REVIEW ARTICLE

The Intricate Nexus: The Relationship between Oxidative Stress and Inflammation in Obesity

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ABSTRACT

Obesity, defined as excessive fat storage, is linked to chronic low-grade inflammation and increased reactive oxygen species (ROS) generation. Inflammatory cells, such as neutrophils and macrophages, produce ROS during oxidative bursts to attack infections. However, in obese people, increased ROS generation in hypertrophic and hypoxic adipose tissue maintains a chronic inflammatory state. ROS and Damage-Associated Molecular Patterns (DAMPs) generated by stressed adipocytes activate inflammatory pathways and transcription factors, including nuclear factor-kappa B (NF-κB). Identifying such mechanisms highlights the possibility of targeting ROS generation and inflammatory pathways to reduce chronic inflammation and enhance metabolic health in obesity. This review seeks to clarify the complex link between oxidative stress, inflammation, and obesity.
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INTRODUCTION

Obesity has emerged as a global epidemic and a significant contributor to various health risks such as insulin resistance, type 2 diabetes mellitus (T2DM) (1), cardiovascular diseases (CVD) (2), immune disorders, non-alcoholic fatty liver disease (NAFLD) (3), as well as multiple types of cancers. Additionally, obesity has been found to have a negative impact on quality of life, leading to a shortened lifespan and increased healthcare expenses (4). Over the past few decades, Malaysia has witnessed a drastic transformation in dietary patterns and lifestyle choices, resulting in an alarming increase in obesity rates, from 45.4% in 2011 to 54.5% in 2023 (5). This phenomenon can be attributed to a confluence of factors, including the pervasive influence of Westernized diets rich in processed foods and sugary beverages (6), the proliferation of sedentary behaviours due to urbanization and technological advancements (7,8), the dearth of nutritional education and awareness (9), and the aggressive marketing of unhealthy foods, mainly aimed at vulnerable populations like children (10).

Oxidative stress is frequently observed in individuals with obesity, as evidenced by the notable presence of reactive oxygen species (ROS) (11) and reduced levels of antioxidant enzymes (12). Typical characteristics associated with oxidative stress include chronic low-grade inflammation, proliferation and apoptosis of endothelial cells, and increased vasoconstriction, which can contribute to endothelial dysfunction. Extensive research has provided evidence supporting the link between oxidative stress, endothelial dysfunction, atherosclerosis, and cardiovascular disease (13). Oxidative stress refers to a state of cellular damage resulting from an imbalance between ROS and antioxidant enzymes. ROS, generated during cellular metabolism through the chemical reduction of oxygen, are oxidizing agents that produce unstable free radicals with unpaired electrons (14). Physiologically, ROS plays a crucial role in gene expression, the immune system, cellular growth, and the modulation of endothelial function (15). However, antioxidants are necessary to maintain ROS levels at a beneficial physiological range. Antioxidants encompass enzymatic and nonenzymatic substances that effectively reduce or prevent the oxidative harm caused by ROS, either by inhibiting ROS synthesis and activity or by repairing ROS-damaged cells (16).

In recent years, the intersection of oxidative stress

and inflammation has gained significant attention in revealing the pathogenesis of obesity and its associated complications. This review investigates the multifaceted relationship between oxidative stress and inflammation in the context of obesity, revealing their intricate mechanisms and exploring their collective impact on health.

OXIDATIVE STRESS AND ITS CULMINATION IN OBESITY

Oxidative stress is a state characterised by an imbalance between the generation of ROS and the body's ability to counteract them with antioxidant defense systems. This situation is crucial in the development of obesity-related health complications. ROS, such as superoxide anion, hydrogen peroxide, and hydroxyl radicals, are naturally occurring compounds produced during cellular metabolism. While they serve as essential signaling molecules in various physiological processes, their excess generation leads to oxidative damage to cellular components, including lipids, proteins, and DNA (17).

Several factors catalyze oxidative stress in the context of obesity. The foremost contributor is the excess calorie intake characteristic of obesity, leading to increased mitochondrial activity to meet the augmented energy demands. While mitochondria are essential cell powerhouses, they are also primary sources of ROS production through processes such as the electron transport chain (ETC) leakage. The augmented metabolic activity in obesity consequently elevates ROS production, contributing to the oxidative stress condition (18).

Furthermore, once regarded as a passive energy reservoir, adipose tissue has been revealed as a dynamic endocrine organ. Adipocytes, the predominant cell type in adipose tissue, release adipokines, cytokines, and other factors that influence metabolism and inflammation. As adipocytes expand in obesity due to lipid accumulation, they release more pro-inflammatory adipokines and fatty acids, fostering an environment conducive to oxidative stress. The pro-inflammatory nature of these molecules, including tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contributes to immune cell infiltration, particularly macrophages, into adipose tissue (19). Additionally, adipose tissue becomes a pivotal contributor to oxidative stress due to the release of free fatty acids from enlarged adipocytes. These fatty acids can undergo oxidation, producing ROS.

INFLAMMATION AND ITS AUGMENTED ROLE IN OBESITY

Inflammation, a fundamental physiological response designed to protect the body from insults, can also have positive and negative effects. Acute inflammation is intended to facilitate tissue repair and pathogen clearance. However, chronic inflammation, a hallmark of obesity, leads to prolonged immune activation characterised by the release of pro-inflammatory cytokines and chemokines.

In obesity, adipose tissue transforms into a microenvironment with immune cells, particularly macrophages. The pro-inflammatory signals produced by adipocytes fuel this transformation. Leptin, an adipokine, and the concentration of leptin in the blood plasma are linked to the quantity of adipocytes. Leptin affects hunger levels, and a mutation in its receptor causes increased appetite in obese individuals (20). Leptin is crucial in the development of oxidative stress caused by obesity. It induces the production of reactive molecules including hydrogen peroxide (H2O2) and hydroxyl radicals by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX). Leptin injection in a mouse model resulted in elevated amounts of lipid hydroperoxides in both plasma and urine, as well as increased levels of malondialdehyde (MDA), isoprostane, and protein carbonyl content. In addition, leptin promotes the synthesis of pro-inflammatory cytokines and reduces the function of the cellular antioxidant paraoxonase-1 (PON-1) (21); The reduction is associated with elevated concentrations of 8-iso prostaglandin F2α (8-iso PGF2α) in the plasma and urine, as well as increased levels of MDA and hydroperoxides in the plasma. (22).

Leptin additionally enhances the proliferation of monocytes and macrophages, hence facilitating the generation of pro-inflammatory cytokines. Leptin exposure stimulates protein kinase C (PKC) activity and lipoprotein lipase activity in monocyte-derived macrophages (23). Macrophages play a crucial function in controlling inflammation associated with obesity by influencing the differentiation of T helper (Th) cells towards the Th1 subtype, which promotes inflammation (24). Within the Th1 immune response, the most potent trigger for macrophage-induced ROS production is interferon-gamma (IFN-γ) (25). The generation of ROS by macrophages, including superoxide anion (O^{2-}), hydroxyl radical (OH-) and H_2O_2 has been shown to enhance the activation of Th1 cells through positive feedback mechanisms (26).

Macrophages, once considered mediators of tissue repair, become agents of inflammation in this context. They secrete pro-inflammatory cytokines, perpetuating a chronic inflammatory state beyond adipose tissue and affecting other tissues and organs. The complexity of this transformation is underscored by the role of immune cells beyond adipose tissue. Systemic inflammation, driven by adipose tissue inflammation, extends its influence on various organs, including the liver, skeletal muscles, and the vasculature. Macrophages also infiltrate these organs, propagating inflammation and contributing

to the development of insulin resistance and other metabolic disturbances associated with obesity.

OXIDATIVE STRESS AND INFLAMMATION: A BIDIRECTIONAL RELATIONSHIP

Obesity is defined as a condition of systemic oxidative stress, resulting from a compromised antioxidant defense mechanism that fights against ROS (27). Obesity leads to excessive production of O^{2-} due to multiple causes, such as the stimulation of PKC, NOX, glyceraldehyde auto-oxidation, and oxidative phosphorylation. Furthermore, there is a correlation between chronic inflammation and oxidative stress in individuals with obesity (28). The relationship between oxidative stress and inflammation in obesity is not a unidirectional process but rather a bidirectional interplay with profound consequences. This interaction can be summarised in two key facets: oxidative stress promoting inflammation and inflammation amplifying oxidative stress.

Oxidative Stress Promoting Inflammation:

1) ROS-Mediated Activation of nuclear factor-kappa B (NF-κB):

One key mechanism by which ROS induces inflammation is activating the NF-κB pathway (29). NF-κB is a transcription factor that regulates gene expression in immune and inflammatory responses, cell proliferation, and apoptosis (30). In its inactive state, NF-κB is sequestered in the cytoplasm by a family of inhibitory proteins known as inhibitors of κB (IκB) (31).

ROS can activate the inhibitor of κB kinase (IKK), which usually holds NF-κB in an inactive state in the cytoplasm. This kinase complex, composed of IKKα and IKKβ subunits, is responsible for phosphorylating and subsequently degrading IκB proteins (32). IκB proteins typically mask the nuclear localization signals of NF-κB, preventing its translocation into the nucleus and thereby keeping NF-κB in an inactive state. Under the influence of ROS, IKK phosphorylates IκB proteins (32). This phosphorylation marks IκB for ubiquitination and degradation by the proteasome. Consequently, NF-κB is liberated from its inhibitory complex, allowing it to translocate into the nucleus (33).

Once released from its inhibitory complex, the now-active NF-κB translocates into the cell's nucleus. This translocation is a crucial step in activating NF-κB because it enables the transcription factor to influence gene expression directly (34). Inside the nucleus, NF-κB binds to specific DNA sequences known as κB-binding sites in the promoter regions of target genes (Figure 1). This binding acts as a switch, turning on the transcription of various genes. NF-κB primarily activates inflammation, immune responses, and cell survival genes (35). Among these are genes encoding pro-inflammatory cytokines (interleukin-1β, TNF-α), chemokines, adhesion molecules, and enzymes involved in the inflammatory response (36).

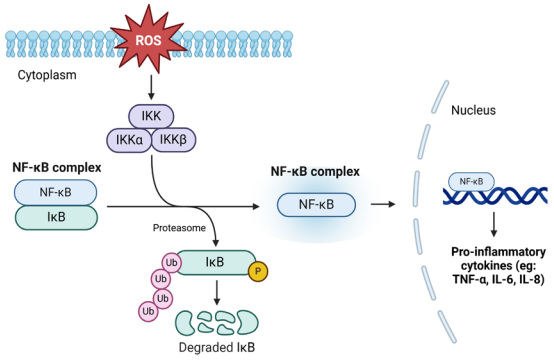

Figure 1: ROS-mediated activation of NF-κB. ROS stimulates the activation of the IKK complex, which includes IKKα and IKKβ subunits. This activation leads to the phosphorylation of IκB, marking it for ubiquitination and subsequent degradation by the proteasome. The degradation of IκB allows the NF-κB complex to translocate into the nucleus, where it binds to DNA and promotes the transcription of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8, contributing to the inflammatory response.

The transcription and subsequent translation of these pro-inflammatory genes lead to the production of inflammatory mediators. The mediators involved in this process are cytokines such as IL-6 and IL-8, chemokines like monocyte chemoattractant protein-1 (MCP-1), and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) (37). These molecules have crucial functions in initiating and regulating the inflammatory response.

Inflammatory mediators released as a result of NF-κB activation serve as signaling molecules that recruit immune cells (neutrophils, macrophages, and lymphocytes) to the site of inflammation (38). These immune cells are essential for defending the body against potential threats, such as infections or tissue damage. Upon recruitment to the inflamed area, immune cells become activated and mount immune responses. This can involve the phagocytosis of pathogens, the production of additional inflammatory molecules, and tissue repair processes. However, in the context of chronic inflammation, such as obesity-related inflammation, these immune responses can become dysregulated, leading to tissue damage and contributing to the development of chronic diseases. On top of that, other studies have documented that consumption of large amounts of glucose leads to an increase in the production of ROS by mononuclear cells and triggers inflammation. This is evidenced by an elevation in the activities of NF-κB and activator protein-1 (AP-1) in healthy individuals. Hyperglycaemia is the beginning of oxidative stress caused by advanced glycation end products (AGEs) (39).

2) Oxidative Damage and Damage-Associated Molecular Patterns (DAMPs) Release:

Oxidative damage occurs when ROS and other free

radicals chemically modify cellular components such as lipids, proteins, and DNA (40). This modification can disrupt these molecules' normal structure and function, leading to cellular dysfunction and injury. Oxidative damage can result from various sources, including mitochondrial dysfunction, exposure to environmental toxins, and chronic inflammation (41).

DAMPs are endogenous molecules usually sequestered within cells but released into the extracellular environment when cells are damaged or stressed (42). Oxidative damage is a potent trigger for the release of DAMPs. DAMPs include various molecules such as high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), uric acid crystals, and heat shock proteins (43). Once released into the extracellular space, DAMPs act as danger signals to alert the immune system to tissue damage or stress (44). Immune cells have specialized receptors known as Pattern Recognition Receptors (PRRs) that can recognize these DAMPs. There are several types of PRRs, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) (45).

DAMPs released from damaged cells bind to specific PRRs on immune cells. For example, HMGB1 can activate TLR4, while ATP can activate the P2X-7 receptor (46). This binding signals to immune cells that tissue damage or cellular stress has occurred. Upon DAMP-PRR binding, a cascade of intracellular signalling events is triggered. This includes the activation of NF-κB, MAP kinases, and other pro-inflammatory signalling pathways (47). The initiation of these signalling pathways results in the transcription and production of pro-inflammatory cytokines and chemokines, including IL-1β, IL-6, and TNF-α. Pro-inflammatory cytokines and chemokines released in response to DAMP-PRR interactions attract immune cells, such as neutrophils and macrophages, to the site of tissue damage (Figure 2). Notably, these immune cells can exacerbate tissue damage and inflammation (48).

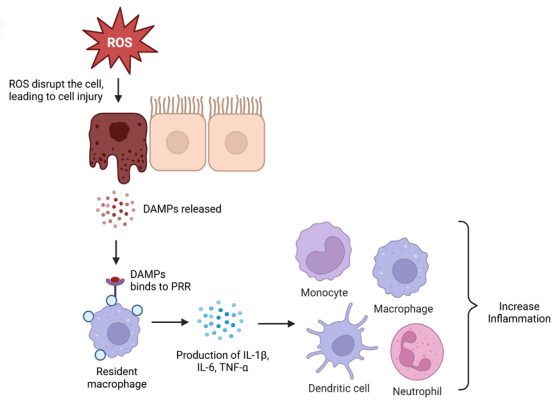

Figure 2: Oxidative damage and DAMPs release. DAMPs are generated after cellular stress or tissue injury caused by oxidative stress, activating the innate immune system through interactions with PRRs to generate proinflammatory cytokines, which then recruit immune cells to the injury site.

3) ROS-Activated Inflammatory Kinases:
ROS can oxidize and chemically modify specific amino acid residues, particularly cysteine residues, within proteins. In inflammatory kinases, ROS can directly oxidize these kinases or their regulatory proteins, leading to their activation. For example, ROS can stimulate the activation of kinases like MAP kinases (ERK, JNK, p38) (49) and the IKK (50). These kinases contribute to the phosphorylation of transcription factors involved in inflammation, including NF-κB and AP-1 (activator protein 1), which collectively induce the expression of pro-inflammatory cytokines (51). Additionally, these activated kinases subsequently initiate intracellular signalling pathways, culminating in the transcription of pro-inflammatory genes. This oxidative modification of kinases represents a critical link between oxidative stress and inflammation, playing a central role in initiating and amplifying inflammatory responses in various diseases and conditions.

Inflammation Amplifying Oxidative Stress:
1) Inflammatory Cells and ROS Production:
Obesity-related inflammation involves infiltrating immune cells, particularly macrophages, into adipose tissue. These immune cells, when activated, release cytokines and generate ROS as part of their antimicrobial defense mechanisms. Macrophages contain NOX, an enzyme complex responsible for ROS generation. NOX generates O^{2-} upon activation by transferring electrons from NADPH to molecular oxygen (52). The process by which NOX generates ROS is often called the "respiratory burst." During this burst, electrons are transferred through a series of proteins within the enzyme complex, leading to the reduction of oxygen to superoxide. Besides NOX-mediated intracellular ROS generation, it has been observed that the mitochondrial respiratory chain is the main origin of cellular ROS, intensifying oxidative stress and inflammatory processes in obesity (53).

2) ROS-Mediated Inflammatory Signaling:
ROS generated by immune cells in the inflamed tissue can trigger further inflammatory signalling cascades. ROS can activate NF-κB in immune cells, creating a positive feedback loop where activated immune cells release more pro-inflammatory cytokines, such as IL-6 and IL-1β. These cytokines, in turn, contribute to oxidative stress by inducing the expression of enzymes like inducible nitric oxide synthase (iNOS), which generates nitric oxide (NO-). NO- can interact with O^{2-} to form peroxynitrite (ONOO-), a potent oxidative molecule.

3) Phagocytic Oxidative Burst:
Phagocytic cells, including neutrophils and macrophages, utilize ROS as part of the oxidative burst to eliminate pathogens. In obesity-associated inflammation, these cells generate ROS during phagocytosis (54). The

respiratory burst complex of phagocytes, including NOX, produces ROS to destroy engulfed particles. Activated NOX generates ROS within the phagosome (55). The primary ROS produced is O^{2-}. Superoxide is highly reactive and can directly damage pathogen components like lipids, proteins, and DNA. Superoxide is rapidly converted into other ROS, including H2O2, through enzymatic reactions facilitated by superoxide dismutase (SOD). H2O2 in adipocytes can further activate PKC and NOX (56) and generate other potent ROS, such as hydroxyl radicals (OH-), through reactions with transition metals. Apart from NOX-mediated intracellular ROS production, evidence suggests that the mitochondrial respiratory chain serves as the primary source of cellular ROS, contributing to heightened oxidative stress and inflammatory processes in obesity (53). This phagocytic oxidative burst contributes to local oxidative stress and cellular damage.

POSITIVE FEEDBACK LOOPS

Table I provides an overview of the primary molecular mechanisms involved in oxidative stress and ROS-mediated inflammation, particularly relevant to obesity-related chronic inflammation. Key signaling pathways, such as NF-κB activation, inflammatory gene expression, and DAMP-mediated immune responses, are highlighted to demonstrate how oxidative stress can perpetuate inflammatory cycles.

ROS initiates pro-inflammatory pathways, triggering the release of cytokines, while immune cells generate ROS as part of their defense mechanisms, further amplifying the inflammatory response. Figure 3 further simplified the intricate molecular connection which contributes to the chronic low-grade inflammation and oxidative stress characteristic of obesity.

Table I: Key Mechanisms and Molecular Pathways in ROS-Mediated Inflammation and Oxidative Stress

Mechanism/ Pathway	Key Molecules	Descriptions
ROS-Mediated NF-κB Activation	ROS, NF-κB, IKK, IκB	ROS activates IKK, which phosphorylates IκB, leading to its degradation and the release of NF-κB. NF-κB then translocates to the nucleus, activating genes for inflammation (29-36).
Inflammatory Gene Expression	NF-κB, IL-1β, TNF-α, IL-6, MCP-1, ICAM-1	NF-κB activation upregulates pro-inflammatory genes, including those for cytokines (IL-1β, TNF-α), chemokines (MCP-1), and adhesion molecules (ICAM-1), driving immune cell recruitment (37-38).
Hyperglycemia-Induced Oxidative Stress	ROS, NF-κB, AP-1, AGEs	Elevated glucose levels promote ROS production, activating NF-κB and AP-1, leading to inflammation associated with obesity-related conditions and hyperglycemia (39).
DAMPs Release	HMGB-1, ATP, Uric Acid Crystals, Heat Shock Proteins	DAMPs are released from damaged cells, signaling immune cells through PRRs to initiate inflammatory pathways such as NF-κB activation (41-43).
PRR Activation by DAMPs	PRRs (e.g., TLRs, NLRs), NF-κB	DAMPs bind to PRRs on immune cells, activating intracellular inflammatory signaling (e.g., NF-κB and MAPK), leading to cytokine production and immune cell recruitment (44-48).
Oxidative Damage and Chronic Inflammation	MAP Kinases (ERK, JNK, p38), iNOS, NF-κB	Chronic oxidative damage triggers inflammatory kinases, such as MAPK, which activate NF-κB and amplify inflammation, contributing to tissue damage in chronic diseases (49-51).
Inflammatory Amplification by ROS	NOX, iNOS, IL-1β, IL-6, NO, $ONOO^-$	Activated immune cells release ROS via NOX, amplifying inflammation through a feedback loop that increases cytokine production and further ROS generation (52-53).
Phagocytic Oxidative Burst	NOX, SOD, ROS, Superoxide, H_2O_2	Phagocytes generate ROS, including superoxide, which is further converted to H_2O_2, intensifying local oxidative stress and inflammation (53-56).

This summary emphasizes the complex interplay between ROS, inflammatory mediators, and immune cells, underscoring the role of oxidative stress in amplifying inflammation and contributing to chronic disease pathogenesis.

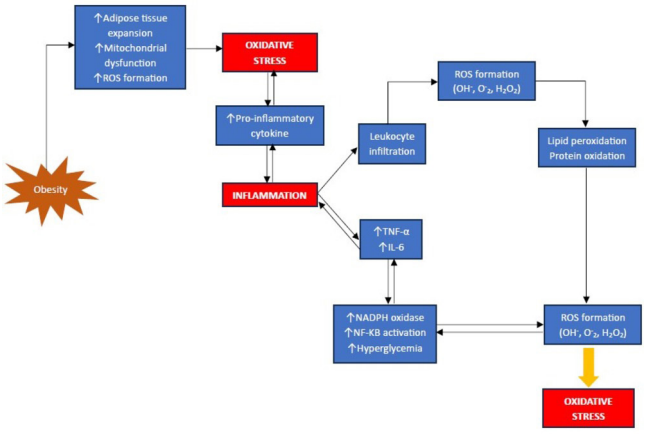

Figure 3: Bidirectional relationship between oxidative stress and inflammation. Obese individuals experience an elevated pro-inflammatory response and the infiltration of white blood cells, which leads to the production of reactive oxygen species (ROS) and ultimately causes oxidative stress.

IMPLICATIONS FOR HEALTH: THE CASCADE OF CONSEQUENCES

The synergy between oxidative stress and inflammation in obesity has profound health implications and is a driving force behind the development of obesity-related complications. These implications can be broadly categorised into metabolic disruptions, cardiovascular consequences, and accelerated ageing.

Chronic inflammation, fueled by oxidative stress, directly interferes with insulin signaling pathways, contributing to insulin resistance. Inflammation impairs cells' ability to respond to insulin, leading to compromised glucose uptake and metabolism. This insulin resistance is a pivotal factor in the development of type 2 diabetes, a common comorbidity of obesity.

Other than that, the interplay of oxidative stress and inflammation significantly elevates the risk of cardiovascular diseases (CVD) in obese individuals. Inflammation promotes the formation of atherosclerotic plaques within arteries, a process exacerbated by the oxidative modification of low-density lipoprotein (LDL) cholesterol. This vicious cycle leads to the development of atherosclerosis, endothelial dysfunction, and, ultimately, an increased risk of heart attacks and strokes.

Lastly, oxidative stress-induced cellular damage plays a crucial role in ageing. DNA damage, telomere shortening, and impaired cellular function contribute to cellular senescence, an irreversible cell cycle arrest state. This premature ageing at a cellular level can lead to a range of age-related diseases, including neurodegenerative disorders and cancer.

INTERVENTIONS

Understanding the dynamic relationship between oxidative stress and inflammation in obesity has significant implications for therapeutic interventions and preventive strategies. Natural products are increasingly recognized for their therapeutic potential in obesity management, largely due to their bioactive compounds that support lipid metabolism while also providing antioxidant and anti-inflammatory effects.

For instance, a clinical trial found that green tea extract, abundant in catechins, promoted fat oxidation and reduced body weight in overweight subjects while simultaneously decreasing levels of malondialdehyde, an oxidative stress marker, indicating its antioxidant efficacy (12). In another study, an antioxidant-rich Tamarindus indica L. leaf extract has been shown to reduce high-fat diet-induced obesity in rats through modulation of gene expression (57) . Animal studies have also demonstrated that curcumin, a polyphenol derived from turmeric, effectively modulates inflammation in obesity. Curcumin supplementation in high-fat diet-induced obese mice not only lowered body weight but also reduced pro-inflammatory cytokines such as TNF-α and IL-6 in adipose tissue, illustrating its dual anti-inflammatory and anti-obesity potential (58). Another study using resveratrol, a natural compound found in grapes, as a treatment in obese diabetic mice, showing that resveratrol supplementation significantly lowered oxidative stress markers and improved insulin sensitivity, which suggests its role in mitigating obesity-associated oxidative damage and inflammation (59). Ginsenosides in ginseng, through a study, have shown to reduce lipid peroxidation and inflammatory cytokines in obese rats, which helped decrease body fat accumulation and improved lipid metabolism (60).

A study has also investigated the effects of honey supplementation on body weight and metabolic parameters in high-fat diet-induced obese rats. The results demonstrated that honey reduced weight gain, improved lipid profiles, and lowered oxidative stress markers, such as malondialdehyde, while increasing antioxidant enzyme activities, including superoxide dismutase and glutathione peroxidase (61).

Gut microbiome and obesity

The intricate relationship between gut microbiome composition and obesity has emerged as a captivating frontier in metabolic research. Numerous studies have revealed distinctive alterations in the gut microbiota of individuals with obesity, reshaping our understanding of this complex condition. Among the hallmark changes, dysbiosis is one of the phenomena associated with disrupted metabolic equilibrium in obesity.

This dysbiosis often manifests as an imbalance in the relative abundance of bacterial phyla, notably an elevation in Firmicutes and a decrease in Bacteroidetes (62). This dysregulation is not merely an esoteric shift; it exerts tangible effects on metabolism, inflammation, and adipose tissue function, thus fundamentally contributing to the pathophysiology of obesity. The obesity-associated gut microbiome can mechanistically drive enhanced energy extraction from the diet, predisposing individuals to weight gain. Fermentation of complex carbohydrates produces short-chain fatty acids (SCFAs), signalling molecules that exert both metabolic and immunomodulatory effects. SCFAs do play an essential role in the development of obesity. In a study with diabetes-induced rats, SCFAs engage with adipose tissue by utilising two G-protein-coupled receptors in adipocytes, namely Gpr41 and Gpr43 (63). In another study, SCFAs also reduce the production of appetite-suppressing hormones such as leptin, peptide YY, and glucagon-like peptide 1 (64). This stimulation encourages the creation of adipocytes and hinders the breakdown of lipids.

Furthermore, the altered composition can cause the production of pro-inflammatory molecules, resulting in chronic low-grade inflammation—a defining feature of obesity-linked metabolic disturbances. This inflammatory environment intersects with insulin resistance and adipose tissue dysfunction, leading to a complex web of physiological disruptions that promote obesity-related complications.

CONCLUSION

Excessive ROS production in obese individuals is often linked to increased fat mass, especially in adipose tissue. Fatty tissue in obese individuals undergoes hypertrophy and hypoxia, which exacerbates oxidative stress. As a result, the oxidative burst and subsequent ROS production become chronic rather than a transient response to pathogens.

Low-grade, chronic inflammation is sustained by the

persistent generation of ROS in adipose tissue, which encourages the activation of inflammatory pathways. By stimulating immune cells' PRRs, stressed or damaged adipocytes generate DAMPs, exacerbating inflammation. Consequently, pro-inflammatory cytokines like TNF-α, IL-6, and MCP-1 are continuously produced due to the ongoing activation of NF-κB and other inflammatory signalling pathways.

The metabolic syndrome and type 2 diabetes, which are frequently linked to obesity, are characterised by insulin resistance, which is exacerbated by this persistent inflammatory state. Chronic inflammation and oxidative stress also have a role in the development of comorbidities associated with obesity, such as fatty liver disease and cardiovascular disorders.

The intricate connection between oxidative stress, inflammation, and obesity can be better understood by considering ROS's function in modulating inflammation. Potential paths for reducing the chronic inflammation linked to obesity and enhancing metabolic health outcomes include therapeutic approaches that target ROS generation, antioxidant defenses, and inflammatory pathways. Investigating the gut microbiome's composition offers a multifaceted lens through which we can understand the intricate pathology of obesity.

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