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Insights into role of adipose tissue as endocrine organ

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Abstract
Adipose tissue, long considered as passive reservoir of fat is now recognized as an important largest endocrine organ in the body. It sends chemical and hormone signals to other tissues and organs not only by endocrine but also by autocrine and paracrine mechanism. Adipose tissue, commonly called 'fat' is a type of loose connective tissue comprised of mainly lipid-filled cells adipocytes surrounded by matrix of collagen fibers, blood vessels, immune cells and fibroblasts. Adipose tissue is a major source of numerous bioactive compounds called adipocytokines or adipokines that are involved in the control of nutritional intake, sensitivity to insulin and inflammatory processes. Now adipose tissue and adipokines are regarded as functional part of endocrine system. Adipose tissue is not just mere site for inert lipid storage. But it is a complex, essential and highly active metabolic and endocrine organ. Present review is focused on the role of adipose tissue as an endocrine organ.

Keywords: adipose tissue, visceral fat, adipokines, leptin.

Introduction

Importance of adipose tissue as an endocrine organ has received considerable attention and arose interest among researchers because of metabolic consequences of excess as well as deficient states of adipose tissue. Rising prevalence of obesity that is excess of adipose tissue particularly visceral component is associated with epidemic of non-communicable diseases. Adipose tissue is a major source of numerous bioactive compounds called adipocytokines or adipokines that are involved in the control of nutritional intake, sensitivity to insulin and inflammatory processes. Now adipose tissue and adipokines are regarded as functional part of endocrine system mediating both beneficial and detrimental effects on immunity and inflammation. Along with adipocytes, macrophages also accumulate in adipose tissue in obesity leading to increased expression of inflammatory substances with rise in levels of circulating insulin levels [1]. Because of presence of undifferentiated cells, adipose tissue has a potential role as stem cells for regeneration of the tissues [2]. Present review is focused on the role of adipose tissue as an endocrine organ.

Adipose tissue- largest endocrine organ

Deficiency of adipose tissue or lipodystrophy has been reported in metabolic syndrome and also in patients on antiretroviral therapy for management of human immunodeficiency virus infection [3]. Both the conditions of excess or deficiency of adipose tissue result in its dysfunction and associated consequences. Obesity is a state of chronic low-grade systemic inflammation where adipose tissue plays crucial endocrine role through production of adipokines. Characteristically adipokines imbalance is observed in obesity that includes low level of adiponectin; raise leptin, inflammatory mediators and anti-fibrinolytic factors. This leads to oxidative stress and endothelial dysfunction that predispose to various cardio-metabolic disorders. This effect is further aggravated by lipotoxicity due to insulin resistance in obesity [1].

White fat comprises of adipocytes, pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leukocytes. It actively participates in hormonal and inflammatory systems.Adipose tissue crucially maintains systemic glucose and lipid homeostasis. With the advances in the field of obesity and related disorders, adipose tissue has been recognized as an active endocrine organ that synthesize and secret multiple immune-modulatory bioactive factors termed as adipokines or adipocytokines. They include hormones leptin, adiponectin, visfatin, apelin, vaspin, he pcidine, chemerin, omentin, and inflammatory cytokines tumor necrosis factor alpha (TNF), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator protein (PAI). In addition to production of adipocyte-derived proteins with endocrine function, several receptors are expressed in adipose tissue like receptors of insulin, glucocorticoids, growth hormone, thyroid stimulating hormone, angiotensin II type 1 and 2. Nuclear hormone receptors include glucocorticoids, vitamin D, thyroid, androgen, estrogen and progesteron receptors. Adipokines perform multiple diverse roles in metabolic and inflammatory responses [4, 5]. Visceral fat and subcutaneous fat differ in endocrine function. It sends different hormone signals with respect to quality and quantity and also respond to hormone stimuli differently [6]. Impaired regulation of adipokines is one of the proposed mechanisms for development of systemic insulin resistance and metabolic disorders [7]. Adipose tissue dysfunction is caused due to complex interplay of genetic, behavioral and environmental factors leading to adipocyte hypertrophy, accumulation of ectopic fat, hypoxia, impaired mitochondrial function, inflammation and stress within adipose tissue. This is manifested by secretion of proinflammatory adipokines that mediate auto/paracrine and endocrine

communication along with infiltration of inflammatory cells specifically in intra-abdominal fat [8]. Dysfunctional adipocytes resulting in imbalance of adipokines contribute to pathogenesis of obesity related disease.

Adipocytes- site of synthesis of hormones

Leptin is a 16kDa hormone product of obese (ob) gene, secreted by adipocytes in direct proportion to adipose tissue mass and nutritional status. Predominantly it is synthesized in subcutaneous fat and to lesser extent in visceral fat. Endocrine role of adipose tissue is best characterized by leptin. It plays prominent role in energy homeostasis via hypothalamic pathways and control of body weight. In addition it is involved in regulation of neuroendocrine function and traditional endocrine systems. Leptin resistance has been observed in obesity. Leptin has diverse endocrine effects that include regulation of immune function, angiogenesis, hematopoiesis and development of bone [9]. Concentration of leptin in adipose tissue and in circulation depends on amount of energy storage as fat and status of energy balance. Nutritional regulation of leptin is regulated partially by insulin. Hence its levels are high in obese persons and get increased with overfeeding [10]. Leptin is also regulated by other elements like acute infections, smoking, glucocorticoids, growth hormone, thyroid hormone, melatonin, and inflammatory cytokines. It has multi-systemic actions that mediate the metabolic, endocrine actions and cardiovascular complications associated with obesity.

Adiponectin is widely studied most abundant adipocyte-derived adipokine which exerts protection against obesity and obesity-linked metabolic disease. It is synthesized in high concentration among lean individuals, while its expression is downregulated in obesity [11]. Several researchers reported anti-inflammatory, anti-atherogenic and anti-diabetogenic properties of adiponectin. Plasma adiponectin level has been proposed to be a good predictor of ther isk of type 2 diabetes mellitus [12]. Adiponectin induces several beneficial effects. It promotes insulin sensitivity by activating AMP-activated protein kinase in skeletal muscles and liver. Also it regulates polarization of macrophages towards anti-inflammatory phenotype via various mechanisms conferring protection against obesity-linked disorders. Data from experimental studies suggested beneficial actions of adiponectin on endothelial function by regulating endothelial nitric oxide synthase and promoting ischemia-induced revascularization in muscle through cyclooxygenase-2 dependent mechanisms [13]. It down-regulates the expression of adhesion molecules and decreases oxidative stress on endothelial cells. Thus it helps in protection against development of cardiovascular diseases also. Its levels correlate positively with the levels of high-density lipoproteins and negatively with triglycerides, insulin resistance, inflammatory markers, and coronary artery calcium. Thus it exerts anti-atherogenic and anti-inflammatory effects on cells of vessels [14].

Adipose tissue has ability to metabolize sex steroids and glucocorticoids by expression of enzymes required for activation, interconversion and inactivation of steroid hormones [15]. Cortisol is produced from cortisone in adipose tissue. There are newly identified adipocytokines like secreted frizzled-related protein 5 (Sfrp5), adipolin (adipose-derived insulin-sensitizing factor) that are associated with anti-inflammatory actions and improvement in insulin sensitivity. These represent new potential targets for prevention of obesity-related disorders. (Ouchi 2, Enomoto) Tan *et al.* studied effect of administration of metformin on levels of plasma adipolin in humans. They reported that rise in plasma adipolin levels might prove as a novel therapy for treatment of insulin resistance and related disorders [16]. Adipose tissue synthesizes and secretes number of inflammatory cytokines like TNFα, progranulin (PGRN), pigment-epithelium derived factor (PEDF) and interleukin 6. TNFα inhibits lipogenesis, favors lipolysis and facilitates adipocyte death by apoptosis. It may play direct role in the development of atherosclerosis by induction of expression of adhesion molecules in endothelial and smooth muscle cells leading to endothelial cells apoptosis [17]. Also it is proposed as mediator of insulin resistance in obesity [10]. PEDF and PGRN plays important role in the causation of insulin resistance, metabolic syndrome and obesity. PEDF is gaining attention as a potential therapeutic target molecule in the prevention of insulin resistance. PRGN is the most abundant pro-inflammatory adipokines from adipocytes correlate with systemic insulin resistance [18]. Adipsin is adipose tissue-derived complement component required for synthesis of acylation stimulating protein (ASP) in glucose and lipid metabolism. Adipsin and ASP correlate positively with adiposity, insulin resistance. Visfatin is an adipocytokine predominately secreted from visceral adipose tissue with endocrinal role in glucose metabolism, insulin sensitivity and cardiovascular disease [19]. Omentin is a 38-40 kDa adipokines predominantly expressed in visceral adipose tissue. Experimental studies suggested it could have beneficial protective effects against coronary atherosclerosis, obesity-related cardiovascular disorders, and hypertension via its vasodilatation effects on blood vessels. Also it is an enhancer of insulin sensitivity [20]. Resistin is another peptide hormone, which regulate inflammatory process by immuno-competent cells and adipocytes. Its levels are correlated with insulin resistance and reported to be predictor of cardiovascular diseases [21]. Some proteins of renin angiotensin system (RAS) like angiotensinogen, renin, angiotensin II, angiotensin converting enzymes, non-renin angiotensin enzymes, angiotensin II receptors are expressed in adipose tissue. RAS plays key role in the regulation of blood pressure via angiotensin II. Adipose tissue appears to possess RAS that might be a potential link between obesity and hypertension [3].

Adipose tissue is not just mere site for inert lipid storage. But it is a complex, essential and highly active metabolic and endocrine organ. Visceral fat differs from subcutaneous fat significantly in terms of morphology and expression and secretion of adipokines. Visceral adipose tissues secretes more pro-inflammatory cytokines, while subcutaneous adipose tissue secrets more amount of leptin, anti-inflammatory and insulin-sensitizing agents. Hence visceral fat accumulation is a predisposing factor for development of metabolic health diseases. With the growing prevalence of obesity, extensive scientific data has been published about endocrine functions of adipose tissue. It expresses and secretes range of soluble bioactive products with significant local and distant endocrine functions [22]. These endocrine functions are regulated by nutritional status as adipose tissue is actively involved in energy homeostasis. Also they are involved in regulation of glucose and lipid metabolism, vascular function, immunity and insulin sensitivity and inflammation.

Adipokines regulate microenvironment of adipose tissue and communicate with brain, heart, liver, vasculature and muscles. In obesity, dysfunctional adipose tissue impairs critical balance between proinflammatory and anti-inflammatory mediators. This results in a state of low-grade chronic systemic inflammation, which is main culprit in the causation of obesity, related cardiovascular diseases. Endocrine function of adipose tissue might provide a mechanistic link between obesity and its related metabolic disorders by imbalance in the production of adipokines. Adipokines work as a network to regulate numerous physiological and biochemical reactions. Decreased production of beneficial adipokines with anti-inflammatory properties like adiponection, Sfrp5 and adipolin leads to obesity and its associated disorders [23-25]. Exact role of adipose tissue and adipokines is still unclear in human beings. Maintenance of delicate balance of interplay between metabolic and immune systems via adipokines is important. Studies are ongoing to assess effectiveness of inhibition of leptin receptors by monoclonal antibodies or mutant leptin.

Conclusion

Advances in experimental and clinical research emphasized active endocrinal role of adipose tissue in inflammation, insulin sensitization, feeding behavior in addition to its primary function in energy homeostasis. Adipose tissues synthesize proinflammatory or anti-inflammatory adipokines. Crucial balance between these two components plays vital role in the causation of metabolic disorders. Rising prevalence of obesity is a major threat all over the world. So development of possible strategies with new therapeutic treatment remains crucial medical challenge. Therapeutic approach in the context of obesity and related metabolic disorders would be changed drastically by exploring endocrine function of adipose tissue in depth.

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