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Adipose Tissue: A Regulator for Obesity and Its Complications

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Authors' contributions

This work was carried out in collaboration between all authors. Author SR collected references and drafted the manuscript. Authors THEM and DS edited the manuscript for final submission. All authors read and approved the final manuscript.

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ABSTRACT

Adipose tissue is a key player in whole body metabolism and excess adipose tissue poses a major risk factor for the development of metabolic disorders such as type 2 diabetes. In response to nutritional overload, de novo adipocyte differentiation can serve as an adaptive mechanism by increasing the storage capacity of adipose tissue and maintaining normal adipocyte function. This in turn prevents systemic lipid overload, which is a major cause for insulin resistance. Adipose tissue is of two types; the fat storing white adipose tissue and the thermogenic brown adipose tissue. While the former is implicated in obesity, insulin resistance and diabetes, the latter is a physiological anti-obesogenic and antidiabetic through adaptive thermogenesis by uncouplers proteins. Obesity results from the imbalanced energy intake for expenditure with excessive fat accumulation in adipose tissue. Obesity is associated with numerous metabolic disorders, including hyperlipidemia, diabetes mellitus, hypertension, stroke, osteoarthritis, infertility and certain types of cancer. Obesity is associated with chronic subclinical inflammation in which the metabolism of

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adipose tissue plays an important role. The adipose tissue is an endocrine organ which has a fundamental role in metabolic, inflammatory, cardiovascular homeostatic regulation through lipogenesis, lipolysis, steroidogeneis, and secretion of several biologically active adipokines and pro-inflammatory cytokines with diverse protein structures and functions. This review article will mainly focus on the pathophysiological changes of adipose tissue fat during obesity in relation to energy expenditure towards prevention or development of obesity and its complications.

Keywords: Obesity; metabolic syndrome; insulin resistance; diabetes; adipose tissue; white adipose tissue; brown adipose tissue; adipokines; adaptive thermogenesis; uncoupler proteins; bile acids.

1. OBESITY AT GLANCE

Obesity is gaining attention as one of the major leading public health problems. The terms overweight and obesity are both labels for ranges of weight that are greater than generally considered healthy for a given height. Obesity is considered a situation of positive energy balance due to energy intake that exceeds energy consumption (surplus) leading to the storage of triacylglycerols in adipose tissue, ready to be mobilized when expenditure exceeds intake [1]. International Diabetes Federation defined obesity as a metabolic syndrome describing a cluster of factors associated with an increased risk for diabetes and atherosclerotic cardiovascular health problems. The causes of insulin resistance related to obesity are diverse. However the current modern sedentary life style, with lack of physical activity and an uncontrolled over-nutrition and genetic predisposing factors supports metabolic diseases [2]. The prevalence of overweight and obesity has also increased in children and adolescents in developing countries from 1980 to 2013 [3]. International Obesity Taskforce reported that 1.1 billion people are overweight and 312 million are classified as obese [4]. Among the global obesity prevalence, the US has attracted broad public attention as the highest officially reported prevalence of obesity [33.8%] [5] followed by European and less developed countries as a factor of over-nutrition [6]. According to World Health Organization (WHO), obesity is generally more common among women than men [7]. Although reports confirmed the higher rates of obesity in female than in males [8], studies on college students revealed higher rates of obesity in males than in females [9].

Obesity is considered a disorder of multifactorial aetiology since it is the sum of genetic, behavioral, life style and environmental factors, such as fetal programming, control of appetite, energy expenditure and availability, and nutritional content of food [10]. Obesity is commonly defined as body mass index (BMI = weight (in kg) divided by height (in m) squared) of 30 kg/m^2 or higher. This distinguishes it from being overweight as defined by a BMI of between 25-29.9 kg/m^2 (WHO, 2000). The values above this are categorized as clinically obese. Within the defined `obese' category there is further sub-division, as demonstrated in Table 1 [11].

Table 1. The body mass index (BMI) scale, highlighting the classified limits

WHO classification for Europids	BMI (kg/m^2)
Underweight	<18.5
Healthy/Lean	18.5-24.9
Overweight	25-29.9
Obese I	30-34.9
Obese II	35-39.9
Morbid Obesity	>40

2. ADIPOSE TISSUE AND OBESITY

There are different adipose tissue depots within the body. One special subclass is brown adipose tissue (BAT), which is especially developed in infants and small rodents, where it can be induced by cold exposure [12]. Brown adipocytes have many small lipid droplets, in contrast to white adipocytes, which have one large lipid core. The main function of brown adipocytes is the production of heat through expression of uncoupling-protein 1 (UCP1). It has long been believed that only children and rodents have brown adipose tissue, which is located in distinct pads adjacent to the shoulder blades. However, it has recently been shown that brown adipocytes exist in adult humans and are interspersed into the common white fat pads and might also be inducible by cold [13]. Inducing brown adipocytes by specific agents could therefore be an interesting novel therapeutic intervention to increase energy expenditure and treat obesity.

White adipose tissue (WAT) represents the majority of body fat. Based on the localization, adipose tissue depots can be classified as subcutaneous adipose tissue underneath the dermis or visceral adipose tissue within the cavities of the body. Most visceral adipose tissue lies within the abdominal cavity with the gonadal, the mesenteric and the retroperitoneal fat compartments being the most prominent [14]. This distinction is not only of anatomical interest but also has functional implications. It has been shown that visceral and subcutaneous adipose tissue show distinct gene expression patterns [15]. Furthermore, visceral adipose tissue poses a greater risk for metabolic complications than subcutaneous adipose tissue [16]. The reasons for this are currently not clear. Potential explanations include that factors secreted from the visceral adipose tissue drain directly into the portal vein or that adipocyte function itself is altered in different depots, which will be discussed further below. Due to hormonal differences, overweight women tend to have more subcutaneous adipose tissue, whereas overweight men show increased central adiposity and are thus more prone to metabolic complications [17]. Moreover, treatment with glitazones leads, amongst other things, to redistribution of fat to the subcutaneous compartment, thereby ameliorating the metabolic profile without causing weight loss [18].

In human body adipose tissue acts as an endocrine organ and plays an important role in the human metabolism [19]. It has essential metabolic functions in the body, although excess amount of adipose tissue predisposes to several metabolic complications. About 21% of adipose tissue accounts for an average man of 70 kg [20]. The excess of energy is stored in the form of triglycerides in the adipocytes in adipose tissue. Besides its obvious storage function, adipose tissue has mechanical functions such as insulation and protection against mechanical forces. Adipose tissue plays a potential role in obesity-related chronic mild inflammation by secretion of several biologically active adipocytokines (Figure 1) including adiponectin, cytokines (tumor necrosis factor-α [TNF-α], leptin, interleukin-6 [IL-6], C-C motif chemokine ligand-2 [CCL2], and chemo-attractant proteins [CCL receptor-2 [CCR2]) and other proteins with potential role in the regulation of angiogenesis or vascular homeostasis, and blood pressure (plasminogen activator inhibitor-1 [PAI-1] and angiotensinogen). Adipose tissue expresses essential substances that also regulate the carbohydrate, lipid metabolism [adiponectin and resistin], thermogenesis (uncoupling proteins [UCPs], coactivator-1α [PGC-1] and PPAR-γ) and adipogenesis (peroxisome proliferator-activated receptor-γ [PPAR-γ]) [21].

Obesity is associated with a state of chronic, low-grade inflammation characterized by abnormal cytokine production and the activation of inflammatory signaling pathways in WAT [22]. Increased inflammatory cytokines play a critical role in obesity-related inflammation and metabolic pathologies. For example, TNF-α is an important cytokine that induces the production of IL-6 [23] that is one of the major determinant of the acute phase response in the chronic inflammation and also has effects on lipid metabolism, insulin action and glucose transport [24]. Previous studies stated that reduction of adipose mass leads to decrease in the expression levels of TNF-α and IL-6 in obese individuals and animal models [24]. Additionally, TNF-α can also modulates leptin secretions whereas, reduction in body fat positively associated with decreased leptin circulating levels as wells as its gene expression [25].

In cases of lipodystrophy the majority of normal adipose tissue depots are ectopically stored in extra-adipose tissue, leading to risk for a number of diverse conditions such as hypertension atherosclerosis, cancer and insulin resistance [26]. Understanding the pathological and molecular changes in the adipose tissue in the context to obesity and related complications has become complicated. However, adipose tissue malfunction in obesity causes increased lipolysis with concomitant release of excess non-esterifed free fatty acids (FFAs) resulting in the inhibition of glucose uptake in muscle as well as suppression of hepatic glucose output, leading to insulin resistance as a secondary complications [26]. Elevated FFAs also affect the fatty acid-based signaling cascade [27], leads to the decreased vasodilatation and hypertension [28]. Furthermore, intracellular fatty acids lead to activation of inflammatory pathways [29]. Moreover, serum elevated FFAs increase risk for myocardial infarction, cardiomyopathy [30] and enhance atherosclerosis [31]. Whereas, β-cells in the pancreas suffer impaired glucose-stimulated insulin secretion for long term exposure to the elevated FFAs [32,33].

In obesity, the adipocytokines profile of adipose tissue also undergoes diverse changes apart from lipolysis. Hukshorn et al. [34] reported that

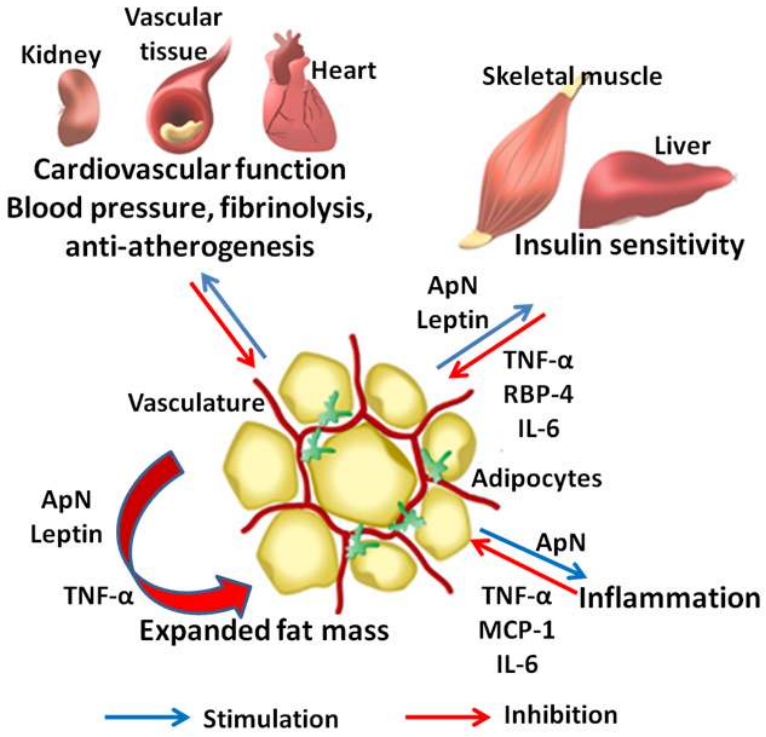

Fig. 1. Regulation of Adipokines in obesity and its complications

Adiponectin (ApN), PAI-1, plasminogen activator inhibitor type 1; AGT, angiotensinogen; TNF-α, tumor necrosis factor-α ; RBP-4, retinol-binding protein-4; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6 [56]

elevated levels of leptin in chronic inflammation state of obesity concomitantly impaired leptin signaling hence, unattractive target for the treatment of obesity. However, the levels of adiponectin are diminished in obesity as a exceptional adipokine [35,36]. In obese individuals the inflammatory cytokines are highly upregulated causing massive infiltration of macrophages due to secretions of high levels of monocyte chemo-attractant protein 1 [MCP-1] from adipocytes [37]. The other proinflammatory cytokines either released from adipocytes or macrophages directly are IL-1β, IL-6, TNF-α, and C-reactive protein [CRP]. It is stated that visceral fat has more severe metabolic effects than subcutaneous fat because most of the cytokines are secreted to a greater extent from visceral adipose tissue [38]. Cytokines released from adipose tissue induce a systemic low-grade inflammation promoting insulin resistance [39]. Moreover, in obesity, TNF-α inhibits triglyceride synthesis through downregulation of PPARγ and its target gene lipoprotein lipase (LPL) as well as glucose transporter GLUT4, and also inhibits insulin-mediated attenuation of lipolysis, down regulates the lipid droplet protein perilipin and up-regulates cAMP pool; all of which further enhances the release of FFAs [40].

3. ADIPOSE TISSUE AND ENERGY METABOLISM

Adipogenesis defined as a development of mature adipocyte from its multipotent mesenchymal stem cell. PPARγ is an adipose tissue secreted molecule that acts as a master regulator of adipogenesis [41,42]. The isoform of PPARγ such as PPAR-γ2 is expressed in adipose tissue and responsible for the differentiation and proliferation of adipocytes leads to an increase in adipose mass and its gender dependency [43-45]. While BAT plays a potential role though adaptive thermogenesis, WAT act mainly as fat storage. BAT contains high number of mitochondria and small, multilocular lipid droplets aided in the adaptive thermogeneisis [46].

Several studies have focused on UCP families [UCP1, UCP2, and UCP3] role in the adaptive thermogenesis as a physiological defense against diabetes and obesity [47]. Argyropoulos

and Harper [48] reported a significant UCP-1 expression in BAT for whole body energy expenditure and its dysfunction leads to the development of obesity. UCP1 is a unique mitochondrial membranous protein devoted to adaptive thermogenesis, a specialized function performed by brown adipocytes. Among the family of mitochondrial metabolite carriers, UCP1 is the only member able to translocate protons through the inner membrane of brown adipocyte mitochondria (Figure 2). UCP1 provokes energy dissipation in the form of heat by uncoupling respiration from ATP synthesis. UCP1 in turn also stimulates high levels of fatty acid oxidation [49]. UCP2 has high degree of sequence similarity with UCP1 [55–60%] and have been identified in both rodent and human tissues [50]. UCP3 is mainly expressed in human skeletal muscle and BAT [51].

The imbalance between energy intake and expenditure represent the major predisposing factor to contributing to obesity and its complications. Nowadays, most of anti-obesity drugs mainly target the energy intake through gastrointestinal mechanisms without altering any central mechanisms such as nutrient digestion and absorption inhibitors. Previous studies showed that administration of bile acids (BAs) to mice increases energy expenditure in BAT, hence, BAs came to light. BAs have long been known to be essential in dietary lipid absorption and cholesterol catabolism. However, BAs are established now as signaling molecules that activate mitogen-activated protein kinase pathways [52], are ligands for the G-protein-coupled receptor (GPCR) TGR5 [53,54]. BAs promote energy expenditure in BAT by activation of TGR5 leads to prevention of obesity and insulin resistance [55]. TGR5 plays an important role in energy expenditure to regulate body metabolism. The cAMP-dependent thyroid hormone activating enzyme type 2 iodothyronine deiodinase [D2] expression is induced by BAs in human skeletal muscle and thermogenic tissues of mouse brown fat. In this tissue, binding of BAs to the plasma membrane G-protein–coupled bile acid receptor 1 [Gpbar1, also known as TGR5] triggers an increase in cAMP formation and, subsequently, D2 expression. D2 subsequently activates thyroxine [T4] into tri-iodothyronine [T3]. T3 is predicted to induce uncoupling protein [UCP] expression in BAT. UCP is known to dissipate the proton gradient in the electron transport chain. Therefore, the activation of BAs/TGR5/cyclic AMP/D2/T3/UCP pathway cascade causes a decrease in the synthesis of ATP while enhancing substrate oxidation and thus regulates energy homeostasis [55].

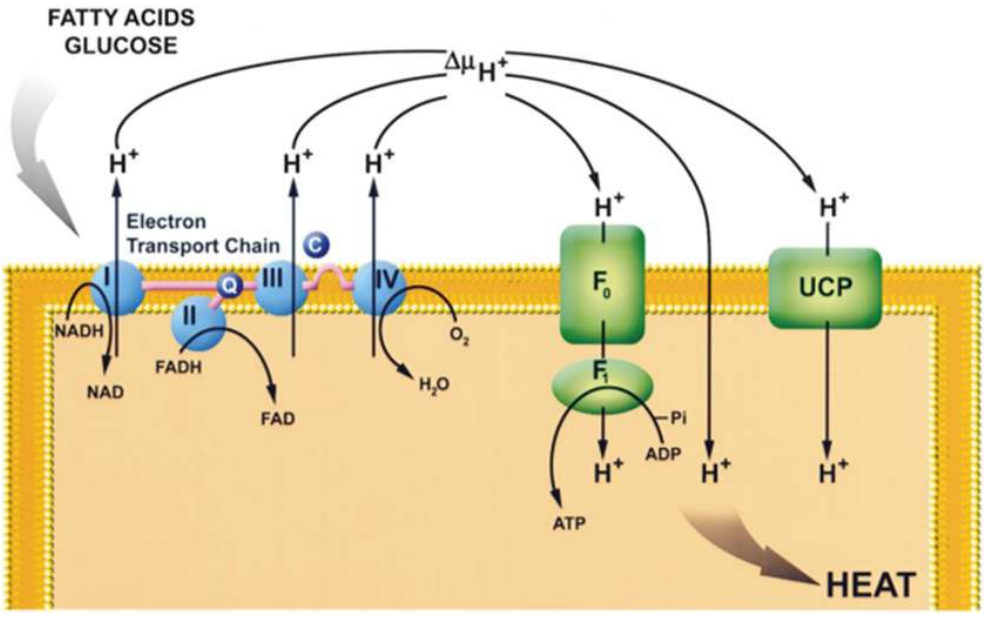

Fig. 2. Mitochondrial ATP metabolism through proton transport chain and adaptive thermogenesis through uncoupler proteins

Ubiquinone (Q), cytochrome c (C), complexes I, II III, and IV of the electron transport chain, uncoupler protein (UCP), Nicotinamide adenine dinucleotide (NAD), Flavin adenine dinucleotide (FAD) [57]

4. OBESITY AND COMPLICATIONS

Obesity as major health concern leads to a reduction in life expectancy of nearly 8 years, and to several co-morbidities, including the metabolic syndrome consisting of insulin resistance, type 2 diabetes, cardiovascular disease, fatty liver disease, cancer, hypertension, stroke, dementia, and obstructive sleep apnoea [10,58-60]. A positive correlation between pain and obesity has also been reported in relation to several pathological conditions [61], and a negative relationship between obesity and quality of life has been identified using health-related quality of life scores, which include measures of pain, fatigue and physical functioning [62]. A number of studies have shown that obese individuals also have increased susceptibility to systemic infections, are more likely to develop infectious complications after surgery, and are more susceptible to nosocomial diseases [63]. In addition, obesity has been found to have a serious negative impact on the individual's psychology and social life as a consequence of abnormal body image, prejudice, discrimination and limitations affecting daily life activities due to increased body weight (Obesity: preventing and managing the global epidemic. WHO consultation, 2000). Clearly the spread of obesity and its association with several complications, e.g., physical impairment, pain and other co-morbid disorders, including diabetes and cardiovascular diseases, strengthens the necessity to further understanding of the mechanisms underlying this pathological state and to achieve better quality of life for obese patients.

5. CONCLUSION

Adipose tissue as an endocrine organ acts as a primary storage of excess energy (in WAT) as well as potential in adaptive thermogenesis (in BAT). Adipose tissue secretes various adipocyte-specific factors known as adipokines such as leptin and adiponectin with beneficial effects on insulin action and lipid metabolism. The derived cytokines (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) from adipose tissue in obese individuals make understand the molecular the link between inflammation, obesity and insulin resistance. The secretion of adipokines are directly proportional to the adipose tissue mass, promoting the idea that reducing total adipose mass may be a strategy for the treatment of obesity and its complications. Additionally, understanding the signaling pathways in target tissues such as the skeletal muscle, brain, and liver by which adipokines control metabolism, the signaling activation cascade of TGR5 by BAs and its role in energy expenditure in BAT, the molecular mechanisms responsible for macrophage polarization and targeting the mechanisms involved in macrophage recruitment from the circulation may also help in the development of novel therapies for the obesity and its related complications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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