SUMMERY

Adipose tissue is a specialized form of connective tissue consisting of fat-storing cells (adipocytes) associated with a rich blood supply. There are two types of adipose tissue: white (or unilocular) and brown (or multilocular).

Origin of adipose tissue:

Adipocytes are derived from mesenchymal precursor cells.

Process of adipocyte differentiation:

Stem cell ⟶ mesenchymal precursor ⟶ preadipocyte ⟶ early &late changes mature adipocyte.

Function of white adipose tissue:

- ***Thermal insulation.***
- ***Mechanical protection.***
- ***Metabolic function:*** lipogenesis, lipolysis, glucose homeostasis
- ***Secreatory function:***

Adipose tissue has long been considered to be a passive, inactive tissue. However, research in the past decade has demonstrated that adipose tissue plays an important role in energy regulation via endocrine, paracrine and autocrine signals. Several hormones and other factors are secreted from adipocytes.

Adipocyte secrets*:*

1- Hormones: leptin, resistin, adiponectin, angiotensinogen and sex steroid hormone.

2- Prostacyclins: PGE2 (prostaglandin E2) PGI_2(prostaglandin I_2).

3- Growth factors: HGF (Hepatocyte growth factor).

4- Enzymes: cytochrome P450 aromatase, I7 Bhsd (17β hydroxyl steroid dehydrogenase), 11 βhsdl (11 β hydroxyl steroid dehydrogenase 1), PAI-1 (plasminogen activator inhibitor-1), LPL (lipoprotein lipase), CETP (cholesterol ester transfer protein), and ACE (Angiotensin converting enzyme).

5- Free fatty acid.

1- Hormones:

A)Leptin:

- Inhibit food intake and increase energy expenditure.
- Increase insulin sensitivity.
- Activate sympathetic nervous system.
- Influence reproductive function.
- Influence neuroendocrine function.

B) adiponectine:

Adiponectin decreases lipid synthesis and glucose production in the liver and causes decreases in glucose and free fatty acid concentrations in the blood. In addition, triglyceride production is decreased and fat oxidation and energy dissipation in the muscle are increased. Adiponectin-linked insulin sensitization is mediated, at least in part, by activation of AMPK in skeletal muscles and the liver, which increases fatty-acid oxidation and reduces hepatic glucose production. Also, adiponectin could regulate body temperature and basal metabolic rate.

Several vascular effects of Adiponectin have been described:

1)Increased endothelium (dependent – independent) vasodilation;

2) Anti-atherosclerotic effect;

3) Reduced expression of TNF-α;

4) Increased production of NO;

5) Stimulation of angiogenesis;

6) Reduction of the thickness of the tunica intima and smooth musculature that is secondary to artery wall injury; and

7) Inhibition of migration and proliferation of endothelial cells**.**

C)Resistin:

Resistin is a protein with proinflammatory properties secreted by monocytes and adipocytes. Resistin antagonizes insulin action in the liver and counterbalance the insulin-sensitizing effects of adiponectin in the liver.

D)Angiotensinogen:

Angiotensinogen is the precursor of the vasoactive peptide angiotensin II. Angiotensin II is a well known hypertensive hormone, generated in the renin angiotensin system.

Increased AGE production could also contribute to enhanced adipose mass because angiotensin II is believed to act locally as a trophic factor for new adipose cell formation**.**

E) Steroid hormones:

Sex steroids are not synthesized de novo in fat, but are formed by the action of stromal enzymes on adrenally derived precursors.

- Aromatase activity converts androstenedione to estrone.

- Androstenedione is converted by 17β-hydroxysteroid oxidoreductase to testosterone.
- 11-hydroxysteroid dehydrogenase regenerates metabolically active cortisol from cortisone.

2) Cytokines:

A)Tumour necrosis factor α (TNF-α):

The effects of TNFα on adipocytes include increased lipolysis, increased leptin secretion, decreased adiponectin secretion, suppressed LPL, decreased glucose transporter-4 expression, impaired insulin signaling, induced insulin resistance and antagonism of TZDs/PPARγ.

TNF-α inhibits the expression of the two master regulators of adipose differentiation, the transcription factor CEBPα and the nuclear receptor PPARγ2.

TNF-α production from the fat cuff around the arteriole origin inhibits insulin-stimulated nitric oxide synthesis and results in unopposed vasoconstriction – a mechanism termed 'vasocrine' signalling**.**

TNF-α showed significant associations with coronary heart disease and congestive heart failure**.**

TNFa stimulates ACTH secretion and inhibits secretion of TSH**.**

B) Interleukine-6 (IL-6):

It has pleiotropic effects on a variety of tissues, including down-regulation of adipocyte LPL, stimulation of acute-phase protein synthesis, increase in the activity of the hypothalamic-pituitary axis (HPA), and thermogenesis.

In contrast to stimulating ACTH, cortisol, GH, and prolactin release, IL-6 suppresses TSH secretion in a dose-dependent manner**.**

C) Interleukine-10 (IL-10):

IL-10 is an anti-inflammatory cytokine**.**

D) Interleukine-8 (IL-8):

IL-8 is a potent chemoattractant and may be responsible for the recruitment of neutrophils and T lymphocytes into the subendothelial space. It also induces adhesion of monocytes to endothelium and migration of vascular smooth muscle cells. All those processes lead to intimal thickening and atherosclerosis.

E)Monocyte chemoattractant protein (MCP-1):

MCP-1 blunted the insulin-stimulated glucose uptake so it is involved in obesity-related insulin resistance**.**

3) Enzymes:

A) Cytochrome P450 aromatase:

It converts androstenedione to oestrone.

B)11-Hydroxysteroid dehydrogenase:

11-β HSD-1 regenerates metabolically active cortisol from cortisone in humans.

C)17β-Hydroxysteroid dehydrogenases:

17β-HSD1 is a key enzyme in the biosynthesis of female sex steroids, catalysing the final step which converts the less potent E1 into biologically active E2.

D)Plasminogen activating inhibitor-1:

Plasminogen activating inhibitor-1 (PAI-1) is the major physiological inhibitor of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). PAI-1 not only inhibits fibrinolysis but also has complex interactions with cellular matrices, and further inhibits proteolysis.

PAI-1 is a significant risk factor for macrovascular and microvascular complications of diabetes. PAI-1 is also linked to insulin resistance.

E) Lipoprotein lipase:

That hydrolyzes lipids in lipoproteins, like those found in chylomicrons and very low-density lipoproteins (VLDL), into three free fatty acids and one glycerol molecule. It requires Apo-CII as a cofactor**.**

F) Angiotensin converting enzyme (ACE):

It has two primary functions:

- It catalyses the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor.
- It is involved in the inactivation of bradykinin, a potent vasodilator.

G) Cholesteryl ester transfer protein (CETP):

It promotes the redistribution of cholesteryl esters, triglyceride, and, to a lesser extent, phospholipids between plasma lipoproteins.

H) Phospholipid transfer protein (PLTP):

Functions of PLTP:

1. Phospholipid transfer activity;
2. HDL conversion; and

3. Cellular cholesterol efflux**.**

I)ApoE:

APOE is essential for the normal catabolism of triglyceride-rich lipoprotein constituents.

3)Growth factors:

a) Vascular endothelial growth factor (VEGF):

VEGF is a paracrine factor that stimulates local physiological and pathological angiogenesis in response to hypoxia.

B) Insulin like growth factor -1 (IGF1) peptide:

The most potent natural activators of the AKT signaling pathway, a stimulator of cell growth and multiplication and a potent inhibitor of programmed cell death. It plays an important role in childhood growth and continues to have anabolic effects in adults.

C) Hepatocyte growth factor (HGF):

Hepatocyte growth factor (HGF) is another endothelial growth factor with potent angiogenic and mitogenic effects that can synergistically augment the angiogenic effects of VEGF in vivo and in vitro**.**

D) The transforming growth factor beta (TGFβ):

TGFβ1 performs many cellular functions, including control of cell growth, cell proliferation, cell differentiation and apoptosis. There is evidence that TGFβ1 is involved in wound healing processes**.**

TGFβ2 is the isoform most strongly linked to heart morphogenesis and neocartilage formation. It has been reported that TGFβ2 also plays a role in normal hematopoiesis.

4) Complement factors:

A) Acylation-stimulating protein (ASP):

ASP acts locally in adipose tissue, where it stimulates glucose uptake, increases the activity of diacylglycerol acyltransferase (DGAT), and inhibits hormone-sensitive lipase activity. These actions of ASP increase the efficiency of triglyceride synthesis and storage in adipocytes. ASP directly stimulated insulin secretion.

B) Adipsin:

Human adipsin is identical to complement D, the initial and rate-limiting enzyme in the alternative complement pathway.

C) Adipose Fatty Acid-Binding Protein:

Fatty acid-binding proteins are abundant low-molecular-weight cytoplasmic proteins that are thought to be involved in the intracellular transport and metabolism of fatty acids.

D)Agouti Protein:

The participation of the agouti protein in the development of insulin resistance has been proposed to be through increasing intracellular free calcium concentrations. Agouti acts as a potent antagonists to hypothalamic MC4-R, a receptor involved in regulation of food intake**.**

5) Prostaglandins:

Prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) are the two major PG produced from rodent and human adipocytes.

PGE_2 negatively modulates cAMP production and thus lipolysis in rat and human adipocytes.

Conversely, PGI_2 and carbaprostacyclin ($cPGI_2$), its stable analog, are proposed as adipogenic-hyperplastic effectors in Ob1771 cell line**.**

Another ($cPGI_2$) promotes differentiation via PPAR. (PGJ_2) is an important ligand for PPARγ, an adipogenic transcription factor. In contrast, $PGF_{2\alpha}$ inhibits the differentiation of 3T3-L1 and rat preadipocytes.

Disorders of adipose tissue:

- Overweigh and obesity
- lipodystrophy

A) Lipodystrophy:

Lipodystrophy is a medical condition characterized by abnormal or degenerative conditions of the body's adipose tissue.A more specific term, lipoatrophy is used when describing the loss of fat from one area (usually the face).

B) Overweight and obesity:

Overweight represents a body weight exceeding the norm for a person's gender, age, height and build. Obesity signifies an excessive accumulation of adipose tissue.

In general, obesity is defined as BMI equals or greater than 30 kg/m^2.

Types of obesity:

- Android Adiposity: also termed: male pattern, "apple-shaped", and visceral.
- Gynoid adiposity: also termed: female pattern, "pear-shaped", and peripheral.

Causes of obesity:

- Primary obesity.
- Secondary obesity. It is due to:

  Genetic disorder or endocrinal disorder.

Comorbid Conditions Linked to Obesity:

The list of comorbid conditions associated with obesity is extensive and including the following:

- The metabolic syndrome,
- Cardiovascular disease,
- Respiratory,
- Gastrointestinal diseases,
- Non-alcoholic fatty liver disease and steato-hepatitis,
- Gallbladder disease,
- Reproductive disorders, Infertility,
- Cancer of the cervix, endometrium, ovaries, prostate, breast, esophagus, liver, gallbladder, pancreas, kidney colon , and rectum,
- Neurological disorders,
- Muscluskeletal problems,
- Immunological,
- Hematological disorders,
- Varicosities,
- Psychological and socioeconomic difficulties.