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Review

Intricate role of oxidative stress in the progression of obesity

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ABSTRACT

Objective: Free radicals attack human body through various pathways, playing significant role in pathogenesis of various disorders. This review enumerate the role oxidative stress in obesity and related metabolic disorders.
Key findings: Obesity is a severe disorder characterized by excessive fat in body that leads to increased body weight and result in various complications such as metabolic syndrome, diabetes, cardiovascular disorders cancer and reduce life expectancy. Data collected over year revealed adipose tissue as an endocrine organ which plays a significant role in controlled several disorders by the release of various active metabolites like adipocytes. A cross link exists between adipokines and obesity, defined is as a complex disorder associated with inflammation of adipose tissue that enhance the level of oxidative stress. Oxidative stress disturbed equilibrium between the free radicals and antioxidant. Overexpression of oxidative stress result in disruption of cell structure viz, membranes, protein as well as DNA strand breakage, base damage with under-production of antioxidant species, resulting in development of obesity related disorder.
Summary: The present review emphasizes on the oxidative stress in obesity and its related complications.

1. Introduction

Obesity is a complex disorder accompanied by accumulation of excessive fat in body, manifested by genetic and environmental factors. It is the core of many chronic illness viz. cardiovascular disease, diabetes, arthritis, gastrointestinal disorder, asthma, cancer and high blood pressure. The major cause of obesity are high caloric intake, or due to lack of physical activity. In some cases it may occurs due to mental and endocrine disorder or genetically. It can be prevented by combination of social changes and personal choices, that is proper diet, adequate exercise (Sikaris, 2004) and by taking medications to reduce fat (Alberti and Zimmet, 1998). Obesity regulates immune system in adipose tissue further activating inflammatory mediators and oxidative stress, resulting in systemic responses (Office of the Surgeon General, 2010). It is principally responsible for induction of several chronic diseases (Xu et al., 2003). (see Figs. 1 and 2)

Oxidative stress leads to the production of peroxidase and free radicals that causes damage to cell viz. membranes, protein and strand breaks in DNA that result in cytotoxicity, genotoxicity. The cell damage proliferates to other organs of body, due to presence of xenobiotics, regulation of microorganism mediated by immune system and radiation hence a contributing in toxicity. Reactive oxygen species act as messenger in redox signaling and disrupts normal cellular mechanism. The presence of excessive amount of adipokines due to high intake of fat, generates ROS that activate inflammatory response and thus result in obesity. The present article highlights the functional link between oxidative stress and obesity and related metabolic disorders.

2. Role of oxidative stress in obesity

The level of reactive oxygen species (ROS) hydrogen peroxide, superoxide and hydroxyl, however an increases due to high caloric intake or inflammation, hence result in obesity. Adipose tissue is an endocrine organ surrounded by widely network of microvasculature stimulating the production of consist of hormones, free fatty acids, angiogenic factors, cytokines growth factors including leptin, adiponectin, tumor necrosis factor alpha (TNF-α), vascular endothelial growth factors (VEGF), interleukin-6 (IL-6) and adipokines that regulates endocrine and paracrine action of body (Cristancho and Lazar, 2011). During obesity the adipose tissue undergoes pathological change due to absorption of fat viz. inflammation, and oxidative stress and this in turn enhance to secretion of adipokines and affect the peripheral tissues that produce ROS, which stimulates oxidative stress and inflammatory response (Hensley et al., 2000; Redman and Sargent, 2003). The inflammatory cytokines such as tumor necrosis alpha (TNF-alpha), interleukin (IL)-1beta and IL-6 result in pathogenesis of various disorders

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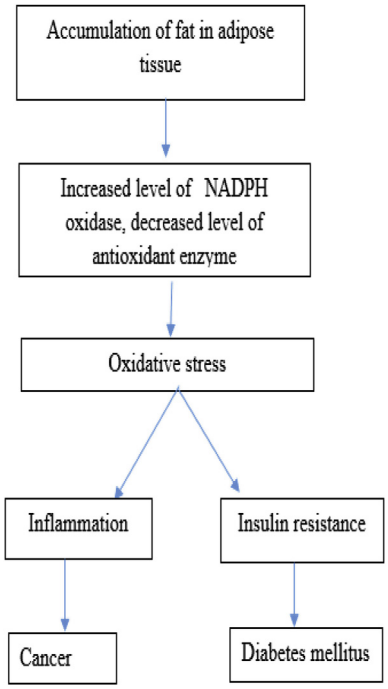

Fig. 1. Disorders associated with progression of obesity.

(Fonseca-Alaniz et al., 2007). TNF –alpha plays a vital role in regulating the inflammatory responses, insulin signaling, apoptosis, inducing OS and also influence the production of ROS by binding to specific receptors, thus activating the NF kappa signaling (Chandel et al., 2001; Wang and Trayhurn, 2006). Interleukin-1 (IL)-1beta is secreted from the monocytes in response to damage of tissue and infection. Various studies revealed that interleukin is involved in various pro-inflammatory responses thus inducing obesity (Stienstra et al., 2012). Interleukin-6 (IL-6) is released from the macrophages, monocytes. It regulates energy homeostasis and initiates the synthesis of inflammatory cytokines activating the negative inflammatory response (Naugler and Karin, 2008). The higher level of IL-6 induces diabetes mellitus, high blood pressure and obesity (Curti et al., 2011; Stenlöf et al., 2003).

Adipose tissue mediated the synthesis of TNF-α and IL-6 by increases the concentration of ROS which promotes release of cytokines and growth factor (Lavrovsky et al., 2000). The NF- κB and NADPH (Nicotinamide adenine dinucleotide phosphate) oxidase pathway [NADPH oxidase (NOX4)] (Han et al., 2012). NOX4 transfer electrons to oxygen and generates oxygen radicals that convert into hydrogen peroxidase. Further regulating the expression of IL-1 and IL-6 gene expression which are release by redox factor −1 dependent pathway (Bedard and Krause, 2007; Frossi et al., 2003; Han et al., 2012).

In obese people higher level of free fatty acids have been tend to accumulates in the hepatic and adipose tissue (Tereshin, 2007). This result in production of free radicals, imbalance in glucose metabolism (Duvnjak et al., 2007) and induces injury to mitochondrial DNA, ultimately damaged the cellular structure of fatty acids (Goossens, 2008; Khan et al., 2006). Leptin is a hormone released from adipocytes which mainly circulates in plasma and diffuses in central nervous system (CNS) to induce satiety (Wang and Trayhurn, 2006). Elevated level of leptin induce OS and initiates the synthesis of inflammatory mediators (TNF alpha, interleukin and IL-1) (Hukshorn et al., 2004; Ferri et al., 1999). The level of leptin is decreases during weight loss. Visfatin, an adipokines synthesized from bone marrow, lungs, liver, heart and pancreas (Beltowski, 2006; Marseglia et al., 2014a) shows pro-oxidant and inflammatory effects (Martos-Moreno et al., 2011). Moschen concluded that visfatin level is increased during obesity leads to regulation of ROS and induce the OS (Moschen et al., 2007). Visfatin is regulated by phosphorylation of NF-κB pathway and inhibition of this pathway result in partial reduction in the production of oxidative stress (Kim et al., 2008). Resistin, an adipokine molecule circulate in blood monocytes and responsible for the appetite regulation, energy balance and insulin resistance (Kawanami et al., 2004). It has been concluded from the research that resistnin is responsible for the OS related cardiovascular disease by activating endothelial cells and upregulating inflammatory cytokines or mediators (Chen et al., 2010). Apelin is an endogenous peptide secreted from adipocytes in response to the excessive fat present in body. It act on specific receptor and induces the synthesis of anti-oxidant (Than et al., 2014). Plasminogen activator inhibitor type 1 stimulates adipokines (Gottschling-Zeller et al., 2000) which in turn increase fatty acids and risk of insulin resistance and this in turn release cytokines as well as NF Kappa B increasing oxidative stress (To et al., 2013; Samarakoon et al., 2012).

3. Obesity related disorders

3.1. Metabolic syndrome

Metabolic syndrome is a medical condition characterized by obesity, hypertension, hyperglycemia, low high density lipoprotein cholesterol level (Alberti et al., 2005). Obesity is considered an important component in the development of metabolic syndrome (Spiegelman and Flier, 2001). Various inflammatory mediators are involved in the development of metabolic syndrome such as IL-6, leptin, visfatin, apelin, resistin and TNF- α. IL6 dysregulates glucose transport by inhibiting the process of phosphorylation, resulting in insulin resistance (Juge-Aubry et al., 2005). Leptin and resistin mediates insulin sensitivity thus result in insulin resistance (Rosenbaum et al., 2008; Maury and Brichard, 2010). Adiponectin and apelin elicit a protective role in the pathogenesis of metabolic syndrome by inhibiting the activity of IL6 and TNF-α (Lago et al., 2007). Increased level of oxidative stress in vascular walls leads to the production of arthrosclerosis, insulin resistance, hypertension and hepatic steatosis (Grundy, 2005; Matsuoka, 1997; Hopps et al., 2010). Mitochondrial dysfunction and oxidative stress are the contributing factors in the development of metabolic syndrome. The accumulated free fatty acids in the mitochondria leads to disorder in mitochondrial fuel metabolism and impairment in fatty metabolism, hence resulting in incomplete oxidized product (Mullarkey et al., 1990).

3.2. Diabetes mellitus

Diabetes mellitus is an endocrine disorder with altered level of glucose in blood (Kristina, 2007), about 75% population are suffering worldwide. The imbalance in serum glucose level indicates the progression of diabetes that involves various cellular mechanism i.e. change in glucose transport, pancreatic beta cell dysfunction, increase oxidative stress. Furthermore, hyperglycemia enhance the production of ROS and breaks DNA strands and result in diabetes mellitus (Kristina, 2007; Paneni et al., 2014; Brownlee, 2005). The cells with higher amount of intracellular glucose concentrations are metabolized by the tricarboxylic acid. This leads to increased influx of NADPH in mitochondria, thereby stimulating the overproduction of ROS by uncoupling NO synthase, worsening the diseased state (Brownlee, 2005; Pitocco et al., 2013). OS dysfunction the pancreatic beta cells by inducing the glucotoxicity, lipotoxicity and glucose induce insulin secretion (Sakai et al., 2003). The level of IL-6 and TNF alpha are also responsible in inducing diabetes mellitus (Pradhan et al., 2001; Peraldi and Spiegelman, 1998; Pickup, 2004). IL-6 may disrupt the insulin signaling whereas TNF alpha level is increased in the adipose tissue of obese and diabetes patients (Pickup and Chusney, 2000).

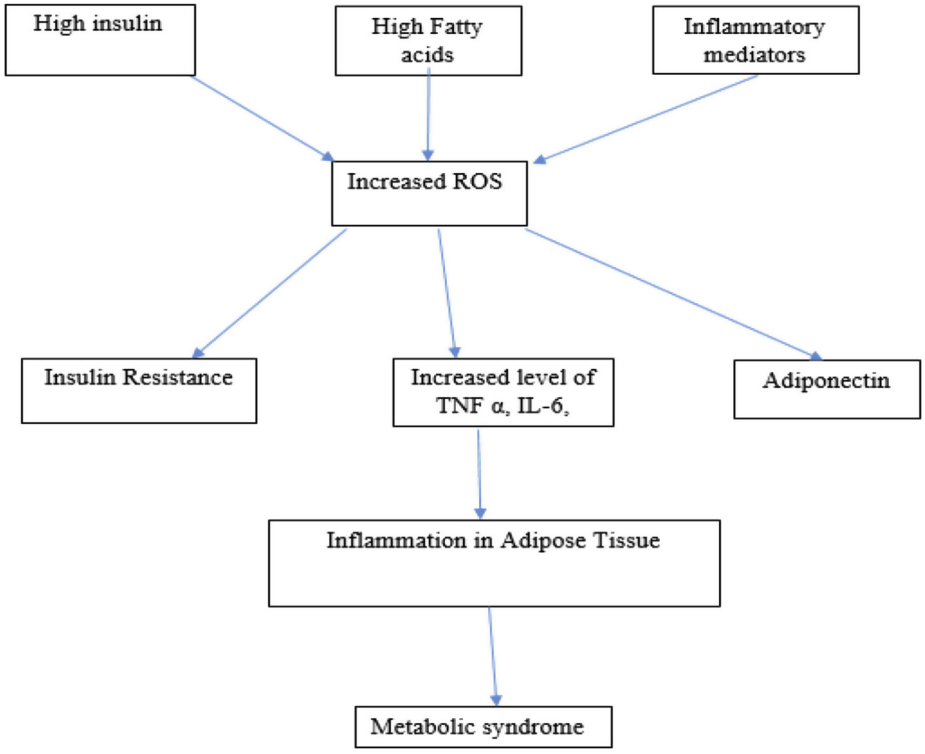

Fig. 2. Factors that mediate metabolic syndrome in obesity.

3.3. Cardiovascular disease

Oxidative stress result in various cardiovascular related diseases namely hypertension and hyperlipidemia in obese patients.

3.3.1. Hyperlipidemia

Dyslipidemia is a medical condition characterized by high cholesterol and triglyceride (Bolkent et al., 2004). The correlation between obesity and hyperlipidemia has shown to promote cardiovascular diseases (Yang, 2008). Hyperlipidemia is associated with low level high density lipoprotein, elevated triglyceride level stimulates the production of ROS in endothelium (Ceriello et al., 2002). ROS in turn damage the lipids, proteins and other intracellular pathway that leads to irreversible oxidative damage (Ceriello et al., 2002). Oxidative low density lipoprotein leads to cardiovascular disease [98], by promoting adipocytes progression by elevated infiltration of macrophages (Nishimura and Manabe, 2007) due to accumulation of fatty acids in adipose tissue (Merkel et al., 2002), result in high oxidative stress.

3.3.2. Hypertension

Hypertension is a medical condition associated with high blood pressure. Nitric oxide induces vasodilation in endothelium (Touyz, 2004) but it is degraded by superoxide anion, which is released from endothelial nitric oxide, causing vasoconstriction and elevating blood pressure (Redon et al., 2003; Pedro-Botet et al., 2000).

The sympathetic nervous system in hypertension act by activating renin angiotensin –aldosterone system (RAAS) and stimulate renin release. The RAAS metabolites synthesized are stimulated by release of NADPH mediated synthesis of reactive oxygen species and redox dependent signaling cascade, thereby inducing hypertension.

3.4. Cancer

Cancer is a chronic disorder characterized with abnormal growth of cells further invading other organs of the body. The correlation between the obesity and cancer has been reported worldwide as high body mass index is the major cause of cancer. The person with high BMI are more prone to certain types of cancer namely rectal, prostate, endometrial, gastrointestinal postmenopausal and breast cancer (Renehan et al., 2008). Various hypothesis have been made in association with pathophysiological mechanism of cancer in obese patients. The pathways that induce cancer are genetic factors, Adipokines, chronic low grade inflammation, gut microbiota and insulin IGF-1 signaling pathway (Laiyemo, 2014). Genetic factors promote variation in the BMI (Bouchard and Tremblay, 1997) therefore increasing the risk of gastrointestinal and thyroid cancer (Bhaskaran and et at, 2014). The liver releases IGF and IGF-1 in response to hypothalamic signals which further binds to IGF biding receptor and is transported into the blood where they express the insulin in the gastrointestinal tract (Vongsuvanh et al., 2013). Thus IGF absorbs nutrients from the endocrine pathway and initiates cell progression (El Yafi et al., 2005) resulting in development of tumors (Van Goudoever et al., 2008). Gut microbiota affects the obese patients by increasing the caloric salvage of indigestible polysaccharides and fat storage (Shibata et al., 2004) and promote gastro intestinal inflammation that result in the production of intestine and pancreatic neoplasms (Turnbaugh et al., 2009). Obese patients have high oxidative stress byproducts and lower levels of antioxidant resulting in increased secretion of IL-17, IL-22, IL-6 and TNF alpha. This results in generation of ROS by downregulating the anti-inflammatory mediators like TGF alpha, IL-10, hence progressing to carcinogenesis.

4. Conclusions

Obesity is a severe disorder accompanied by increase body weight with excessive fat in body, has been considered as the major cause for various disorders like cancer, cardiovascular disease, metabolic syndrome and diabetes mellitus, and are associated with increased production of oxidative stress and result in mortality (Ding et al., 2010). The pathogenesis of obesity related disorders in obese patients occurs due to overexpression of inflammatory mediators (Huffman and Barzilai, 2009) such as adipokines that result in development of ROS (Neels and Olefsky, 2006; Sengenes et al., 2007). Increased level of

oxidative stress leads to imbalance of adipokines resulting in obesity and its related metabolic complications. Numerous contributions are made to allocate the oxidative stress attributed in regulation and progression of inflammatory mediators. Furthermore, predisposition of oxidative stress in younger population results in several disorders (Marseglia et al., 2014b). Although by understanding the molecular mechanism of obesity and its related diseases, it would be helpful in identifying new therapies for treatment and management of various obesity related disorders.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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