AMPK signaling via the AMPK - Forkhead box O (FoXO3) pathway induced the expression of thioredoxin (Trx), a disulfide reductase which defend cellular proteins against cysteine oxidation [65]. The ER is a sensitive stress sensor in the maintenance of cellular protein quality and nutrient balance [68,69]. Oxidative stress impairs homeostasis in ER and leads to misfolding of proteins in ER and calcium release into the cytoplasm. ER stress triggers set of transducer proteins that stimulate the unfolded protein response (UPR) [69]. Studies have explored that the UPR involves the activation of NF-κB system which can trigger a low-grade inflammatory response [70-72]. Study reports showed that AMPK activity can decrease the ER stress, e.g., in Oxidized-LDL-exposed aortic endothelial cells and in hypoxic cardiomyocytes [73,74]. Dong *et al*. demonstrated that the deletion of AMPKα2 augmented ER stress in endothelial cells and responsible for aortic lesions in the knockout mice. They also noted that several antioxidants were able to suppress the manifestation of ER stress. This indicates that ER stress is provoked by oxidative stress induced by the deletion of AMPKα2 [73]. Salminen *et al*. reviewed that AMPK signaling can inhibit the inflammatory responses which are induced by the NF-κB system. The NF-κB subunits are not direct phosphorylation targets of AMPK, but the suppression of NF-κB signaling is mediated by several downstream targets of AMPK, e.g., SIRT1, PGC-1a, p53, and FoxO factors. AMPK signaling appears to improve energy metabolism while it can repress inflammatory responses related to chronic stress, e.g., in nutritional overload [75].

SUMMARY AND CONCLUSION

MetS is defined by a constellation of integrated physiological, biochemical, clinical, and metabolic factors that directly increases the risk of dyslipidemia, cardiovascular disease, Type II diabetes, and all-cause mortality. Oxidative stress in metabolic tissues has emerged as a widespread feature of MetS and its co-morbidities. The consumption

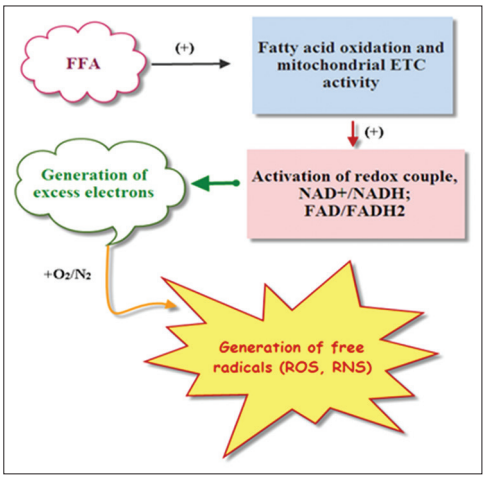

Fig. 1: Mechanism involved in high-fat diet-induced increased level of free fatty acid (FFA) production. These FFAs undergoes mitochondrial β-oxidation process and are responsible to generate oxidative stress through production of reactive oxygen species and reactive nitrogen species

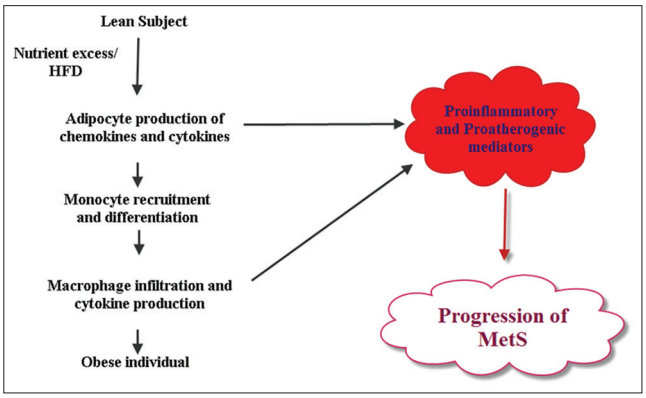

Fig. 2: Potential mechanism for high-fat diet - induced alterations in the adipose tissue cells. The accumulation of lipids in adipose tissue and the expansion of the fat mass lead to the initiation of an inflammatory process and progression of metabolic syndrome

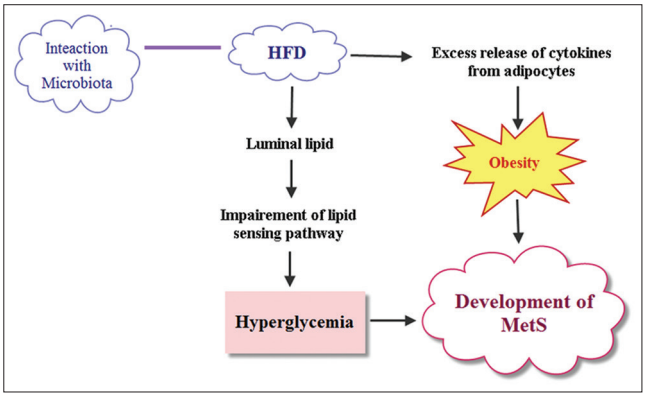

Fig. 3: A mechanism that contributes to high-fat diet (HFD) - induced gut pathophysiological changes. HFD impairs gut lipid-sensing mechanisms and affects glucose homeostasis through increased hepatic glucose production. Interaction between microbiota and HF leads to the excessive release of adipocytokines, consequently obesity, and metabolic syndrome development

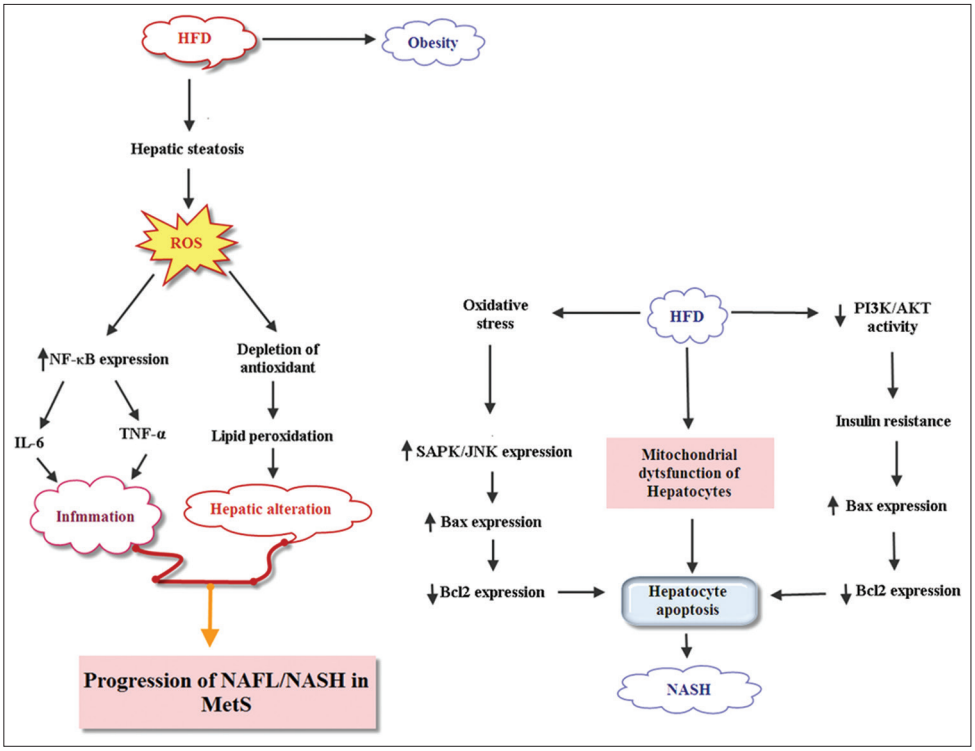

Fig. 4: A multipronged mechanism that contributes to high-fat diet (HFD) - induced oxidative stress and NAFL/NASH in metabolic syndrome. HFD is responsible for hepatic alterations and inflammation through the production of inflammatory cytokines and lipid peroxidation. Involvement of PI3K/Akt, Jun NH2-terminal kinase, Bax, Bcl2 pathways is responsible for hepatocyte apoptosis which is one of the important features for the development of non-alcoholic steatohepatitis. ↑↓ arrow indicates increased and or decreased outcome, respectively

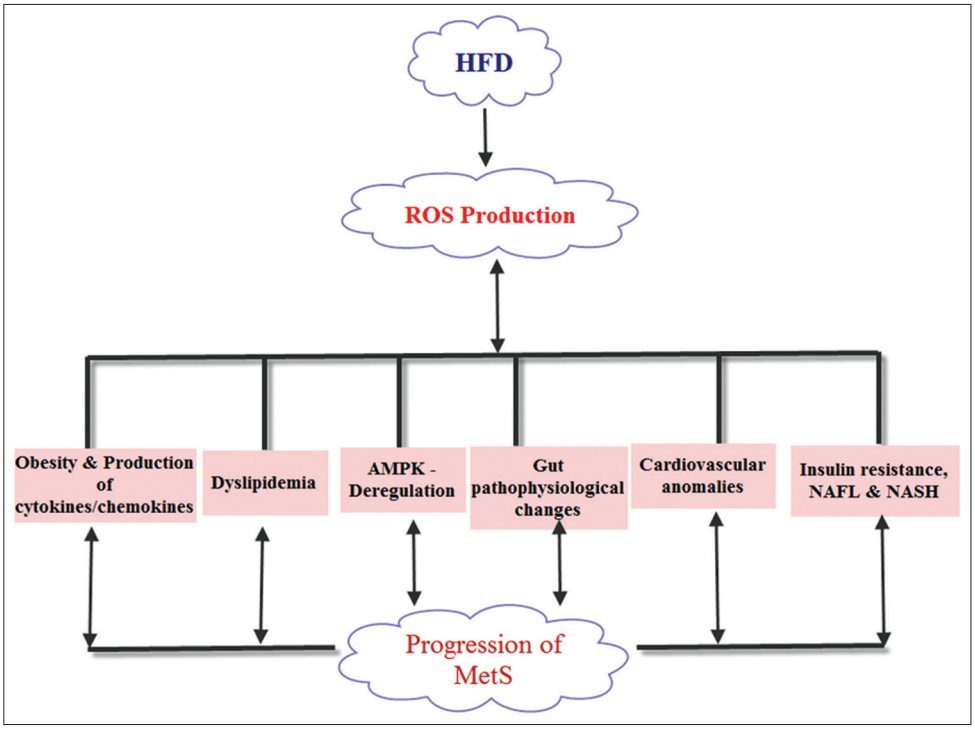

Fig. 5: Systemic metabolic alterations associated with high-fat diet (HFD) contribute to the increase in oxidative stress. Altogether, metabolic parameters such as obesity, dyslipidemia, AMPK deregulation, gut pathophysiological changes, insulin resistance, Type II diabetes, cardiovascular anomalies, and non-alcoholic fatty liver/non-alcoholic steatohepatitis, are closely related with HFD - induced reactive oxygen species production and this dysregulation played crucial role for progression of metabolic complications

of high energy diets (carbohydrate, protein, and fat) has turned out to be a practice in modern societies regardless of the lessening in daily energetic requirements. Oxidative stress has come into view in recent years as a characteristic of the metabolic disorders, fundamentally

associated with chronic low-grade inflammation. Close relations exist between MetS and oxidative stress due to an imbalance between pro-oxidant and antioxidant species in favor of oxidized entities. In reality, patients with MetS show signs of damage due to oxidative stress. In general, systemic oxidative stress-associated HFD and obesity directly impacts insulin sensitivity of metabolic organs, promotes inflammation. Overall, oxidative stress shows as an essential contributor of metabolic ailment associated HFD like obesity, derangement of lipid profiles, Type II diabetes, cardiovascular diseases, NAFL/NASH, and AMPK dysregulation. MetS is a condition that is an outbreak and has inflated in current decades. The study of MetS has undergone substantial development parallel to the increase of this metabolic disorder. Proficient and skilled research in various fields allowing changes in views on HFD, oxidative stress, MetS, and the pathophysiology of the disease that prevail at present. The perturbation of old paradigms and the new knowledge platform provide a solid base for understanding the disease and for developing strategies for prevention and management. Overall, further studies are wanted to clearly comprehend and manage the degree of ROS generation, types, and distribution in metabolic tissues as well as at the organismal level. This can show the way to develop new strategies to combat the disorders associated with HFD and MetS.

ACKNOWLEDGMENTS

The authors remain grateful to Dr. Vivekanand S Waghmare, (Professor & Head) and other Faculties of the department of Physiology, Government Medical College Rajnandgaon for their inspiration and moral support. The authors are thankful to Dr. R. K. Singh, Dean, Government Medical College Rajnandgaon for providing the necessary provisions, are also praiseworthy and acknowledged here, with sincerity.

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