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REVIEW / DERLEME

Mitophagy and Obesity

Mitofaji ve Obezite

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ABSTRACT

Overfed and high-fat diets lead to many metabolic changes such as deterioration in energy homeostasis and aerobic respiration, increase ROS (reactive oxygen species) products, and inflammation status in obesity. Obesity-mediated occurred oxidative stress and low-level chronic inflammation can result in impaired mitochondrial homeostasis, which has been involved in the pathophysiological of metabolic syndrome-related diseases such as Type 2 Diabetes Mellitus. The mitochondria organelle plays an effective role in energy and calcium homeostasis, cell metabolism, and even cancer cell metabolism. Mitophagy known as a mitochondrial-recover operation has been thought as a critical factor in supporting mitochondrial hemostasis, which can make a great contribution to recovery from cellular abnormalities in obese patients. This review's aim is to ensure a current and comprehensive summary of the role of developing mitochondrial-related dysfunction and protective effect of mitophagy in the pathophysiology of obesity.

Keywords: Obesity, Mitophagy, Mitochondrial Dysfunction, Adipose Tissue

ÖZ

Obezitede aşırı beslenme ve yüksek yağlı diyetler, enerji homeostazında ve aerobik solunumda bozulmalara, reaktif oksijen türlerinin (ROS) üretiminde artışa ve inflamasyon durumu gibi bir çok metabolik değişikliğe sebep olmaktadır. Obezite aracılı meydana gelen oksidatif stres ve düşük seviyeli kronik inflamasyon, Tip 2 Diabetes Mellitus gibi metabolik sendromla ilişkili hastalıkların patofizyolojisinde rol oynayan mitokondriyal homeostazın bozulmasına neden olabilir. Mitokondri organeli enerji ve kalsiyum homeostazında, hücre metabolizmasında hatta kanser metabolizmasında etkin rol oynamaktadır. Mitokondriyal operasyonu olarak bilinen mitofaji, obez hastalarda mitokondriyal hemostazın korunmasına ve hücresel anormalliklerin iyileşmesine büyük katkı sağlayan kritik bir faktör olarak düşünülmektedir. Bu derlemenin amacı, obezite patofizyolojisinde mitokondriyal disfonksiyon gelişiminin ve mitofajinin koruyucu etkisinin güncel ve kapsamlı bir özetini sunmaktır.

Anahtar Kelimeler: Obezite, Mitofaji, Mitokondriyal Disfonksiyon, Yağ Dokusu

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INTRODUCTION

Obesity has an epidemiological profile with a major trend worldwide and is characterized as abnormal weight gain or excessive overfat accumulation that may harm health, resulting from impaired energy hemostasis (1). Considering the increase in obesity prevalence from an evolutionary perspective, increasing the fat and sugar content in the diet and adopting a sedentary lifestyle are considered, obesity is multifactorial, which is due to genetic causes as well as environmental factors (2). Increasing adipose tissue in obesity occurs critical and different changes such as oxidative stress, low-level inflammation, mitochondrial dysfunction, apoptosis, insulin resistance (IR), glucose intolerance, and dyslipidemia (3). Furthermore, obesity plays an important role in the development of serious diseases such as Type 2 Diabetes Mellitus (T2DM), heart diseases, atherosclerosis, coronary artery disease, hypertension, and even some types of cancer (4). The World Obesity Federation reported that obesity is approved an epidemic and is accepted as a significant public health issue facing that is correlated with a grown risk of mortality rate and morbidity rate around

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the world (5). Obesity leads to inflammation in related to a progressive increase in reactive oxygen species (ROS) and oxidative stress in adipose tissue. Moreover, İncreasing inflammation can result in mitochondrial imbalance and mitochondrial dysfunction (6,7). Mitochondria play an effective role in fuel and energy hemostasis and all cell metabolism, including, beta-oxidation of fatty acids, adenosine triphosphate (ATP) synthesis from nutrition substrates, ROS, amino acid metabolism, iron metabolism, heme and steroid hormone process, and calcium metabolism (8,9). In addition, the mitochondrial respiratory chain complexes are related to the synthesis and elimination of ROSs during ATP production in mitochondria. The mitophagy pathway is described as a system controlling mitochondria function and content (1,10–14). We discuss the features of pathophysiological changes in adipose tissue and how trigger mitochondrial dysfunction by focusing on the role of mitophagy.

Inflammation in Adipose Tissue

Adipose tissue plays an effective and critical role in fuel metabolism for energy hemostasis and is considered an important endocrine organ. Consuming excessive calories causes adipocyte hypertrophy and hyperplasia, which leads to dysfunctional adipose tissue formation in obesity (6,15). Adipose tissue secretes several bioactive mediators described as pro-inflammatory cytokines, (as well as it is called adipocytokine or adipokines) and it serves both as controllers of the metabolism and immunomodulatory properties (11,16).

In obesity, there are several mechanisms triggering low-level chronic inflammation of the adipose tissue. Increased accumulation of fatty acid causes adipocyte hypertrophy and impaired bloodstream by triggering the production of proinflammatory cytokines, particularly via the nuclear factor kappa B (NF-κB) signaling pathway. As well as enlargement of the volume of infiltrated macrophages causes synthesis of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), adiponectin, visfatin, interleukin-1β (IL-1β), and interleukin-6 (IL-6), in adipocytes that are secreted from infiltrated macrophages that lead to the process described as low-grade chronic inflammation (7,17,18). Low-level chronic inflammation in the long-term may turn into chronic systemic inflammation and lead to the occurrence and advancement of metabolism-related disorders, such as IR, hyperlipidemias, hypercholesterolemia, T2DM, cardiovascular diseases, and atherosclerosis (10–12).

Tumor Necrosis Factor-alpha (TNF-α) leads to lipolysis, which causes the release of saturated free fatty acids that are capable of binding Toll-like receptor 4 on both the adipocyte and the infiltrated macrophages leading to NF-kB activation and secretion of IL-1β and IL-6 via macrophages (as seen in Figure 1). Moreover, TNF-α and IL-1β increase impairs the insulin signaling pathway and may lead to the development of IR. Then, this process is attended by the adipocyte release of monocyte chemoattractant protein–1 (MCP-1) resulting in macrophage aggregation and activation (10).

Consequently, both impaired insulin signaling pathways and increased lipolysis prevent insulin-responsive glucose transporter (GLUT-4) translocation across the plasma membrane and glucose uptake and lead to glucotoxicity and lipotoxicity (19,20). The decrease in glucose oxidation and oxidative phosphorylation (TCA) leads to reduced electron flow during the electron transport chain (ETC), which trigger electron outflow toward oxygen and production of ROS such as superoxide, hydrogen peroxide, and hydroxyl ions followed by oxidative stress (9,21).

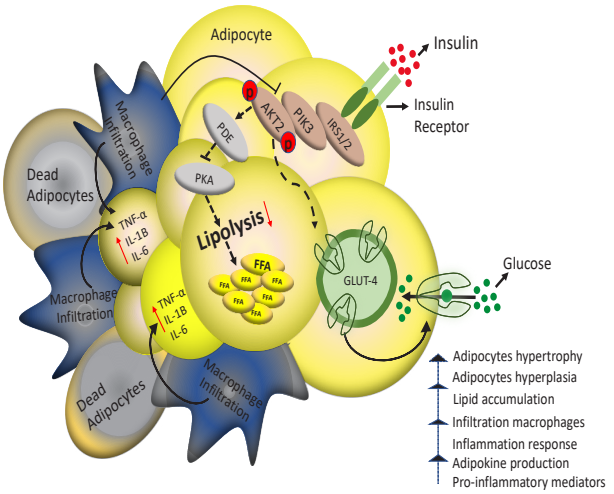

Figure 1. Overfed and a high-fat diet leads to inflammation in obesity. PKA: Protein kinase A, FFA: Free fatty acids, GLUT4: Glucose transporter 4, IRS1/2: Insulin receptor substrate 1/2, PDE: Phosphodiesterase, AKT2: Protein kinase B, PIK3: Phosphoinositide-3 kinase, PKA: protein kinase A

Oxidative Stress and Mitochondrial Dysfunction in Obesity

The antioxidant defense system can both decrease ROSs levels and enhance control of cell damage. The antioxidant defense mechanisms consist of enzymatic (e.g., glutathione peroxidase enzymes, catalase, and superoxide dismutase) and non-enzymatic (e.g., products from nutrients such as vitamins, carotenoids, uric acid, and polyphenols) (21,22).

ROSs are necessary side-products to fuel metabolism in mitochondria that trigger oxidative damage in nuclear DNA, mitochondrial DNA (mtDNA), and bioactive molecules such as nucleic acids, lipids, and proteins, with resulting inhibition of these bioactive molecules' bio-physiologic function. However, if ROSs production overcomes cellular antioxidant defense system capability oxidative stress arises and lead to damage in mtDNA and decreases the rate of beta-oxidation (23–26). Moreover, increased ROS production and oxidative stress can cause mitochondria damage and mitochondrial changes, which is called mitochondrial dysfunction. The different factors have been efficient in the development of mitochondrial dysfunction (as shown in Figure 2). Bonnard et al. found that excessive ROS production in muscle tissue of mice fed a high-fat diet (HFD) and a high-sucrose diet (HSD) caused mitochondrial dysfunction (27). Chattopadhyay et al. showed that increased mitochondrial ROSs production may contribute to developing mitochondrial dysfunction that leads to IR and T2DM in the adipose tissue of patients with diabetic obesity (28).

Lipotoxicity is described as a hepatocellular damage response triggering over products of lipid oxidation products such as triglycerides, free fatty acids, and diacylglycerol. Lipotoxicity causes inhibition of insulin signaling through reduction of GLUT4 transporters on the surface of the liver and skeletal muscle tissue membranes (12).

The maintenance of endoplasmic reticulum (ER) function in insulin-secreting pancreatic beta-cells is important. ER stress plays a critical role in development of metabolic aberrancies that cause occur of mitochondrial dysfunction such as abnormal insulin signaling and an abnormal increase of gluconeogenesis in liver tissue (29). Glucotoxicity is defined as the detrimental impact of blood circulating elevated hyperglycemia and excess glucose uptake on cells connected with insulin. Recent studies showed that increased lipotoxicity and glucotoxicity could induce a signal pathway called unfolded protein response in ER membrane and cause mitochondrial dysfunction (30,31).

Impaired fatty acid oxidation and glucose oxidation may be derived from metabolic derangement, which is mostly defined as changed fuel metabolism switching and energy dysregulation together with emergent mitochondrial dysfunction (32). Consequently, these situations may induce both ectopic lipid accumulation and the development of ROS in mitochondria, leading to mitochondrial damage, and its elimination by mitophagy pathways (as shown in Figure 2). Rong et al. showed that mitochondrial fusion and fission processes are reduced in adipose tissue of mice fed HYD (33). The other studies also presented that reduced capacity of mitochondrial oxidative phosphorylation capacity and ATP production enhanced mitochondrial dysfunction in adipocytes (34,35).

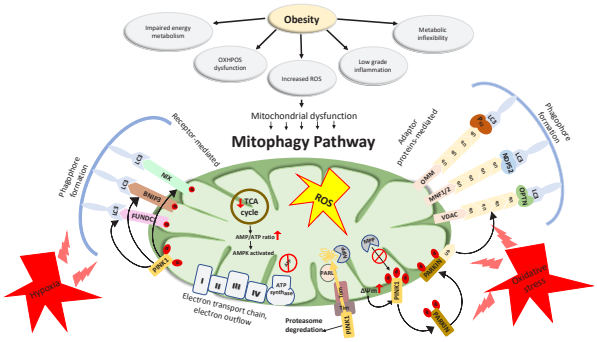

Figure 2. Mitophagy pathway in obesity-related pathologies.

Different factors have been efficient in the development of mitochondrial dysfunction such as impaired energy metabolism, increased production of ROS, occurred oxidative stress, metabolic inflexibility, a situation of low-level chronic inflammation in obesity. Consequently, these factors result in impaired mitochondrial membrane potential and lead to activating of mitophagy pathways.

There are two ways for inducing mitophagy such as hypoxia and oxidative stress. Ubiquitin-dependent PINK1/Parkin-mediated mitophagy pathway (adaptor protein-mediated) is triggered by oxidative stress. Ubiquitin-independent (receptor-mediated) mitophagy pathway is triggered by hypoxia.

Mitophagy and Obesity

Mitophagy also described as mitochondrial autophagy is an adaptive response that includes selective removal of dysfunctional or defective mitochondria via autophagy-related vesicles and lysosomal-dependent degradation. Mitophagy is a necessary process to disposing of detrimental effects of increased levels of ROSs under prolonged hypoxia and inflammation, thereby it is essential in the regulation of mitochondrial quantity and quality control in cells (1,14). The studies reported that mitochondrial autophagy plays a critical role in the elimination of mitochondrial dysfunction in pancreatic beta-cells and is requisite for mitochondria optimum function. Moreover, recent studies showed that type2 diabetes and metabolic syndrome are associated

with dysregulations of mitochondrial autophagy process (1,13,14).

There are two ways for inducing mitophagy; firstly, by an accumulation of mitochondrial defects that trigger ETC impairment, and secondly, by dissipation of mitochondrial membrane potential. The molecular mechanism of mitophagy is usually divided into two pathways (as seen in Figure 2): Ubiquitin-dependent PINK1/Parkin-mediated mitophagy pathway and Ubiquitin-independent receptor-mediated mitophagy pathway (19,36).

The most-studied pathway is mediated by the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) and the E3-ubiquitin ligase PARK2 (Parkin). PINK1 and Parkin's genes are related to autosomal recessive Parkinson's types (37). The PINK1/Parkin mitophagy pathway is activated by oxidative stress, mitochondrial dysfunction and damage (as seen in Figure 2). Under unstress and healthy mitochondrial conditions, PINK1 is replaced in intermembrane via TOM/TIM protein complex and degraded via matrix processing peptidase (MPP) and presenilin-associated rhomboid-like (PARL) protease (19). Increased oxidative stress in the cell causes disruption of mitochondrial membrane potential and inhibition of TOM/TIM complex in mitochondrial intermembrane space (14). PINK1 isn't transported to the mitochondria and accumulates in outer membrane (MOM) and this situation leads to starting Parkin activation to ubiquitination process. Active Parkin protein plays an important role as a signal to autophagy receptors optineurin (OPTN), and nuclear domain 10 protein 52 (NDP52) and leads to polyubiquitination process in MOM proteins such as mitofusin 1/2 (MFN1/2), voltage-dependent anion-selective channel 1 (VDAC), and mitochondrial fission 1 protein (FIS1). Ubiquitin activation via Parkin resulting accumulation of polyubiquitinate MOM proteins such as the autophagosome adaptor protein p62, which initiates autophagosome interactions with autophagy-related 16-like 1 (ATG16L1) complex and LC3 in MOM. The autophagy core complexes such as class III PI 3-kinase (VPS34) and unc-51 like autophagy activating kinase (ULK1/2) are the source of phagophore membrane of the ATG16L1 complex and LC3 that followed the formation of autophagosomes (14,19,38).

Mitochondrial homeostasis is necessary for a balance between mitochondrial biogenesis and mitophagy. Elongated mitophagy leads to bio-energetic setback while excess upregulation of mitochondrial biogenesis cause increased levels of ROSs and supports apoptosis. Although recent studies comprehensively revealed the role of PINK1/Parkin-mediated pathway in mitophagy, the involvement and connection of PINK1/Parkin pathway has been not enough enlightened in obesity and needs future studies. The first studies included that decreased mitochondrial content and impaired activity of mitochondrial enzymes in obese and/or T2DM patients (39,40). Recent studies mostly relate to the expression of genes and proteins associated with mitophagy in metabolic diseases (9,41–44). Wu et al. showed that PINK1/Parkin genes expression were activated and increased as in response to metabolic stress in diabetic obese mice (41). Another study reported that reduction of mitochondrial function is in relationship with IR and mitochondrial dysfunction and is accompanied by downregulation in mitofusin 1/2 (Mfn1/2) expression in skeletal muscle in obesity (9).

Furthermore, another study showed that knockout PARK2 leads to raised regulation of basal macroautophagy/autophagy flux, reduced mitochondrial respiration capacity, and upregulation of dynamin-related protein 1 (DRP1) that increases mitochondrial damage in skeletal muscle (42). Similarly, the study reported that Parkin gene knockout that regularly exercised mice increased of mitochondria amount of skeletal muscle and decreased ROSs production lead to impaired in mitochondrial respiration chain and reduced of mitochondria quality (43). Chen et al. reported that mice fed a HFD have increased gene expression of PINK1/Parkin in adipose tissue but levels of high concentrations of lipid can be inhibited gene expression of PINK1/Parkin in long term (45).

Obesity leads to hypertrophy and hyperplasia of the adipocytes in adipose tissue. Adipocyte hypertropia leads to impaired blood flow and cardiac outflow, increased local necrosis and macrophage infiltration, and proinflammatory responses that result in hypoxia and adipocyte death. Hypoxia-inducible factor-1α is defined as a transcription factor that is secreted under hypoxic conditions and causes mitophagy receptors' activation by dephosphorylation (12,14,19).

The receptor-mediated mitophagy pathway (as seen in Figure 2) is activated as an adaptive response under hypoxia conditions to remove dysfunctional or damaged mitochondria and favors mitochondrial remodeling. The proteins found in the mitochondrial membrane play a crucial role in the receptor-mediated mitophagy pathway such as FUN14 domain-containing protein 1 (FUNDC1), BCL2 interacting protein 3 (BNIP3), and BNIP3-like protein

(BNIP3L, also known as Nip3-like protein X, NIX) (38). These receptors include the conserved LC3 interacting-region (LIR) domain thereby they interact directly via LC3 and other autophagy-related proteins (ATGs) for formation of autophagosomes (14,46). The study reported that these receptor proteins can also coordinate mitochondrial fission via DRP1 by causing its localization to mitochondria (47). Greene et al. investigated how the typical western diet (WD) was affected by obesity of mitochondrial autophagy control mechanisms and found that p62 and BNIP3 gene expression levels were decreased in WD-induced obesity (48). Fu et al. showed that FUNDC1 plays an influential role as a mitophagy receptor protein in preventing HFD-induced obesity, and mitochondrial energy homeostasis is impaired and the LC3-mediated mitophagy pathway is inhibited in FUNDC1 knockout mice fed HFD (13).

CONCLUSION

Taken as a whole, the existence of low-level chronic inflammation and prolonged hypoxia conditions in obesity may lead to oxidative stress and increased ROS products, which in turn, can cause metabolic inflexibility, mitochondrial defect, mitochondrial dysfunction, and mitophagy pathway activation. The investigation of mitophagy pathway involved in obesity is a recent interest field as mitochondrial abnormalities and dysfunction are the foundation of metabolism-related diseases. The important role of mitochondria in regulating fuel homeostasis strengthens the opinion that metabolic diseases such as obesity are the most affected by mitochondrial dysfunction and damage.

Mitochondrial autophagy/mitophagy plays a crucial role in controlling the detrimental effect of mitochondrial abnormalities, hypoxia conditions, and oxidative stress by regulating mitochondrial quality and quantity. Furthermore, impairment of the mitophagy pathway can result in decreased glucose oxidation and thus aggravating lipid accumulation in fat, liver, and muscle tissue. Transcriptional regulatory mechanisms of mitophagy-related genes may be hopeful and quite target-driven therapies for metabolic diseases and for preventing age-related diseases.

In this context, more studies are needed to ameliorate obesity and better understand the mitochondrial processes of the mitophagy pathway and diet-induced mitochondrial degeneration.

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Conflict of interests

The authors declare no conflict of interests.

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