Obesity, adipose tissue types and adipocytokines
(Review of Articles)

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ABSTRACT
The prevalence of obesity has increased worldwide in the last 50 years, reaching pandemic levels. The etiology of obesity is multifactorial, involving a complex of interaction among genetics, hormones and the environment. The adipose tissue plays a central role in regulating whole body energy. In one hand, the adipose tissue stores energy in the form of lipid and controls the lipid mobilization and distribution in the body, and on the other hand, adipose tissue acts as an endocrine organ and produces numerous bioactive factors such as adipocytokines. Moreover, brown and beige adipose tissue burn lipid by dissipating energy in the form of heat to maintain euthermia and have been considered as a new way to counteract obesity. In this review, we will summarize the recent findings of the types of adipose tissue and their role in controlling metabolism, focusing on its endocrine function. This review describes the molecular actions and clinical significance of some important adipocytokines.

Keywords: obesity, adipose tissue, white adipose tissue, brown adipose tissue and adipocytokines.

INTRODUCTION
The prevalence of obesity has increased worldwide in the last 50 years, reaching pandemic levels. Obesity represents a major health challenge because it substantially increases the risk of diseases such as type 2 diabetes mellitus, hypertension, fatty liver disease, myocardial infarction, stroke, dementia, obstructive sleep apnoea, osteoarthritis and several cancers, thereby contributing to a decline in both the quality of life and life expectancy.1,2
Adipose Tissues

Adipose tissues is a loose connective tissue which is primarily composed of adipocytes as well as pre-adipocytes, macrophages, fibroblasts, endothelial cells and leucocytes. Adipose tissue is not only a passive fuel reservoir, but also an endocrine organ. Extensive effort has been made to understand adipose tissue derived hormones and their physiological functions in the past two decades. These bioactive factors secreted from adipose tissue circulate and transport information to other metabolically active organs such as muscle, liver, brain, and pancreas via endocrine mechanisms, so modulating the systemic metabolism. 4

Types Of Adipose Tissues

In mammals, there are two types of adipose tissues: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT and BAT have distinct morphologies and functions, but recent studies discover a third adipose tissue type named beige or brite adipose tissue.

1. White adipose tissue (WAT) or white fat: In a normal non-overweight human beings, white adipose tissue composes about 20% of the body weight in males and 25% in females. WAT adipocytes store triglycerides as energy source and each has a single large lipid (fat) droplet which squeezes the nucleus to the periphery, adipocytes have receptors for insulin, sex hormones, norepinephrine, and glucocorticoids. 5

2. Brown adipose tissue (BAT): Brown adipose tissue was first identified in 1951. It is present in newborn, but adults either lack or have only a small amount of it. BAT is primarily located around the neck and large blood vessels of the thorax. In contrast to white adipose tissue brown adipose tissue, adipocyte contains multiple small lipid droplets and many mitochondria. 6 Brown fat is a specialized form of adipose tissue important for adaptive thermogenesis in humans and other mammals. BAT can generate heat by uncoupling the respiratory chain of oxidative phosphorylation within mitochondria through tissue-specific expression of uncoupling protein 1 (UCP1). BAT is activated upon cold exposure by the release of catecholamines from sympathetic nerves that results in uncoupling protein 1 activation. BAT activation may also occur in response to overfeeding or spicy food. 7, 8

The physiological role of brown adipose tissue in humans is debated, but it is quite clear that brown adipose tissue in rodents has an important role in the prevention and therapy of obesity and diabetes and specific drugs can induce brown fat development in adult animals. This rised a hope in the development of brown adipose tissue in human adults as a new challenge for the treatment of obesity and related diseases. 9

3. Beige or brite adipocyte: More recent studies discovered a third adipose tissue type. They demonstrate that many subcutaneous adipose depots traditionally classified as white adipose tissue also express brown adipose-specific markers and are thus referred to as “beige” or “brite” adipose. A process called browning of white adipose tissue is discovered; by which multilocular brown adipocytes expressing an uncoupling protein 1 appear at anatomical sites characteristic of white adipose tissue only. This phenomenon occurs after prolonged exposure to high levels of catecholamine (epinephrine and nor-epinephrine) like in patients with a pheochromocytoma - or a thermogenic stimulus after prolonged cold exposure, which also causes the recruitment of brown adipose tissue at their classical anatomical sites (eg, interscapular depots). The browning process can be mimicked by chronic treatment with β3-adrenergic receptor activators, all β3-AR activators are in the developmental stage to treat obesity and DM, but mirabegron is the only drug proved by FDA and used for urinary incontinence. 10

Adipocytokines

Until 1994, the only known role of adipose tissue was energy storage in the form of lipids; but in the recent years, it has been recognized as a major endocrine organ as it produces hormones such as leptin, estrogen, resistin, and the cytokine tumor necrosis factor-alpha (TNFa). 11 These cell signaling proteins that is secreted by adipose tissue is named the adipokines, the first adipokine to be discovered was leptin in 1994. Since that time, hundreds of adipokines have been discovered. 13-15

Examples of these adipokines are apelin, leptin, retinol binding protein 4 (RBP4), adiponectin, plasminogen activator inhibitor-1 (PAI-1), chemerin, interleukin-6 (IL-6), TNFalpha, progranulin, visfatin, resistin, omentin, vaspin.

1. Apelin

Apelin is a peptide that was identified in 1998. It participates in the control of blood pressure and its activation promotes the formation of new blood vessels (angiogenesis). 16, 17

Apelin hormone has hypotensive effect which partially results from the release of nitrogen oxide, a potent vasodilator, which induces relaxation of
the smooth muscle cells of the arterial wall. Moreover, apelin receptors in the brain are involved in regulating water and food intake. It was found that apelin injection increases water intake and decreases the hypothalamic secretion of the antidiuretic hormone (vasopressin). This diuretic effect of apelin is also associated with its hypotensive effect.

2. Leptin
It is one of the most important adipose derived hormones. It is a 16 kDa protein hormone that plays a key role in regulating energy intake and energy expenditure. In 1950, a severely obese mouse trait with an autosomal recessive inheritance was discovered. This was associated with a syndrome that includes hyperphagia, infertility, and a variety of hormonal and metabolic disturbances. The mutation, located at chromosome 6, was designated “obese” and the mouse trait as ob/ob.

In 1966, a mouse trait with a very similar phenotype was found. This mutation “diabetes” was found on chromosome 4, and the trait was called db/db. In 1994, research showed that the ob gene encodes a peptide chain of 167 amino acids in length, soon designated as leptin.

In addition to white adipose tissue, the major source of leptin, it can also be produced by brown adipose tissues, placenta, ovaries, skeletal muscle, stomach (lower part of fundic glands), mammary epithelial cells, bone marrow, pituitary and liver.

Leptin acts on receptors in the hypothalamus of the brain where it inhibits appetite. In women, leptin concentrations are approximately three fold that in men, the secretion is highest in the middle of the night, the opposite of what is seen for cortisol.

Obese individuals generally exhibit an unusually high circulating concentration of leptin. These people are said to be resistant to the effects of leptin, in much the same way that people with type 2 diabetes are resistant to the effects of insulin.

3. Retinol binding protein 4 (RBP4)
This protein belongs to the lipocalin family and is the specific carrier for retinol (vitamin A) in the blood. It delivers retinol from the liver stores to the peripheral tissues. RBP 4 has been a drug target for eye diseases which is an essential nutrient for the visual cycle.

4. Adiponectin
This is a 244-amino acid long polypeptide hormone. Adiponectin was first characterized in 1995 and was shown to be involved in regulating glucose levels as well as fatty acid breakdown. In humans it is encoded by the ADIPOQ gene and it is produced in adipose tissue. Adiponectin hormone decreases gluconeogenesis, increases glucose uptake and increases insulin sensitivity so it has a favorable effect on blood glucose level. Moreover, it enhances triglyceride clearance and weight loss so it protects from atherosclerosis.

Contrary to expectations, despite being produced in adipose tissue, adiponectin was found to be low in obesity. This down regulation has not been fully explained. The gene was localized to chromosome 3q27, a region that increases genetic susceptibility to type 2 diabetes and obesity. Supplementation by adiponectin was able to improve blood glucose, insulin control and triglyceride levels in mouse models.

5. Plasminogen activator inhibitor-1 (PAI-1)
In mammals, two plasminogen activators have been identified: tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA); both are activators of plasminogen and hence activation of fibrinolysis. PAI-1 is a serine protease inhibitor (serpin) that functions as the principal inhibitor of tissue plasminogen activator and urokinase plasminogen activator, so elevated level of PAI-1 is a risk factor for thrombosis and atherosclerosis.

(PAI-1) is present in increased levels in various disease states such as obesity, a number of forms of cancer as well as the metabolic syndrome. It has been linked to the increased occurrence of thrombosis in patients with these conditions.

6. Chemerin
Also known as retinoic acid receptor responder protein 2 (RARRES2), chemerin has been implicated in signaling for adipocyte differentiation and also stimulation of lipolysis.

Studies in mice have shown that chemerin is not highly expressed in brown adipose tissue, indicating that chemerin plays a role in energy storage rather than thermogenesis. In humans, chemerin levels are significantly different between individuals with normal glucose tolerance and individuals with type II diabetes and first degree relatives. Moreover, chemerin levels show a significant correlation with body fat percentage, plasma triglyceride levels and body mass index.

7. Interleukin-6 (IL-6)
Interleukin 6 (IL-6) is encoded by the IL6 gene, it acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine, which means a cytokine produced from muscle and elevated in response to muscle contraction. It is significantly
elevated with exercise, and precedes the appearance of other cytokines in the circulation.  
There is some early evidence that IL-6 can be used as an inflammatory marker for severe COVID-19 infection with poor prognosis, in the context of the wider coronavirus pandemic.  
Obesity is a known risk factor in the development of severe asthma. Recent data suggests that the inflammation associated with obesity, potentially mediated by the cytokine IL6, plays a role in causing poor lung function and increased risk for developing asthma exacerbations.  
IL-6 stimulates the inflammatory and autoimmune processes in many diseases like diabetes, atherosclerosis, rheumatoid arthritis, depression, Alzheimer disease and intracerebral hemorrhage.  
Hence, there is an interest in developing anti-IL-6 agents as therapy against many of these diseases.  

8. Progranulin  
Progranulin is the precursor protein for granulin, while progranulin is associated with anti-inflammatory, its cleaved granulin peptides have been implicated in pro-inflammatory behavior. Increased serum and plasma progranulin levels in patients with type 2 diabetes and visceral obesity implicate a role of progranulin in metabolic diseases.  
Progranulin is a pleiotropic protein and it plays diverse roles in the brain. Frontotemporal dementia (FTD) is caused by progranulin mutations. Many genetic variation in progranulin is linked to multiple neurodegenerative disorders.  

9. Visfatin  
Visfatin is an adipokine that is localized to the blood stream, also known nicotinamide phosphoribosyl transferase (NAMPTase or Nampt). It is an enzyme that in humans is encoded by the NAMPT gene. This protein is the rate-limiting enzyme in the nicotinamide adenine dinucleotide (NAD+) salvage pathway that coverts nicotinamide to nicotinamide mononucleotide in mammals to enable NAD+ biosynthesis and has various functions; including the promotion of vascular smooth muscle cell maturation and inhibition of neutrophil apoptosis. It also activates insulin receptor and has insulin-mimetic effects, lowering blood glucose and improving insulin sensitivity. The protein is highly expressed in visceral fat and serum levels of the protein correlate with obesity.  

10. Resistin.  
Resistin was discovered in 2001, it is a cysteine-rich peptide hormone, the length of the resistin pre-peptide in human is 108 amino acid residues and the molecular weight is 12.5 kDa. In humans, resistin is encoded by the RETN gene. In primates, pigs and dogs, resistin is secreted by immune and epithelial cells, while in rodents and human beings it is secreted by adipose tissue.  
It was called resistin because of the observed insulin resistance in mice injected with resistin. Resistin was found to be produced and released from adipose tissue to serve endocrine functions likely involved in insulin resistance so resistin physiologic role has been the subject of much controversy regarding its involvement with obesity and type II diabetes mellitus. Further research has linked resistin to other physiological systems such as inflammation and energy homeostasis.  
Resistin increases the production of low-density lipoprotein (LDL) in human liver cells and also degrades LDL receptors in the liver. As a result, the liver is less able to clear bad cholesterol from the body so resistin has been shown to cause high levels of the bad cholesterol LDL. More-over, resistin accelerates the accumulation of LDL in arteries so increasing the risk of heart disease.  

CONCLUSIONS  
Adipose tissue plays a major role in the regulation of systemic metabolic homeostasis via its profound effects on energy storage, endocrine function and adaptive thermogenesis. The dysfunction of adipose tissue as a causal factor is linked to obesity and its related disorders. Therefore, understanding adipose tissue biology and pathology is of great importance for the identification of novel and potential therapeutic targets for the prevention and treatment of obesity-related disorders.  
It is now recognized that the adipose tissue produces a variety of bioactive peptides, collectively termed adipokines. Alteration of adipose mass in obesity affects the production of most adipose secreted factors. So obesity is associated with multiple metabolic disorders and increased risk of cardiovascular diseases, diabetes mellitus, cancers and many other diseases. The idea has emerged that adipose tissues could be instrumental in these complications by virtue of its secreted factors. Several adipokines are increased in the obese state and have been implicated in hypertension like angiotensinogen, impaired fibrinolysis like plasminogen activator inhibitor (PAI-1) and insulin resistance like TNFα, IL-6, resistin.
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