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Review

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Role of Oxidative Stress and Associated Alteration in Enzyme Activities in Obesity Comorbidities

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ABSTRACT

Obesity is defined as having a body mass index (BMI) of 30 kg/m^2 or above, with progressively increasing prevalence all over the world in recent years. Obesity is characterized by deposition of abnormally increased body fat, resulting from increased energy intake relative to energy expenditure. The condition is associated with several comorbidities that upsurge risk of morbidity. The purpose of this review is to describe the role of oxidative stress in release of pro-inflammatory mediators that influence fat and glucose metabolism and is associated with altered enzyme activity, which results in insulin resistance and other associated comorbidities. The main pathology is through intensified generation of reactive oxygen species (ROS) and diminution of antioxidant defense, creating a chronic inflammatory situation that is critically important in development of comorbidities. New strategies to combat resultant comorbidities concentrate on weight reduction either solely or coupled with moderately regular exercise. This policy may be sufficient to improve insulin sensitivity, regulate fatty acid metabolism together with refining antioxidant defense of the body. Other approaches encourage modulation of dietary pattern through dietary supplements as vitamins, with or without pharmaceutical antioxidants, which may provide a potential therapeutics approach in obesity comorbidities

KEY WORDS: Obesity; Oxidative stress; Insulin resistance.

ABBREVIATIONS: BMI: Body Mass Index; ROS: Reactive Oxygen Species; TG: Triacylglycerol; SFA: Saturated Fatty Acids; PKC: Protein kinase C; GPx: Glutathione peroxidase; GR: Glutathione Reductase; PON: Paraoxonase; HDL: High Density Lipoproteins;

INTRODUCTION

Obesity is a condition of abnormally increased body weight, resulting from increased energy intake relative to energy expenditure. Recently, it is considered as disease state and has been described as an epidemic. The most recognized classifications are (i) World Health Organization (WHO), based on body mass index (BMI). Obesity is defined as having BMI of 30 kg/m^2 or above. (ii) Other experts utilized a definition of obesity based on percentage of body fat, with body fat greater than 25% for men and greater than 33% for women are considered obese.[1,2]

OXIDATIVE STRESS IN OBESITY

The main element in developing associated comorbidities is increased oxidative stress, as result of increased oxygen utilization and subsequent production of reactive oxygen species (ROS) through mitochondrial respiration,which in excess results in decrease antioxidant defense in the body and causes cellular damage.[2]

Oxidative stress is accompanied with infiltration of adipose tissue by inflammatory cells, together with further production of excessive ROS by these cells as part of the immune response. Therefore, adipocyte dysfunction occurs with resultant derangement of several adipose tissue-derived secretory factors, referred to as adipokines, which may possibly contrib-

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ute to the development of various metabolic diseases through altered glucose and lipid homeostasis.[3] However, ROS are normally produced in body in very low level, which is ordinarily required to maintain physiological functions as cell proliferation, host defense, signal transduction, and gene expression.[4]

Mechanisms of ROS Production in Obesity

- Excessive free fatty acids release from adipose tissue provokes lipotoxicity, as they produce oxidative stress to the endoplasmic reticulum and mitochondria.[5] It has been established that storage of fatty acid as triacylglycerol (TG) within adipocytes guards against fatty acid toxicity. Though, excessive storage of TG within the adipose tissue ultimately evokes the release of fatty acids as consequence of enhanced lipolysis, which is boosted by the increased sympathetic state usually prevailing in obesity.[6]
- Over-consumption of oxygen, due to increased cardiac load which generates free radicals in mitochondrial respiratory chain, coupled with oxidative phosphorylation in the mitochondria and depletion of ATP.[7,8]
- In addition, dietary habits as lipid rich diets, with high dietary saturated fatty acids (SFA) which stimulate intracellular mechanisms, leading to oxidative stress through various biochemical pathways, such as superoxide generation from NADPH oxidases, glyceraldehyde autoxidation, protein kinase C (PKC) activation, and polyol pathway.[8] Moreover, consumption of diet poor in fruits and vegetables; since fruits and vegetables contain antioxidant as vitamin C and A that protect the body from oxidative injury.[4,9]
- Elimination of ROS depends on the action of antioxidants either enzymatic or non-enzymatic reactions; these antioxidants represent the most important defense mechanisms of cells against oxidative stress.[4]

Key Enzymes in Obesity Comorbidities

Anti-oxidant enzymes:

1. Primary intracellular antioxidant enzymes; comprise five major types: Cu/Zn-superoxide dismutase in the cytosol, manganese superoxide dismutase in the mitochondrial matrix, catalase, glutathione peroxidase (GPx), and glutathione reductase (GR), these are found in all subcellular fractions. Significantly diminished concentration of these enzymes is associated with increased production of ROS leading to various abnormalities, as endothelial dysfunction, characterized by a decreased synthesis of vasodilatorsas nitric oxide (NO) favoring hypertension and atherosclerotic disease in obese subjects.[10]
2. Paraoxonase (PON) is a calcium-dependent esterase. PON family aroused as a new class of antioxidant enzymes: PON1, PON2, and PON3. Particularly PON1 and PON3 are synthesized in liver and play an important role in obesity-associated disease, as atherosclerosis and diabetes mellitus; these enzymes are predominately present on the surface of high density lipoproteins (HDL). PON1 protects low density lipoproteins (LDL) against lipid peroxidation and oxidative damage, thus preventing inflammatory responses in arterial wall cell.[11,12]
3. Heme oxygenase-1 (HO-1) is a microsomal enzyme that is not detected under normal conditions. However, in response to inflammatory stresses, they are produced in red blood cells. They offer protection against insulin resistance and excessive inflammation in most tissues. This enzyme also catalyzes degradation of heme to produce ferrous iron, carbon monoxide, and biliverdin. Carbon monoxide exerts cytoprotective effects; as it has potent anti-inflammatory, anti-apoptotic, and vasodilator properties. Also, Biliverdin is subsequently converted into bilirubin. Both of which are cytoprotective antioxidants, they scavenge peroxylradicals.[13]

Several Factors Contribute to Abnormal ROS Generation in Morbid Obesity, these Factors Include:

a. Reduction in antioxidant defense

ROS stimulates the production of inflammatory cytokines, which further exacerbate ROS release, thus establishing a vicious circle, promoting increased adipocyte proliferation, differentiation.[3] Inability of body to eradicate excessive ROS as result of diminution in antioxidant defense and subsequent imbalance in antioxidant defense; may be a major factor in the pathogenesis of obesity co-morbidities.[4]

b. Cytokines release in adipose tissue

Elevated levels of ROS induces adipose tissue hypoxia, which consequently promote the expression of pro-inflammatory cytokines; as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1). Adipose tissue macrophage (ATM) is much more active than adipocytes in the production of TNF-α and other pro-inflammatory cytokines. For example, inhibition of macrophage by thiazolidinediones (TZDs) was found to improve insulin sensitivity.[10,14] In addition, pro-inflammatory cytokines cause the activation of nuclear factor-kappa (NF-κB) and signal transducer and activator of transcription-3 (STAT3) pathways; with resultant transcription of genes that regulate inflammation, cell proliferation, differentiation, and apoptosis.[15] Chronic inflammation then damages the cells of the heart, arterial walls, and other anatomic structures; this damage leads to various inflammatory chronic diseases.[16]

OBESITY COMORBIDITIES

Insulin Resistance and Type 2 Diabetes Mellites

Insulin resistance is defined as the decreased response of tissues to insulin action, it represents a characteristic feature of metabolic syndrome and is a major predictor of the development of type 2 diabetes, and assists in the pathological development of other comorbidities.[17]

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a. Normal mechanism of insulin signaling

Insulin signaling is initiated when insulin binds to its receptor on the cell membrane, leading to phosphorylation/activation of insulin receptor substrate (IRS) proteins that are coupled with the activation of two main signaling pathways: the phosphatidylinositol 3-kinase (PI-3K)-AKT/PKB pathway and the Ras-mitogen-activated protein kinase (MAPK) pathway.[18,19]

The PI-3K-AKT/PKB pathway is important for the metabolic actions of insulin; IRS-1, which is phosphorylated by the insulin receptor, activates PI-3K by binding to its SH2 domain. Eventually, it results in several signaling actions with consequent translocation of glucose transporter-4 to the plasma membrane, and increase in adipocyte glucose uptake. Also, PI-3K results in AKT signaling cascades, causing phosphorylation of glycogen synthase by glycogen synthase kinase-3 (GSK-3); inhibition of GSK-3 by AKT promotes glucose storage as glycogen and decreases the expression of gluconeogenic enzymes in the liver.[20] While, overactivity of GSK-3 in skeletal muscle obese type 2 diabetic subjects is accompanied with compromised ability of insulin to initiate glucose disposal and glycogen synthase.[20,21]

On the other hand, MAPK pathways are not involved in increasing mitogenic and cell growth effects of insulin.[18] In addition, In the adipose tissue, insulin has an anti-lipolytic effect, activation of PI-3K promotes phosphodiesterase-3 so that more adenosine 3′,5′-cyclic monophosphate is hydrolyzed in adipocytes, which in turn controls the delivery of fatty acids from adipocytes.[19,21]

b. Impairment of insulin signaling

First, various inflammatory cytokines from adipose tissue impair insulin signaling, coupled with increased release of transcription factors, including adipocyte differentiation factor 1/sterol regulatory element-binding protein-1c (SREBP1-c), that regulates the expression of several genes responsible for adipocyte differentiation, lipogenesis, lipolysis and fatty acid oxidation.[20,22]

Inflammatory cytokines as TNF-α also stimulates ceramide accumulation by activating sphingomyelinase, an enzyme that catalyzes the hydrolysis of sphingomyelin to ceramide.[20,21]

Second, increased circulating free fatty acids and their metabolites as glycerol, ceramides due to increased adipose tissue fat and altered lipolytic activity.[21]

Also, HFD-stimulated sphingolipid production through either *de novo* synthesis or the salvage pathway. *De novo* sphingolipid synthesis commences with the action of serine palmitoyltransferase (SPT) enzyme, through SPT condensation of serine and palmitoyl-CoA (or myristoyl-CoA) resulting in 3-ketosphinganine, followed by reduction to form dihydrosphingosine by NADH-dependent reductase. Then ceremide synthesis by ceramide synthases.[4,10] In insulin resistance, target organs or tissues do not fully respond to insulin; with consequent is hyperglycemia and hyperlipidemia caused by preserved lipogenesis.[18]

c. The consequences of insulin resistance on pancreas

Insulin inactivity caused by down regulation of insulin receptor IRS expression and inhibition of insulin action affects pancreatic acinar cells, resulting in loss of insulinotropic action on these cells, together with decreased secretion of pancreatic enzymes as pancreatic amylase.[22] Therefore, insulin resistance is associated with low serum amylase levels, since endogenous insulin potentiates zymogen release. Similarly, low-levels of pancreatic lipase which hydrolyzes digested fat.[22,23]

d. Hyperuricemia and insulin resistance

Hyperuricemia has been suggested a marker of insulin resistance,[24] excess consumption of fructose through added sucrose or high-fructose corn syrup, these dietary components initiate fructose metabolism by an enzyme called keto-hexokinase, also known as fructokinase.[25] This ATP-dependent step in fructose metabolism lacks a negative feedback mechanism, therefore as a consequence of excessive fructose metabolism, ATP is rapidly diminished and lots of the dephosphorylated adenosine compounds are catabolized, resulting in increased uric acid.[26,27] Thus, hyperuricemia can be potential risk factor for insulin resistance, hypertension and atherosclerosis.[25]

Dyslipidemia

Dyslipidemia is a condition characterized by abnormal concentration of lipids in blood, such as cholesterol and triglyceride, and is a widely recognized as risk factor for cardiovascular disease.[28] It is characterized by increased plasma levels of free fatty acids and triglycerides, decreased levels of high-density lipoprotein (HDL), and abnormal low-density lipoprotein (LDL) composition.[28,29]

a. Enzymes implicated in Dyslipidemia

First, the most important contributing factor is increased release fatty acid from adipose tissue, especially visceral adipose tissue, as result of increased lipolysis. This is associated with increased delivery of fatty acids to the liver and synthesis of very-low-density lipoprotein (VLDL). Increased levels of free fatty acids can decrease activity of lipoprotein lipase (LPL) in adipose tissue and skeletal muscle, and increased synthesis of VLDL in the liver can inhibit lipolysis of chylomicrons, with resultant hypertriglyceridemia. The later stimulates a cholesteryl-ester transfer -mediated exchange of triglycerides for cholesterol esters between triglyceride-rich lipoproteins (VLDL) and lipoproteins, which are relatively richer in cholesterol esters (LDL, HDL), which leads to a decreased HDL-cholesterol concentration and reduced triglyceride content in LDL. Increased triglyceride con-

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tent in LDL is then hydrolyzed by hepatic lipase enzyme, leading to formation of small, dense LDL particles that are associated with increased risk of cardiovascular disease.[29,30]

Second, significantly lower Paraoxonase 1 Activity (PON) activity in obese subjects.[12] HDL-PON is a calcium-dependent esterase that hydrolyzes oxidized phospholipids, thus defending lipoproteins (LDL, HDL) and cell membranes from oxidative damage.[31,32] A relationship between HDL-PON and lipid peroxidation was found in both HDL and LDL-cholesterol, thereby lower PON activity are associated with increased risk of oxidative damage. Also, diminished levels of PON1 activity is correlated with low levels of HDL-cholesterol.[11,32]

b. Mechanisms contributing to altered enzyme activities in dyslipidemia

Leptinis a hydrophobic peptide that binds to HDL and inhibits PON1 enzyme directly. Also, leptin augments oxidative stress through the generation of ROS, thereby promotes the secretion of inflammatory cytokines.[33] In addition, leptin stimulates the production of acute phase proteins including serum amyloid A protein, which can replace apolipoprotein-A1 (apo A-I) in HDL. Apo A-I has an important function in stabilizing the structure of PON1.[31]

Moreover, alteration in the activity of enzymes that has antioxidant role on HDL particles, such as plasma platelet-activating factor acetyl-hydrolase, lecithin cholesterol acetyl transferase (LCAT), and cholesteryl ester transfer protein (CETP).[34,35]

Cardiovascular Complications

Obesity is associated with a variety of structural and functional alterations to the cardiovascular system, apparently due to increased metabolic rate, growth of the organs in response to increased metabolic needs and local accumulation of vasodilators.[28] These consequences include increased peripheral resistance, left ventricular hypertrophy, and inferior left ventricular systolic function.[33]

Obesity is also established to impact coronary risk indirectly through its effect on other comorbidities, such as dyslipidemia, hypertension, endothelial dysfunction, and inflammation.[34]

a. Pathophysiology of cardiovascular system in obesity

Heart undergoes structural remodeling due to excess adipose tissue deposition, as result of elevated levels of free fatty acids (FFA) in blood; lead to increased influx of FFA into cardiomyocytes while the rate of glucose uptake is reduced; accordingly, the heart utilizes more FFAs for its energy requirements. Also, FFA triggers the activation of NADPH oxidase, increased ROS production and chronic inflammation with resultant interstitial fibrosis and cardiomyocyte hypertrophy leading to functional alterations.[35] Recent studies claim that cluster differentiation (CD36) protein plays a prominent role in delivering long chain FFAs to the heart and induces ROS production.[36,37]

b. Enzymes implicated in cardiovascular complications

Excessive ROS generation results in PON family are stimulation; these enzymes include PON1 with a protective role against atherosclerosis and cardiovascular disease. While PON2 and PON3 both have antioxidant effects and hydrolyze aromatic and long-chain aliphatic lactones, however, they lack paraoxonase or arylesterase activities.[12]

Moreover, ROS production at the vascular endothelium level, result in endothelial dysfunction with consequent development of hypertension and atherosclerosis, through several mechanisms:

1. Adipokines released by adipose tissue as result of lipids deposition as oxidized LDL lipoproteins induce endothelial dysfunction, hypercoagulability, and systemic inflammation.[4] These adipokines interact and influence immunologic pathways, such as vascular reactivity (through release of adiponectin, leptin and TNF-α), inflammation (further aggravates oxidative stress and increases production of monocyte chemotactic protein 1 and IL-8) and coagulation activation (through release of plasminogen activator inhibitor).[30] Also increased Leptin release from adipocytes induces functional damage in endothelial cell through induction of induced nitric oxide synthase (iNOS) and NADPH oxidase, caused the peroxynitrite-mediated oxidative stress.[28,30,38]

2. The adipocytes possess a local renin-angiotensin-aldosterone system (RAAS) that contributes to adipose tissue inflammation and disease progression. Renin, aldosterone, angiotensinogen, angiotensin converting enzyme (ACE) and angiotensin II types 1 and 2 receptors are all components of RAAS.[38] High-levels of pro-inflammatory cytokines as IL-6, TNF-α stimulate the secretion of angiotensin-II (ANG-II) from adiopocytes, ANG-II is the biologically active component of the RAAS, it binds to ANG-II angiotensin type 1 receptor (AT1R) in various cell types, including skeletal muscle and cardiomyocytes, and activate NADPH oxidase, producing superoxide ions through one-electron reduction of oxygen and the oxidation of NADPH, with resultant increased oxidative stress.[38,39] It also induces an inflammatory response through the activation of nuclear factor-κB (NF-κB) in cardiac tissue, and increases the expression of inflammatory mediators such as monocyte chemoattractant protein 1(MCP-1) in monocytes and toll-like receptor-4 (TLR4) in vascular smooth-muscle cells, thus it contributes to cardiovascular and renal pathology.[40,41]

3. Deficiency of the amino acid arginine is caused by increased arginase enzyme activity. This enzyme breaks down arginine. Although, arginase is present throughout the body, it is primarily found in the liver. Its role is to assist in the breakdown of ammonia, which is eventually flushed out in urine. However, nitric ox-

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ide produced from arginine, plays an important role in relaxation of blood vessels and lowering arterial blood pressure.[39, 42] Thus, deficiency of arginine by arginase reduces nitric oxide levels, leading to the vascular vasoconstriction and hypertension.[42,43]

Hepatic Dysfunction in Obesity

Obesity is associated with a spectrum of liver abnormalities including Nonalcoholic Fatty Liver (NAFLD), a condition characterized by the excessive deposit of intrahepatic triglycerides in the liver (>5 % of the hepatocytes containing macrovesicular fat) and nonalcoholic Steatohepatitis (NASH) with emergence of signs of inflammation and scarring, i.e., fibrosis. This can lead to progressive liver injury resulting in cirrhosis and hepatocellular carcinoma.[44,45]

The condition is closely associated with insulin resistance; in the liver, impairment IRS2 pathway leading to inhibition of gluconeogenesis, while lipogenesis by the IRS1 pathway is preserved, thus causing hyperglycemia and hyperlipidemia.[45]

a. Mechanism of liver cell injury in NAFLD

1. Greater flow of free fatty acids into hepatic circluation results in mitochondrial dysfunction, oxidative stress, and increased NADPH oxidase enzyme activity.[46]

2. Proinflammatory cytokines released from adipose tissue as result of increased ROS and chronic inflammation; including TNF-α, it interferes with insulin signaling by phosphorylation of insulin receptor substrate-1 and provoking insulin resistance and subsequently NAFLD progression. Also, IL-6 is considered hepatoprotective because it reduces oxidative stress and prevents mitochondrial dysfunction.[37] However, IL-6, together with TNF-α, reduces adiponectin levels. Adiponectin is an adipocytokine with anti-inflammatory functions, and declines with subsequent increased fat deposition in liver.[46,47]

3. Endoplasmic reticulum ER stress, resulting from improperly folded proteins accumulating in the ER, which elicits the unfolded protein response (UPR). The UPR activates nuclear factor κB, c-Jun N-terminal kinase, and oxidative stress pathways.[46,48]

b. Enzymes implicated in NAFLD

Lipogenesis is regulated by the FA synthase enzyme complex, acetyl-CoA carboxylase 1 and 2, diacylglycerol acyltransferase through the activation of several nuclear transcription factors (sterol regulatory element binding proteins [SREBPs], carbohydrate responsive element binding protein [ChREBP], which transcriptionally activate almost all genes involved in lipogenesis.[49,50] Concurrently with decreased antioxidant enzymes and increased NADPH oxidase enzyme activity.[46]

c. Clinical presentation of NAFLD

Since the liver is such a resilient organ, most patients with NAFLD do not have symptoms or any laboratory abnormalities. However, abdominal pain in the upper right quadrant along with neuropsychological signs as irritability, and fatigue. Emergence of clinical signs denotes hepatomegalia (enlargement due to fatty infiltration of the liver parenchyma) and acanthosis nigricans (cervical, inguinal, and/or axillary discoloration; a predictable sign of insulin resistance).[44]

Manifestations of NAFLD are the "hepatic manifestation" of the metabolic syndrome; any of the five components of the metabolic syndrome (hypertension, BMI >97th percentile, high plasma triglycerides, reduced plasma HDL cholesterol, and hyperuricemia).[45,46]

d. Laboratory findings in NAFLD

Elevation of liver enzymes occurs as Alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase (ALK) and gamma glutamyltranspeptidase (GTT).[44,51]

In addition, alkaline phosphatase enzyme (ALP) is a hydrolase enzyme responsible for removing phosphate groups and it is mainly derived from the liver, bones, intestines, kidneys, and leukocytes. Several studies have found high serum ALP levels occur in obese subjects with dyslipidemia, is associated with increased the risk of vascular calcification and cardiovascular disease (CVD). The mechanism may be due to chronic inflammatory process and associated failure of dephosphorylation of potentially harmful molecules, which further increases oxidative stress, and inflammation.[52]

Renal Impairment

Obesity is considered a risk factor for development and progression of chronic kidney disease. Obesity-related glomerulopathy (ORG) has been described as a secondary form of focal segmental glomerulosclerosis (FSGS), and is characterized by the presence of glomerulomegaly.[53]

a. Pathogenesis of obesity-related glomerulopathy (ORG)

Morbid obesity is frequently associated with glomerular hyperfiltration due to increased production of ROS, with increased glomerular filtration rate and increased renal blood flow. The preliminary clinical characteristic of renal impairment is the presence of albuminuria or proteinuria.[53]

Adipose tissue release of inflammatory cytokines as well as leptin, Additionally, the kidneys contain a leptin receptor chiefly in the renal medulla. Leptin exerts a fibrogenic effect by enhancing the expression of glomerular transforming growth factor-β1, that is accompanied with the appearance of proteinuria.[54,55]. Also, leptin acts on the renal tubules by increasing tubular reabsorption of sodium, and stimulates glomerular hyperfiltration.[55] Other mechanisms are also being implicated, such as insulin resistance, activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS).[56,57]

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Glomerular insulin resistance is an important factor for the impairment of renal function. Insulin signaling through IRS1 is inhibited, while IRS2 is preserved; in which deficiency of IRS1-mediated pathway induces unsuppressed gluconeogenesis contributing to hyperglycemia, glomerular dysfunction, and subsequent nephropathy. On the other hand, preserved IRS2-mediated pathway stimulates sodium reabsorption, sodium retention and subsequent hypertension.[58,59]

b. Renal lipotoxicity

Excessive lipid deposition into the kidney can lead to accumulation of toxic metabolites, such as diacylglycerols and ceramides, derived from metabolism of fats and fatty acids. These metabolites lead to mitochondrial dysfunction, endoplasmic reticulum stress, apoptosis, and ultimately renal injury.[60,61]

METABOLIC SYNDROME

The biological signaling is required for the integration of metabolic functions of adipocytes/adipose tissue with other adipose tissue depots and various body organs, such as liver. Disruption of biological signaling contributes to metabolic syndrome.[6,61]

Fatty Acid Metabolism

Disturbed fatty acid metabolism in peripheral adipose tissue, is associated with increase in adipose tissue growth (adipocyte hypertrophy and visceral adiposity), and consequently requires additional blood supply, then relative hypoxia may impair adipogenesis and aggravates metabolic dysfunction of adipocyte, and further promote increased proinflammatory response.[5]

Chronic increase in circulating free fatty acids often results in 'lipotoxicity', which is characterized by ectopic fat deposition in various organs as muscle and liver contributing to insulin resistance.[61,62] Moreover, hyperlipidemia is accompanied increased steroid hormones synthesis. For example, glucocorticoids increase the differentiation of visceral adipocytes) relative to subcutaneous, peripheral adipocytes, while decreasing adipocyte proliferation, causing hypertrophy of visceral adipocytes, and contributing to insulin resistance and hypertension.[62,63]

Polycystic Ovary Syndrome (PCOS)

Obesity associated oxidative stress contributes to development of polycystic ovary syndrome (PCOS) in ovaries.[64] PCOS is always considered as component of metabolic syndrome, characterized by multiple hormonal imbalances particularly hyperandrogenemia.[64]

a. Pathophysiology of PCOS

The association between hyperinsulinemia and hyperandrogenemia in PCOS is explained by the fact that despite systemic state of IR, the ovary remains sensitive to insulin activity and is associated with subsequent androgen production.[65] Insulin is reported to stimulate ovarian androgen secretion through luteinizing hormone-(LH) stimulated androgen secretion. Moreover, ROS are reported to enhance the activities of ovarian steroidogenesis enzymes, which stimulate hyperandrogenemia.[66] Furthermore, inflammatory mediators have the ability to promote proliferation of mesenchymal cells of follicular membrane and the synthesis of androgen.[65]

A steroidogenic regulatory protein (StAR) controls the rate-limiting step in steroidogenesis. It regulates the transport of cholesterol from the outer to the inner mitochondrial membrane. Insulin acts synergistically with LH within the theca cells of polycystic ovaries (in which theca cell hyperplasia is present) to augment not only StAR expression, but also cholesterol side-chain cleavage enzyme, 17-α-hydroxylase, 3-β-hydroxysteroid dehydrogenase and aromatase expression, contributing to an excess in the production of progesterone, 17-α-hydroxyprogesterone, and testosterone in polycystic ovaries.[65,67]

Skeletal Muscle Changes in Obesity

Skeletal muscle plays a vital role in regulating fatty acid oxidation (FAO) due to its mass and metabolic characteristics. At rest FAO is the chief activity of skeletal muscle; thus, disturbed fatty acid metabolism would provoke ectopic fat deposition.[68]

a. Altered fatty acid metabolism in muscle

Carnitine palmityltransferase (CPT-1) key regulatory enzyme that controls FAO, it regulates the transport of long-chain fatty acids across the mitochondrial membranes. This enzyme is severely reduced with morbid obesity.[69]

In addition, increased glycolytic enzymes (adenylate kinase, GAPDH, aldolase A, and creatine kinase activity) which suggest a metabolic shift towards glycolytic energy production with the decrease in FAO in skeletal muscle with morbid obesity. Furthermore, skeletal muscle strips revealed increased production of lactate at rest. Both conditions; increased intramuscular lipid content and a decline in FAO are associated with insulin resistance.[68]

b. Insulin resistance in skeletal muscle

Skeletal muscle in insulin resistance displays reduced capacity for insulin-dependent glucose transport activity. Since oxidative stress stimulates serine kinase p38 mitogen-activated protein kinase (p38 MAPK), only one of many stress-activated kinases as JNK and IKKβ, leading to increased expression of various proinflammatory molecules such as IL6. This impairs insulin signaling that regulate GLUT-4 translocation in myocytes.[69,70] Besides, skeletal muscle in obesity tends to have increased intramuscular lipid content. This is accompanied with reduced oxidative enzymes activities; suchas citrate synthase, cytochrome C oxidase, and hydroxyacyl dehydrogenase. Collectively with increased glycolytic activity as phosphofructokinase activities and α-glycerolphosphate dehydrogenase (GPDH).[71]

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c. Structural changes in skeletal muscle fibers

Skeletal muscle composition differs in obese individuals, with increased proportion of type II muscle fibers, called glycolytic fast-twitch fibers. Type II fibers show increased glycolytic enzyme activity and decreased oxidative enzyme activity relative to other fiber types. Type I muscle fibers (oxidative slow-twitch) and type IIa (oxidative fast-twitch). In which type I fibers had highest oxidative enzyme activity followed by type IIa, and the lowest oxidative capacity is found in type II fibers.[71,72]

Osteoporosis

Obesity conceivably influences bone metabolism through various mechanisms. Since both adipocytes and osteoblasts originate from a common multipotential mesenchymal stem cell. Obesity causes adipocyte hypertrophy and fat accumulation whereas decrease osteoblast differentiation and bone formation.[73]

a. Enhanced bone reabsorption

Increased circulating and tissue proinflammatory cytokines may provoke osteoclast activity and bone resorption *via* modulating the receptor activator of NF-κB (RANK)/RANK ligand/osteoprotegerin pathway; Increased osteoclastic activity is associated with increased bone resorption in morbid obesity and is concurrently linked with the upregulation of RANKL.[74]

Additionally, elevated levels of leptin and reduced adiponectin production by adipocytes affect bone formation directly or indirectly through increased bone resorption *via* upregulated proinflammatory cytokine production.[75,76] Moreover, high-fat intake may interfere with intestinal calcium absorption and therefore decrease calcium availability for bone formation.[77]

b. Factors affecting bone formation

Obesity is coupled with high levels of pancreatic hormones such as insulin, and amylin which are anabolic to bone. Moreover, chronic tissue inflammation is accompanied with elevated levels of adipose tissue derived peptides and enzymes, such as hydroxyl steroid dehydrogenase, aromatase. 17 beta-hydroxysteroid dehydrogenase (17 beta-HSD) enzyme converts inactive cortisone into active cortisol; glucocorticoids are necessary for osteoblast differentiation and development of a mineralized extracellular matrix.[78] Aromatase uses androstene or testosterone to produce estrogen, which is essential to protect against osteoporosis. Estrogen reduces osteoclast-mediated bone resorption and stimulates osteoblast-mediated bone formation.[75,76]

Leptin influences bone development through the activation of fibroblast growth factor 23 (FGF-23). It also regulates osteocalcin, a non-collagenous protein in bone. While Adiponectin is reduced in obesity and it increases osteoblastic activity.[76,78]

Moreover, hyperlipidemia is concomitantly associated with high-levels of plasma estrogen and parathyroid hormone (PTH), lower sex hormone–binding globulin (SHBG) and 25 hydroxyvitamin D (25OHD), The lower levels of 25 OHD are possible due to storage in adipose tissue.[73,79]

Cancer

Oncogenesis is a multi-factorial phenomenon; ROS disrupts the epigenetic pattern by producing carcinogens, with subsequent effects as DNA hypermethylation, histone modifications, DNA damage, which results in genomic instability associated with activation of oncogenes and/or inactivation of tumor suppressor genes.[80,81] Accumulating evidence revealed a positive correlation between increased cancer risk and poor prognosis with increased BMI and fat distribution.[82]

Methods Applied to Investigate Oxidative Stress in Morbid Obesity

Oxidative stress is generally evaluated by measuring markers of antioxidant defense and, or oxidative stress. Antioxidant defense is determined by measuring plasma concentrations of molecules as vitamin E, vitamin C and or minerals as zinc and selenium.[83,84] Oxidative stress can be evaluated by estimating end-products of oxidative damage; proteins as advanced glycosylation end products (AGEs), lipids (as malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARs) and nucleic acid (such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), in blood and urine.[85]

Strategies to Decrease Oxidative Stressin Morbid Obesity

Those strategies include weight loss, physical activity, and antioxidant-rich diet.

Weight loss reduces oxidative stress biomarkers, increases antioxidant defenses and improves metabolic and cardiovascular risk factors.[85] Weight reduction can be achieved through hypocaloric diet coupled with regular moderate physical exercise, which is more effective than hypocaloric diet alone in reducing oxidative stress and improving insulin sensitivity.[85,86] Moreover, Mediterranean diet comprises food rich in fruits, legumes, whole grains, fish and low-fat dairy products; usually contains beneficial macronutrients such as monounsaturated fatty acids (MUFA) and ω-3 polyunsaturated fatty acids (ω-3 PUFA) and vitamins as vitamin C. They suppress inflammation and reduce the risk of cardiovascular disease.[86,87]

Dietary Supplements in Diet

a. Vitamins

Vitamins with antioxidant properties such as vitamin C, vitamin E, and carotenoids, they have valuable outcomes in reducing oxidative stress and improving dyslipidemia.[86] An example of these antioxidants is Astaxanthin (keto-carotenoid, present in

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salmon fish, shrimps, and other sea food), it reduces lipid peroxidation and stimulates antioxidant defenses in obese subjects.[88,89]

b. Polyphenols

Polyphenols comprise the most copious phytochemicals provided by food of plant origin as fruits, vegetables and whole cereals. Polyphenols provide antioxidant effect depending on their ability to inhibit ROS generating enzymes and enhance antioxidant enzymes.[90] Polyphenols are classified into different categories: phenolic acids, stilbenes, flavonoids, chalcones, and curcuminoids.[91]

Examples include:

- Resveratrol; a stilbene primarily present in apples. it acts through several mechanisms; it enhances mitochondrial activity, reduces inflammation, decreases ectopic lipid deposition, and improves insulin sensitivity.[91,92]

- Ferulic acid; (phenolic acid) present in whole wheat, apples and oranges. It is effective in reducing dyslipidemia, by regulating lipogenic enzyme activities and improving antioxidant defense and consequently improve insulin sensitivity.[92,93]

- Quercetin and Catechins (flavonoids) present in apples, onions, broccoli, and tea. They exert anti-oxidant and anti-inflammatory properties. Also, Curcumin a curcuminoid with anti-inflammatory, antioxidant and improve insulin signaling.[92,93]

c. Amino acids

They represent a new promising strategy for obesity comorbidities, through supplementation of specific amino acids.[94] For instance, arginine administration stimulates gene expression, especially of PPAR-γ coactivator 1 (transcriptional coactivator and metabolic regulator as cAMP pathway), Endothelial nitric oxide synthase (eNOS) and antioxidant enzyme heme oxygenase-1 (HO-1). L-arginine also improves blood flow, improves antioxidant defense and regulates fatty acid metabolism.[94]

Another amino acid supplement is leucine; it promotes protein synthesis and reduces ectopic fat deposition (by regulating fatty acid metabolism and mitochondrial biogenesis in both muscle and adipose tissue). Nutraceutical supplementation (leucine and pyridoxine), provides effective antioxidant and anti-inflammatory influences, enhances fat oxidation and improves insulin signaling.[95,96]

CONCLUSION

The underlying mechanism for obesity comorbidities is mainly through abnormally increased oxidative stress, with subsequent upsurge of proinflammatory mediators that could induce altered enzyme function, resulting in IR and other comorbidities. Moreover, it induces DNA damage which may be a key factorin disease pathology and malignancy.

New strategies to reduce obesity associated comorbidities focus on reduction of energy supply through weight reduction which can solely improve antioxidant defense of body. Also, other practices include dietary and pharmaceutical antioxidants, which may be a potential therapeutic approach in obesity comorbidities.

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