

Adipose tissue : A regulator for obesity and its complications

Abstract :

Obesity is a growing public health problem, resulting in significant morbidity and mortality due to weight-related diseases, as well as a reduced quality of life. 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 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, steroidogenesis, and secretion of several biologically active adipokines with diverse protein structures and functions. 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. 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.

Obesity at glance:

Obesity is gaining attention as one of the major leading public health problems. Though obesity itself is not a disease, but in later ages it becomes a major risk factor for developing cardiovascular disease type II diabetes, and certain types of cancer [1]. International Diabetes Federation defined obesity is 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 controlled 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 high prevalence of obesity [33.8%][5] followed by European and less developed countries as a factor of over-nutrition [6]. According to WHO, obesity is generally more common among women than men [7]. Previous reports revealed higher rates of obesity in female than in males [8]. However, studies on college students revealed higher rates of obesity in males than in females [9].

Adipose tissue and obesity

In human body adipose tissue acts as a endocrine organ and plays an important role in the human metabolism [10]. It has essential metabolic functions in the body. Although excess amount of adipose tissue predisposes several metabolic complications. About 21% of adipose tissue accounts for an average man of 70 kg [11]. The excess of energy has 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 chemoattractant proteins [CCL receptor-2 [CCR2]) and some proteins have potential role in the regulation of angiogenesis or vascular homeostasis, blood pressure (plasminogen activator inhibitor-1 [PAI-1] and angiotensinogen). Adipose tissue essential substances also regulates the carbohydrate, lipid metabolism [adiponectin and resistin], thermogenesis (uncoupling proteins [UCPs], coactivator-1 α [PGC-1] and PPAR- γ) and adipogenesis (peroxisome proliferator-activated receptor- γ [PPAR- γ]) [12].

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 [13]. 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 [14] 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 [15]. Previous studies stated, reduction of adipose mass leads to the decrease the expression levels of TNF- α and IL-6 in obese individuals and animal models [15]. Additionally, TNF- α can also modulates leptin secretions whereas, reduction in body fat positively associated with decreased leptin circulating levels as well as its gene expression [16].

However, 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 [17]. To understand the pathological and molecular changes in the adipose tissue in context to obesity and related complications has

become complicated. However, adipose tissue malfunction in obesity causes increase lipolysis with concomitant release of excess non-esterified fatty acids results in the inhibition of glucose uptake in muscle as well as suppression of hepatic glucose output leading to insulin resistance as a secondary complications [17]. Elevated Free fatty acids (FFAs) also effect the fatty acid based signaling cascade[18], leads to the decreased vasodilatation and hypertension [19]. Furthermore, intracellular fatty acids lead to activation of inflammatory pathways[20]. Moreover, serum elevated FFAs prove increase risk for myocardial infarction , cardiomyopathy[21] and enhance atherosclerosis [22]. Whereas, β -cells in the liver impaired glucose-stimulated insulin secretion for long term exposure to the elevated FFAs[23,24].

In obesity the adipocytokines profile of adipose tissue also undergoes a diverse changes apart from lipolysis. **Hukshorn, C.J., et al., [25]** reported that 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 [26,27]. In obese individuals the inflammatory cytokines are highly upregulated. For example, massive infiltration of macrophages due to secretions of high levels of monocyte chemoattractant protein 1 [MCP-1] from adipocytes [28]. The other proinflammatory cytokines either released from adipocytes or macrophages directly are IL-1 β , 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 [29]. Cytokines released from adipose tissue induce a systemic low-grade inflammation promoting insulin resistance [30]. Moreover, in obesity, TNF α inhibits triglyceride synthesis through downregulation of PPAR γ and its target gene LPL as well as glucose transporter GLUT4 and also inhibits insulin-mediated attenuation of lipolysis, downregulates the

lipid droplet protein perilipin and upregulates the cAMP pool, all of which further enhances the release of FFAs[31].

Adipose tissue and Energy Metabolism

Adipogenesis defined as a development of mature adipocyte from its multipotent mesenchymal stem cell. PPAR γ is a adipose tissue secreted molecule acts as a master regulator of adipogenesis [32,33]. The isoform of PPAR γ such as PPAR- γ 2 is expressed in adipose tissue and responsible for the differentiation and proliferation of adipocytes leads to an increase in adipose mass and its gender dependent. [34-36]. In contrast, Brown adipose tissue [BAT] plays an potential role adaptative thermogenesis, White adipose tissue [WAT] act mainly as fat storage. BAT contains high number of mitochondria and small, multilocular lipid droplets aided in the adaptive thermogenesis [37].

Several studies have focused on UCP families [UCP1, UCP2, and UCP3] role in the adaptive thermogenesis as a physiological defense against diabetes and obesity [38]. Argyropoulos G and Harper ME, [39] reported that 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 uncouples respiration from ATP synthesis. UCP1 also stimulating high levels of fatty acid oxidation [40]. UCP2 is high degree of sequence similarity with UCP1 [55–60%] have been identified in both rodent and human tissues [41]. UCP3, is mainly expressed in human skeletal muscle and BAT [42].

115 The imbalance between energy intake and expenditure represent the major predisposing factor to
116 contributing to obesity and its complications. Now a days the most of the drugs using in the
117 treatment of obesity mainly targeting to the energy intake through gastrointestinal mechanisms
118 without altering any central mechanisms such as nutrient digestion and absorption inhibitors.
119 Previous studies showed that administration of BAs to mice increases energy expenditure in
120 brown adipose tissue, hence, Bile acids (BA's) came to light that, BAs have long been known to
121 be essential in dietary lipid absorption and cholesterol catabolism. BAs acts as signaling
122 molecules to activate mitogen-activated protein kinase pathways[43], are ligands for the G-
123 protein-coupled receptor (GPCR) TGR5 [44,45]. Bile acids (BAs) promotes energy expenditure
124 in BAT by activation of TGR5 leads to prevention of obesity and insulin resistance[46]. TGR5
125 plays an important role in energy expenditure to regulate body metabolism. Cyclic-AMP-
126 dependent thyroid hormone activating enzyme type 2 iodothyronine deiodinase [D2] expression
127 induced by BAs in human skeletal muscle and thermogenical tissues of mouse brown fat. In this
128 tissue, binding of bile acids to the plasma membrane G protein-coupled bile acid receptor 1
129 [Gpbar1, also known as TGR5 triggers an increase in cyclic AMP formation and, subsequently,
130 D2 expression. D2 subsequently converts thyroxine [T4] to tri-iodothyronine [T3]. T3 is
131 predicted to induce uncoupling protein [UCP] expression in BAT. UCP is known to dissipate the
132 proton gradient in the electron transport chain. Therefore, the activation of BAs/TGR5/cyclic
133 AMP/D2/T3/UCP pathway cascade causes a decrease in the synthesis of ATP and thus regulates
134 energy homeostasis [46].

135

136 **Conclusion :**

Adipose tissue as a endocrine organ acts as a primary storage of excess energy (WAT) as well as potential in adaptive thermogenesis (BAT). Adipose tissue secretes various adipocyte-specific factors known as adipokines such as leptin and adiponectin which show 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 helpful in the development of novel therapies for the obesity and its related complications.

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Figure 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 [47].

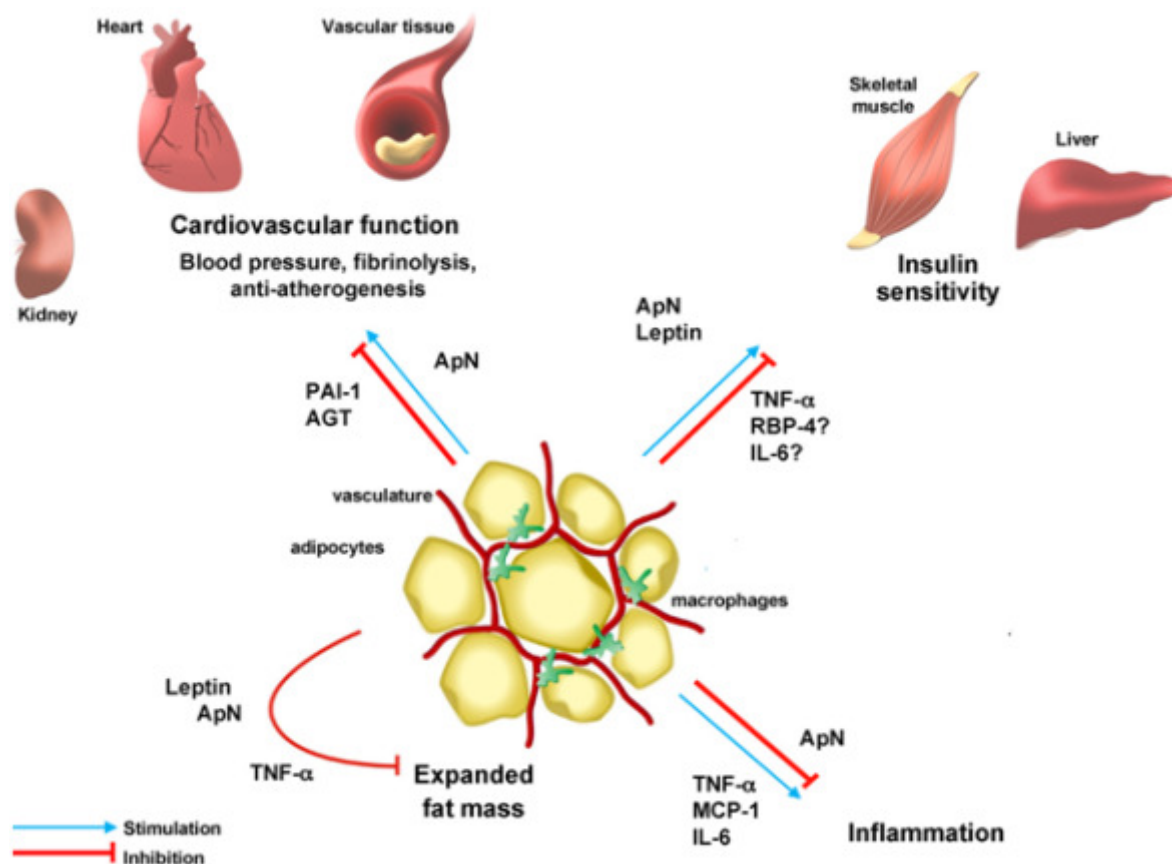


Figure 2. Mitochondrial ATP Metabolism and adaptive thermogenesis through Proton Transport chain.

Ubiquinone (Q), cytochrome c (C), complexes I, II III, and IV of the electron transport chain, uncoupling protein (UCP), Nicotinamide adenine dinucleotide (NAD), Flavin adenine dinucleotide (*FAD*) [48].

