

Review Article

Obesity and adipose tissue endocrine function

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Abstract

Many studies have profoundly changed the concept of adipose tissue from being an energy depot to an active endocrine organ. Adipose tissue secretes bioactive peptides, termed as 'adipokines'. They act through autocrine, paracrine and endocrine pathways. In obesity, increased production of most adipokines affects multiple functions such as appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and haemostasis. Increased activity of the tumor necrosis factor and interleukin 6 are involved in the development of obesity-related insulin resistance. Angiotensinogen has been implicated in hypertension and plasminogen activating inhibitor-1 in impaired fibrinolysis. Decreased levels of adiponectin indicate adipose tissue dysfunction in obesity. Thus increased adipose tissue mass plays a key role in the development of obesity-associated diseases and the development of obesity alters adipocyte-derived hormones or cytokines expression. This provides a link between obesity, impaired insulin sensitivity and metabolic defects in other tissues. The present review will focus on effect of obesity on adipose tissue endocrine function.

Keywords: Adipose tissue, Adiponectin, Interlukin-6, Leptin, Resistin, Tumor necrosis factor

1. Introduction

Prevalence of obesity in children and in adults is rapidly increasing in India.¹ It is an emerging major public health problem in both developed and developing countries. Obesity is defined as 'chronic condition that develops when energy intake exceeds energy expenditure, resulting in abnormal or excessive fat accumulation that may impair health'.² Environmental factors such as increased availability of high calorie food or decreased need for physical activity contribute to its development and their influence is amplified by genetic predisposition.³

Hippocrates wrote, "Corpulence is not only a disease itself, but the harbinger of others". He recognized that obesity is a medical disorder that also leads to much co-morbidity. While obesity itself is not considered a specific disease, it is responsible for accelerating degenerative changes. This leads to multiple organ specific pathological consequences like atherosclerosis, Type II diabetes, hypertension and gall bladder diseases.⁴

1.2. Adipose Tissue

Adipose tissue is the most abundant tissue in humans, representing approximately 10–29% of body weight. It consists of two major forms, white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is the main site for the storage of energy. It stores energy in the form of triglycerides which are located in large lipid droplets. They occupy most of intracellular space of many adipocytes. BAT, on the other hand, usually consumes energy to produce heat by catabolizing lipids. Thus brown adipocytes store fewer triglycerides within small lipid droplets.⁵

Adipose tissue is a complex, essential, and highly active metabolic and endocrine organ. It is composed of the lipid-storing adipose cells and a stromal or vascular compartment and immune cells. In stromal compartment preadipocytes and macrophages are present. Adipose tissue not only responds to afferent signals from traditional hormone systems and the central nervous system but also expresses and secretes factors with important endocrine functions. These factors include leptin, other cytokines such as tumor necrosis factor (TNF- α) and interleukin-6 (IL-6), adiponectin, complement components, plasminogen activator inhibitor-1 (PAI-1), proteins of the renin-angiotensin system and resistin.⁶

The important endocrine function of adipose tissue is emphasized by the adverse metabolic consequences of both adipose tissue excess and deficiency. Adipose tissue mass is increased due to lipid deposition in adipose cells and by increase in number of adipocytes. Adipose tissue excess or obesity, particularly in the visceral compartment, is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and prothrombotic and proinflammatory states. The prevalence of obesity and these associated morbidities is known as the metabolic syndrome. Obese adipose tissue also has increased number of infiltrating macrophages.⁷

1.3 Obesity

Obesity results from both quantitative and qualitative changes at the adipose tissue level. An excess of adipose tissue frequently includes both hyperplastic and hypertrophic development⁸. The fat tissue responds to stress by reprogramming its normal functions. It comprises a change in the level and nature of the secreted adipokines and mobilizes stored lipids. These lipid substances are released into circulation as free fatty acids. Thus it leads to lipotoxicity within other metabolic tissues. These responses are further exacerbated by the proliferation and differentiation of preadipocytes. Also progenitor cells within adipose depots provide more adipocytes for hypertrophic expansion.⁹ Due to these reasons pathophysiological complications associated with increased fat mass are increased.

The efficiency of fat deposition is affected by local secretion of adipocyte-derived factors. Studies suggest that besides many other mechanisms and factors these factors influences insulin signaling, decrease lipogenic gene expression, increase lipolysis, control blood flow to organs, and also regulate intracellular triglyceride synthesis.¹⁰

In addition to the classical actions of insulin and counter regulatory hormones on adipocyte metabolism, fat cells play an active role in modulating their own metabolism, and hence their size, via autocrine and paracrine mechanisms. Newly discovered roles which include the production of the cytokines IL-6, TNF- α , and leptin, play decisive roles in the development of obesity and insulin resistance.¹¹ The local production of angiotensinogen may play an etiological role in the development of obesity-related hypertension. Furthermore, synthesis of estrogens by adipose tissue may mediate effects of obesity on the risk for osteoporosis and cancer.¹² Thus increase in the adipose tissue mass has pleiotropic effects on endocrine and metabolic events at the whole body level that may contribute to pathogenesis of detrimental complications.

The present review will focus on effect of obesity on adipose tissue endocrine function.

2. Obesity and adipose tissue endocrine function

a) Leptin: One of the most important hormone of adipose tissue is leptin. It is a peptide hormone and has been named leptin, from a Greek word 'for thin'. It influences energy homeostasis, neuroendocrine and immune function. It is also produced in gastric epithelium¹³ and placenta.¹⁴

Circulating leptin levels reflect both energy stores and acute energy balance. It acts on hypothalamus to decrease food intake and increase energy consumption. Exogenous leptin administration in rodents, both centrally and peripherally, reduces spontaneous and fasting induced hyperphagia while chronic peripheral administration reduces food intake resulting in loss of fat mass and body weight.¹⁵ The absence of leptin has profound effects on body weight. In mice, lack of leptin, due to a gene mutation, leads to hyperphagia and obesity. It also leads to neuroendocrine and immune disturbances which can be normalized by leptin administration.¹⁶

Similarly it has been observed that leptin deficiency in both children and adults caused severe obesity and hypogonadism.¹⁷ This can be ameliorated by recombinant leptin therapy.¹⁸ Thus defective leptin receptor signaling was associated with altered body weight and endocrine syndrome.

Majority of obese humans have raised plasma leptin but do not have mutations of either leptin or its receptor.¹⁹ It is suggested that they have a form of functional 'leptin resistance'. The mechanism of leptin resistance is not yet established.

Studies revealed that leptin may not effectively cross blood brain barrier as levels rise. Animal studies showed that leptin signaling inhibitors were involved in leptin resistant state.²⁰

Leptin is not only a central regulator of body fat mass, but it could also be involved in insulin resistance induction, possibly via peripheral mechanisms of action. In fact, leptin can act through some components of the insulin-signaling cascade and can modify insulin-induced changes in gene expression *in vitro* and *in vivo*.²¹

It has been observed that leptin production was markedly increased in large adipocytes.²² It was stimulated by insulin and also affected by TNF- α , estrogens, free fatty acids and growth hormone.^{23,24} Leptin production was not directly influenced by food uptake itself. Therefore, leptin can be considered as a signaling molecule relating the long-term nutritional and fat mass status to the brain (hypothalamus)²⁵.

Apart from central effects, leptin increased hepatic lipid oxidation and lipolysis in skeletal muscle and adipocytes. Leptin-deficient children were not only extremely obese, but remain prepubertal while exogenous leptin substitution had resulted in the onset of puberty in these children.²⁶

Since leptin has a restraining effect on normal insulin secretion by the pancreas, it has been proposed that in obesity, leptin resistance might occur in β -cells, thus adding to hyperinsulinaemia observed in obese subjects.

Many studies suggested that an activated renin-angiotensin-aldosterone system (RAS) and leptin were involved in obesity-associated hypertension by influencing the salt-fluid homeostasis and vascular tone. In obese subjects, plasma angiotensinogen (AGT) and renin concentrations were elevated and angiotensin converting enzyme (ACE) activity was increased.²⁷ Dysfunctional adipocytes of obese subjects produce AGT and angiotensin II, contributing to increased systemic blood pressure levels.²⁸ Angiotensin II may impair intracellular insulin signaling similarly to TNF- α and FFAs leading to reduced glucose uptake and diminished adipocyte differentiation.²⁹

Leptin-deficient subjects were normotensive despite the presence of considerable obesity.³⁰ The concept of leptin-provoked hypertension was based on the findings that leptin up regulates Na⁺/K⁺-ATPase in the renal cortex and medulla. Leptin also leads to an increased sympathetic activity which leads to increased heart rate and elevated blood pressure levels in mice.³¹

The high prevalence of non-alcoholic fatty liver disease in obese, insulin-resistant, and diabetic subjects may, at least in part is due to adipose tissue dysfunction. The increased flux of fatty acids and IL-6 through portal circulation results in increased hepatic lipid accumulation. Leptin is considered to be a mediator of liver fibrosis after chronic liver injury in mouse models. However, this action of leptin may be reduced in leptin resistance.³²

b) Adiponectin: This adipocyte complement related protein is exclusively produced by adipocytes and circulates in plasma in three different full-length isoforms (trimer, hexamer, and multimers) and as globular form. The function of adiponectin is to regulate energy homeostasis. Plasma levels of adiponectin are reduced in obesity, insulin resistance, metabolic syndrome, and type 2 diabetes. The adiponectin receptors are present in skeletal muscle, liver, brain and hypothalamus.³³

Studies showed that plasma adiponectin levels negatively correlated with insulin resistance³⁴ and treatment with adiponectin reduced body weight, increased insulin sensitivity and decreased lipid levels in rodents.³⁵ It also had vascular protective effect. Although exact mechanism is not yet fully understood, it is postulated that these changes are mediated through metabolic pathways that include regulation of food intake, gluconeogenesis and lipogenesis.³⁶

Being solely produced by adipocytes, low plasma adiponectin concentration is a good representative of adipocyte dysfunction. Adiponectin has antiatherogenic properties, as shown *in vitro* by its inhibition of monocyte adhesion to endothelial cells, macrophage transformation to foam cells (through down-regulation of scavenger receptors) and endothelial cell activation (through reduced production of adhesion molecules and inhibition of TNF- α). Thus in obesity decreased levels of adiponectin were associated with increased risk of atherogenesis³⁷.

In various populations of healthy subjects and high risk patients, low plasma levels of adiponectin were independent predictions of future vascular disease.³⁸ However, other studies showed discrepant results.³⁹ The discrepancy might be explained by functional differences between adiponectin isoforms and their ratios in plasma.⁴⁰ The high molecular weight (HMW)-form has better correlations with insulin sensitivity in subjects with and without type 2 diabetes compared

with total or LMW-adiponectin levels, suggesting that HMW-adiponectin is the most active form.⁴¹ It has been observed that HMW-adiponectin levels were selectively suppressed in obese patients with ischemic heart disease and were restored after weight loss.⁴²

Two adiponectin receptors (AdipoR1 which mainly binds globular adiponectin and AdipoR2 which predominantly binds the full-length isoforms) have been identified which differ in part in distribution and potential actions. Although both receptors are expressed throughout the body, AdipoR1 is highly present in muscle tissue while AdipoR2 is abundantly expressed on liver cells.⁴³ On human adipocytes and muscle cells both types are expressed.⁴⁴ In insulin resistance and obesity the expression of these receptors is reduced enhancing insulin resistance.⁴⁵

Type 2 diabetes is now generally accepted to be due to a combination of insulin resistance and relatively diminished insulin secretory function of pancreatic β -cells. In most studies low adiponectin and elevated levels of other adipocytokines (e.g. leptin, TNF- α , IL-6) were associated with an increased risk of diabetes. This presumably relates not only to their effects on insulin sensitivity but also to their effects in the pancreas leading to β -cell failure.⁴⁶ Thus although the mechanism by which adiponectin secretion is reduced in obese subjects is not clear it can be considered that insulin resistance and increased TNF- α may contribute to this effect.

It has been observed that in mice models of obesity and hyperlipidemia, adiponectin decreased plasma concentration of fatty acids and triglycerides. The effect was mediated by accelerated fatty acid oxidation in muscle cells, which leads to decreased cellular triglyceride content^{47,48}.

c) Resistin: Resistin/FIZZ3 is a member of the newly discovered cysteine-rich secretory protein family, referred to as 'resistin-like molecules'.⁴⁷ Initial studies in rodents suggested that resistin was up regulated in obesity and might be involved in the development of insulin resistance. Later studies failed to confirm this hypothesis and demonstrated reduced resistin expression in adipose tissue of obese animals.⁴⁸ In human adipose tissue resistin is detectable at a very low level, and there is no relationship between resistin expression and obesity. Although resistin may contribute in the development of insulin resistance leading to diabetes in obese individuals^{49,50} its role in the pathogenesis of obesity is unclear.

d) TNF- α : TNF- α is a cytokine initially described as an endotoxin-induced factor causing necrosis of tumors and subsequently shown to be identical to cachexin.⁵⁰ It exerts its effects via type I and type II receptors. Within adipose tissue, TNF- α is expressed by adipocytes and stromovascular cells⁵¹. It has now been implicated in the pathogenesis of obesity and insulin resistance.^{52,53,54} Adipose tissue expression of TNF- α is increased in obese rodents and humans and is directly correlated with adiposity and insulin resistance.^{52,53,54,55} TNF- α influences gene expression in metabolically important tissues such as adipose tissue and liver.⁵⁶ In adipose tissue, it represses genes involved in uptake and storage of nonesterified fatty acids (NEFAs) and glucose. It also suppresses genes involved in adipogenesis and lipogenesis, and changes expression of several adipocyte-secreted factors including adiponectin and IL-6.⁵⁶ In liver, TNF α suppresses expression of genes involved in glucose uptake and metabolism and fatty acid oxidation.⁵⁶ TNF- α also impairs insulin signaling indirectly by increasing serum NEFAs.⁵²

e) IL-6: IL-6 is another cytokine associated with obesity and insulin resistance.⁵⁵ Within adipose tissue IL-6 receptors are expressed by adipocytes and adipose tissue matrix.⁵¹ Expression and secretion of IL-6 are 2 to 3 times greater in visceral relative to subcutaneous adipose tissue.⁵¹ As much as one third of circulating IL-6 originates from adipose tissue.⁵⁵ Adipose tissue IL-6 expression and circulating IL-6 concentrations are directly correlated with obesity, impaired glucose tolerance, and insulin resistance.⁵⁵ IL-6 decreases insulin signaling in peripheral tissues by reducing expression of insulin receptor signaling components and inducing suppressor of cytokine signaling 3.⁵⁷ It also inhibits adipogenesis and decreases adiponectin secretion.⁵⁵ These effects of IL-6 suggest role for IL-6 in obesity and insulin resistance.

The central role of IL-6, however, suggests a more complex role in energy homeostasis. IL-6 levels in the CNS are inversely correlated with fat mass in overweight humans, suggesting central IL-6 deficiency in obesity.

f) Macrophages and monocyte chemoattractant protein (MCP)-1: Obesity is associated with increased adipose tissue infiltration by macrophages.⁵⁸ Activated macrophages secrete inflammatory factors that contribute to insulin resistance, including TNF α and IL-6. MCP-1, a chemokine that increases monocytes migration to sites of inflammation, is expressed and secreted by adipose tissue.⁵⁸ Adipose tissue expression of MCP-1 and circulating MCP-1 levels are increased in rodent

obesity. This suggest that MCP-1-mediated macrophage infiltration of adipose tissue may contribute to the metabolic abnormalities which are associated with obesity and insulin resistance.^{59,60}

MCP-1 has local as well as endocrine effects. Incubation of cultured adipocytes with MCP-1 decreases insulin-stimulated glucose uptake and insulin-induced insulin receptor tyrosine phosphorylation, suggesting that MCP-1 directly contributes to adipose tissue insulin resistance. MCP-1 also inhibits adipocyte growth and differentiation by decreasing the expression of a number of adipogenic genes.^{60,61}

g) Plasminogen activator inhibitor (PAI)-1: It is the primary inhibitor of fibrinolysis which acts by inactivating urokinase-type and tissue-type plasminogen activator. It also takes part in angiogenesis and atherogenesis. PAI-1 expression and secretion are greater in visceral relative to subcutaneous adipose tissue.^{51,62}

Plasma PAI-1 levels are elevated in obesity and insulin resistance. They are directly correlated with features of the metabolic syndrome.⁶³ Plasma PAI-1 levels are strongly associated with visceral adiposity.⁶² TNF- α contributes to the elevated PAI-1 levels observed in obesity and insulin resistance.^{51,62,63} Thus, PAI-1 may contribute to the development of obesity and insulin resistance and may be a causal link between obesity and cardiovascular disease.

h) Adipsin and acylation stimulating protein (ASP): Adipsin (complement factor D) is one of several adipose tissue-derived complement components that are required for the enzymatic production of ASP, a complement protein that affects both lipid and glucose metabolism. Studies done in humans indicate that both adipsin and ASP positively correlate with adiposity, insulin resistance, dyslipidemia, and cardiovascular disease.⁶⁴

i) Proteins of the renin angiotensin system (RAS): Several proteins of the classic RAS are also produced in adipose tissue. These include renin, angiotensinogen (AGT), angiotensin I, angiotensin II, angiotensin receptors type I (AT1) and type 2 (AT2), angiotensin-converting enzyme (ACE), and other proteases capable of producing angiotensin II (chymase, cathepsins D and G, tonin).^{65,66} Expression of AGT, ACE, and AT1 receptors is higher in visceral compared with subcutaneous adipose tissue. Plasma Circulating levels of AGT, renin activity, ACE activity, and adipose tissue AGT expressions are positively directly correlated with adiposity in humans. Thus adipose tissue RAS is a potential link between obesity and hypertension. Angiotensin II increases vascular tone, aldosterone secretion from the adrenal gland, and sodium and water reabsorption from the kidney. These effects contribute to blood pressure regulation. In obesity increased secretion of angiotensin II induces hypertension. Thus, It has been observed that adipocyte-derived components of the RAS may play important autocrine, paracrine, and endocrine roles in the pathogenesis of obesity, insulin resistance, and hypertension.^{67,68,69}

3. Conclusions

Obesity, associated with changes in adipokine expression such as increased levels of TNF- α , IL-6, resistin, PAI-1 and leptin, and reduced levels of adiponectin affect insulin sensitivity, vascular endothelial function and the coagulation system. These effects accelerate atherosclerosis. Adipokines and a 'low-grade inflammatory state' may be the link between the metabolic syndrome with its cluster of obesity and insulin resistance and cardiovascular disease. Thus considering the new findings about actions of adipokines, researchers should focus back on obesity as an essential primary target to reduce the risk of developing the metabolic syndrome and type 2 diabetes, with its associated cardiovascular complications.

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