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Mechanisms of Endothelial Dysfunction in Obesity: A Mini-Review

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Abstract

Obesity is associated with excess accumulation of macronutrients on the adipose tissue, can facilitate the synthesis and secretion of inflammatory biomarkers. Inflammatory markers in turn suppress the secretion of adiponectin and initiate the proinflammatory state. Endothelial cells synthesise bioactive substances that maintain the integrity of the blood vessels through constant regulation between pro-inflammatory and anti-inflammatory, proliferative and anti-proliferative markers of vascular smooth muscle cells. They also maintain the balance between the oxidants and antioxidative substances, vasodilators and vasoconstrictors of the endothelium, coagulation and fibrinolytic systems. However, during obesity, these delicate metabolic balances are altered, which may have great influence on endothelium, a condition characterized by atherosclerotic plaque formation. Endothelial dysfunction forms the basis of this discussion since it was recognized to be the major contributor of cardiovascular complications during obesity. Modification of the inflammatory markers and control of obesity will help to alleviate obesity-related complications linked to cardiovascular diseases.

Keywords: Obesity; Inflammation; Atherosclerosis; Endothelial dysfunction

Introduction

Over 1.9 billion individuals were recorded to be obese or overweight worldwide, with estimated figures of 50 million children within 5 years of age that were identified [1]. The increased in the incidence of obesity and overweight is believed to be associated with the modification in lifestyle and physical inactivity [2]. Obesity is described as a low-grade chronic inflammation characterized by several types of chronic conditions, including cardiovascular diseases (CVDs), diabetes mellitus (DM), hypertension, non-alcoholic fatty liver diseases (NAFLD), hypercholesterolaemia, asthma, arthritis, some malignancies, and generally poor hygiene [3]. Normally, the endothelium maintains the balance between the secretion of constricting and endothelial-derived relaxing agents. Changes in this critical balance promote the endothelium to the proatherogenic and prothrombotic states, facilitated through platelets activation and adhesion, leukocytes adherence, vasoconstrictions, inflammation, oxidations, mitogenesis, coagulation and fibrinolytic disturbances, atherosclerosis, and thrombosis predisposition to CVDs [3]. The inability of the adipose tissue during obesity, to effectively regulate the ingested fat, results to excessive fat deposition at the delicate organs, such as the heart, kidney and liver, leading to metabolic disorders. Endothelial dysfunction (ED) is initiated by the imbalance between the secretions of vasodilators, including nitric oxide (NO), endothelial-derived hyperpolarizing factors (EDHF), prostacyclin (PGI2), and vasoconstricting agents, such as prostaglandin (PGH2), endothelin-1 (ET-1), and angiotensin-II (Ang-II) [3]. This mini review summarizes the molecular mechanisms through which adipose tissues secretion during obesity influences endothelial dysfunction. Knowledge of the basic mechanisms associated with ED in obesity is required for an efficient therapeutic program to control and prevent obesity-induced endothelial dysfunction.

Impact of Obesity on Adipose Tissue

The adipose tissues are mostly the collections of pre-adipocytes, adipocytes and few leukocytes. However, in obesity, the activities and composition of the adipose tissues are distorted. High energy consumption without balanced utilization leads to adipocytes hypertrophy. Adipocytes hypertrophy modifies the balanced between the adipose tissue-derived cytokines and adipokines, leading to pro-inflammatory state and eventual adipocytes cellular abnormality [4]. Inflammation of the adipose tissues is associated with the infiltration of the immune cells, such as macrophage, neutrophil, and B- and T-lymphocytes. Adipose tissues infiltration by the macrophages is the keystone contributing to the progress and development of endothelial dysfunction (Figure 1) [5].

Obesity Promotes Vascular Endothelial Dysfunction: The Molecular Mechanisms

The endothelium regulates the proliferation and migrations of vascular smooth muscle cells (VSMC), cellular and vascular adhesions [6]. Endothelium inhibits platelet adhesion and aggregation by the secretions of PGI2 and NO through ecto-adenosine diphosphate (ADP)-ases and prostaglandin E2 (PGE2) induced by glycosaminoglycans on the surfaces of the endothelial cells. However, during obesity, this crucial balance is altered, facilitating the progress to ED and subsequent end organs damage [7]. Endothelial dysfunction results due to an imbalance between the secretions and system

utilization of vasodilating and vasoconstricting factors, which predisposes the vascular endothelium to prothrombotic and pro-atherogenic states. The major contributing agents include insulin resistance (IR), oxidized LDL (oxLDL), adipose tissues-associated inflammation, increased ROS, human gut microbiota and reduced NO bioavailability.

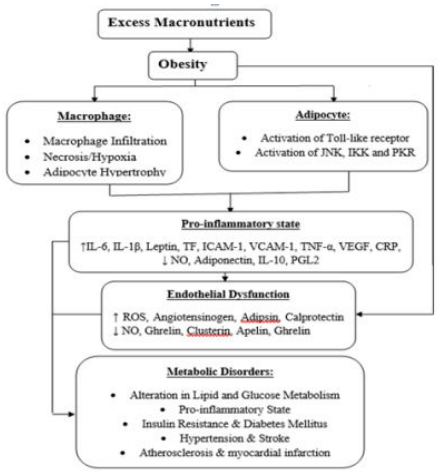

Figure 1: Complications in Obesity. Obesity pronounced the deposition of excessive nutrients on the adipose tissue, which facilitates the secretions of inflammatory markers. This predisposes the endothelium to a pro-inflammatory state, leading to ED. ICAM-1; intracellular adhesion molecules-1, VCAM-1; vascular cells adhesion molecule-1, ROS; reactive oxygen species, IL; interleukins, JNK; c-junk N-terminal kinase, VEGF; vascular endothelial growth factor, IKK; inhibitor of k kinase, PKR; protein kinase R, CRP; C-reactive protein, TNF-α; tumour necrotic factor-α. (Modified from Kwaifa et al., 2020).

Reactive oxygen species (ROS) induce endothelial dysfunction

ROS are generated due to an imbalance between the body's production of prooxidative and antioxidative agents, which could lead to platelets aggregation, formation of thrombus and subsequent endothelial dysfunction [8]. Obesity is characterized by increased generation of oxidative stress radicals and high secretion of NEFAs, TNFa, CRP, IL-6, TNF-α, and LDL cholesterol. ROS initiates Ox-LDL formation, which contributes significantly to the progress of atherosclerotic lesions. Adipocytes hypertrophy induces lipids peroxidation, that eventually promotes the formation of ROS, especially, the aldehyde species (4-hydroxyalkenals), derived from polyunsaturated fatty acids. The peroxidation of non-enzymatic ω-3 PUFAs, including α-linolenic acid, eicosatetraenoic acid, and docosahexaenoic acid have been identified to promote 4-HHE generation. More importantly, various free radicals, including hydrogen peroxide (H_2O_2), oxide radical (O-), superoxide radical (SO-), and the level of 8-oxo-deoxyguanosine (8-oxodG) were reported to be elevated in VSMCs and macrophages, which have significant contributions to endothelial dysfunction [9].

Obesity promotes atherosclerosis

During obesity, LDL enters the vascular endothelium and binds to proteoglycans through apolipoprotein B100 and remains within the sub-endothelial spaces [10]. The LDL is oxidized to Ox-LDL by ROS. This activates many pro-inflammatory markers through the action of lectin-like oxidized LDL receptor-1 (LOX-1). Activation of ICAM-1 and VCAM-1 by ox-LDL increases monocytes and other inflammatory cells adhesion molecules in the endothelium [5]. Monocytes are transformed to macrophages and express several related markers, including the scavenger receptors (SRs), CD36, LOX-1, and Toll-like receptors (TLRs). The retention of macrophage together with macrophages SRs facilitates ox-LDL uptake and generation of foam-cells [11,12]. Also, the retention of ox- LDL in the endothelium leads to inflammatory progression and foam cell apoptosis. Ox-LDL also promotes the mobilization of PDGF and basic fibroblast growth factor (bFGF) for the proliferation of the SMCs. The initial proliferation of the SMC promotes the thickening and atherosclerotic plaques formation, and subsequent necrotic core formation. The Ox-LDL–CD36 complex then binds to resting platelets and induce platelets activation and aggregation. The activated platelets express LOX-1 to stimulate endothelial cell adhesions and endothelin-1 release, leading to endothelial dysfunction.

Vascular aging and cellular senescence during obesity promote endothelial dysfunction

Cellular senescence has been recognized as one of the mechanisms that contribute to the progress of several metabolic conditions, including obesity and type-2 diabetes. It ensures that the damaged cells are removed through the activation of the immune system. However, during natural ageing and other metabolic conditions, senescent cells are accumulated, possibly due to the failure of the ageing immune system to remove them [13]. Although cellular senescence is a defensive mechanism to prevent tumorigenesis, its manifestation in adipose tissue facilitates defective adipogenesis, inflammation, aberrant adipocytokines production and insulin resistance, leading to adipose tissue dysfunction [14]. Obesity is a metabolic condition well-known to develop due to excessive accumulation of senescent and abnormal adipose tissues associated with systemic inflammation. Adipose tissue from obese individuals exhibits increased oxidative stress and telomere shortening, which are considered to activate and facilitate adipose tissue senescence. Deposited intracellular ROS activates p38 mitogen-activated protein kinases (MAPKs), which subsequently induces p53-p21CIP1/WAF1-dependent senescence. Telomeres act to regulate the replication of cells. Telomere shortening and losing trigger DNA damage, which has a profound effect on the endothelial cells. Adipocytes hypertrophy during obesity is reported to cause increased cellular senescence markers, such as adipose tissue β-galactosidase, p53, cyclin D kinase inhibitors, PAI-1 and p16Ink4a. Also, accumulation of non-dividing senescent cells within the adipose tissues was identified during advanced ageing [15]. Vascular endothelial cells essentially regulate adipose tissues lipid metabolic activity, but its functions gradually diminished during ageing and obesity. Induction of cellular senescence is believed to be among the mechanisms that promote endothelial dysfunction. Study on Immunofluorescence indicated that endothelial cells show an elevated secretion of the senescent γ-H2AX marker in obese human, mediated by VEGF. The alteration of lipid metabolisms in senescent endothelial cells might explain the declined activation of peroxisome proliferator-activator receptor γ (PPARγ) [14].

Vascular calcification in obesity and endothelial dysfunction

Vascular calcification (VC) referred to the accumulation of calcium phosphate in the intima or media of arterial walls and was considered as a risk factor for CVDs (Figure 2). Obesity has been considered to promote arterial calcification, through which VSMCs would be transformed into osteoblast-like cells. Even Though the senescent cells are attributed with NF-kB activations and increased ROS, it could be considered that induction of senescent state is the initial mechanism that promotes vascular calcification and subsequent endothelial dysfunction in obesity [16]. VC is characterised by vascular remodelling due to dedifferentiation of VSMC, modifications of elastin, collagen, and endothelial functions. During vascular calcification, the atherosclerotic process begins from the fatty streaks at an early age and progress to young adults. This might eventually progress to calcified lesions and subsequent atherosclerotic plaques. Many researchers have demonstrated the connection between ROS formation, especially the H_2O_2, and the development of vascular calcification [17].

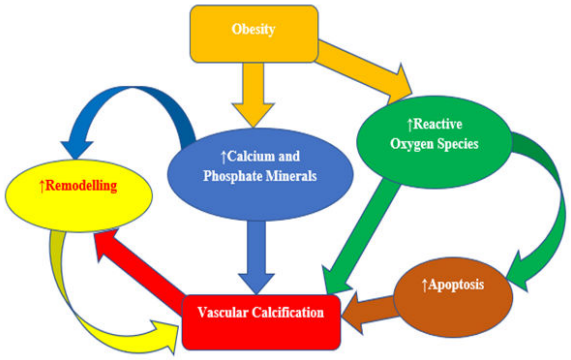

Figure 2: Mechanisms of Vascular Calcification in Obesity: Obesity is characterized by increased calcium phosphate production, increased ROS production, apoptosis, and osteogenic programming, which stimulate VSMC dedifferentiation, thus modulating vascular remodelling, and subsequent vascular calcification. VC promotes elastocalcynosis that causes the rapture of the elastin fibres and favours vascular remodeling.

Contributions of human gut microbiota to vascular endothelial dysfunction

Human gut microbiota (HGM) is a group of bacteria confined to the gastrointestinal tracts and are commonly found greatly in obese patients. Various studies have identified the contributions of human gut microbiota to the progress of atherosclerosis predisposition to endothelial dysfunction. HGM stimulate inflammation processes through the secretions of microbial proteins [18]. Previous reports have investigated the implications of gut dysbiosis to the progress and development of atherosclerosis, leading to CVD. HGM utilizes energy from the dietary fibre by the fermentation process and produces short-chain fatty acids (SCFAs) to enhance lipid metabolisms. Furthermore, recent reports have also shown that the gut microbiota activities on high-fat diet contribute to obesity while a fibre-rich diet has therapeutic ability to lower the risk of obesity [19,20]. Gut microbiotas, particularly the gut dysbiosis has been shown to participate in the progress and development of several types of diseases, such as CVDs, obesity, T2DM, NAFLD, and other forms of cancers [21].

Epigenetic modifications and vascular endothelial dysfunction

Epigenetic modifications, including histone acetylation and DNA methylation, are recognised as post-replication changes within the chromatin that did not affect the basal nucleotide code [22]. These modifications are sometimes useful, especially, in regulating genes expression and silencing. Epigenetic modifications are associated with several age-related diseases, such as atherosclerosis [23]. Thus, epigenetic modifications are employed to study vascular endothelial activities during cellular senescence [22]. Histone acetylation and deacetylation are recognized to participate greatly in the development of atherosclerosis during ageing and obesity, by which inflammations, VSMC proliferation, and ECM compositions can be modified [23].

Clinical Approaches to Endothelial Dysfunction

The endothelium is characterized by its regulatory capacity, through its terminal differentiating cells which control its proliferative activities. Thus, its damage- repair mechanism is accomplished by the influences of the endothelial progenitor cells (EPCs) within the circulation [24]. Drugs with lipids lowering properties, including statin were shown to contribute significantly in controlling and prevention of obesity-related endothelial dysfunction. Repeated Intravenous injection of glucagon-like peptide-1 (GLP-1) has been demonstrated to show therapeutic potentials on endothelial dysfunction. Physical activity together with lifestyle modifications were recognised to drastically reduce the levels of inflammatory markers associated with endothelial dysfunction in obesity [25]. Other drugs with both anti-inflammatory and anti-oxidative activities, including Paraoxonase-1 were reported to promote the synthesis of HDL-Mediated eNOS, that suppresses myeloperoxidase inflammatory processes within the endothelium [26]. Modern antioxidant therapy geared at decreasing the levels of radicals generated during lipid peroxidation and neutralization may reduce obesity-related inflammations and normalize adipose tissues activity during obesity.

Conclusion

Obesity contributors significantly to the progress and development of vascular endothelial dysfunction predisposing to CVDs. The imbalance between the circulating pro-inflammatory and anti-inflammatory mediators could promote vascular endothelial dysfunction during obesity. Knowledge of the mechanisms of endothelial dysfunction in obesity will create insight in the prevention and control of obesity-associated endothelial dysfunction.

Author Contributions

S.M.N. designed the study, S.M.N., H.B., and Y.K.Y. reviewed and edited the manuscript while I.K.K. wrote the manuscript.

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Conflict of Interest

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