Arh. farm. 2024; 74: 375 – 390 *Review article/Pregledni rad*

Know your Enemy: Nature and Biochemistry of Obesity

Jasna Bjelanović[1], Ognjan Skrobić[2]

[1]Center for Medical Biochemistry, University Clinical Center of Serbia,
[2]Clinic for Digestive Surgery, University Clinical Center of Serbia

Corresponding author: Jasna Bjelanović, e-mail: jasna_bjelanovic@yahoo.com

Received: 3 May 2024; Revised in revised forme: 13 June 2024; Accepted: 14 June 2024

Abstract

Obesity represents a serious medical condition and has nowadays reached pandemic proportions. Comorbidities associated with obesity are severe, and affect almost all organ systems. Adipose tissue has several important functions: to provide energy storage, maintain body temperature through the process of thermogenesis, and maintain balance in a variety of metabolic patterns. Adipose tissue is an endocrine organ with numerous biochemical roles, and in obese individuals adipose tissue becomes either hypertrophic or hyperplastic, with impaired function. The immune system activity and metabolic regulation in adipose tissue are extremely related processes. A loss of balance on this axis causes numerous disorders associated with obesity, and the basis of these disorders is insulin resistance, which is a hallmark of obesity. Hormones that are almost exclusively produced in adipocytes and studied in various biochemistry processes are leptin, adiponectin and resistin. Successful treatment of obesity nowadays involves lifestyle and diet modification, pharmacotherapy, mainly with glucagon-like peptide-1 agonists, and bariatric surgery, which remains the most effective treatment method for the selected population of severely obese individuals. Positive effects of bariatric surgery are reflected not only in a restriction of food intake, but in hormonal changes, especially those of gut hormones responsible for hunger regulation and energy metabolism.

Key words: obesity, adipose tissue, metabolism, therapeutic approach

https://doi.org/10.5937/arhfarm74-50830

Introduction

Obesity is a chronic relapsing disease that has reached pandemic proportions in the last two decades. It is described as an excessive accumulation of body fat. The current incidence and predictions are appalling. It is recognized that every eighth adult individual in the world is obese. (1). In Serbia, almost every third individual is overweight, and there is also a complex association of obesity with the social/economic status, as well as with the level of education. Therefore, an increase in obesity prevalence is most striking in countries with a lower income and with a lower educational level (2).

Obesity is directly linked to various conditions that may lead to severe deterioration of health, and is classified as a disease in the international disease registry. According to the Body Mass Index (BMI) classification, individuals that have a BMI $\geq$ 25–29.9 kg/m^2 are considered overweight, and those with a BMI $\geq$ 30 kg/m^2 are considered obese (3). It is of great importance that health practitioners realize that treating obesity is as important as the treatment of comorbidities that result from obesity. These associated conditions affect different organ systems. In the cardiovascular system, the most common condition is hypertension (4). Hypertension in an obese individual is explained by the increased activation of the renin-aldosterone-angiotensin system, reduced blood flow in the kidneys, with increased sodium reabsorption and salt retention. Obesity significantly increases the risk of coronary artery disease, heart failure and stroke (5). Type 2 diabetes mellitus (T2DM) may be the most common complication of obesity, with a well-established and proven connection. Almost 80% of T2DM patients are obese, and sometimes successful treatment of obesity may lead to a complete resolution or significantly improved control of the disease. Dyslipidemia is also most likely to occur in obese individuals, along with metabolic syndrome. Severe damages of the respiratory system are also common, such as obstructive sleep apnea and obesity hypoventilation syndrome. Fatty liver diseases have a high prevalence among obese patients. The reproductive system is strongly affected. Obese women often have an irregular menstrual cycle, ovulatory dysfunction, and polycystic ovaries (6-8).

All these conditions, together with the stigmatization of obese individuals, commonly lead to the deterioration of mental health. For example, the incidence of depression is higher in the obese population, and frequently encountered in young female patients (9, 10).

A proper understanding of obesity, especially by health professionals, has been getting more attention, and this review is focused on molecular changes in obese patients. It is of great importance to acquire knowledge in lipogenesis and lipolysis through an understanding of the biochemical processes of adipogenesis, and, based on that, to consider new treatment possibilities.

Adipose tissue in obesity

According to the definition of the World Health Organization (WHO), obesity is “an increase in fat tissue that can impair health” (11). Obesity occurs as a result of a

positive energy balance, that is, a disturbed balance between the anabolism and catabolism of lipids. Adipose tissue is a metabolically active organ that, through the processes of hypertrophy and hyperplasia, can vary to an enormous degree on an intra and interindividual level. However, the premise that adipose tissue is a unique entity and a simple energy storage is wrong. Indeed, adipose tissue is an endocrine organ with various biochemical roles. Through the synthesis of numerous messengers, adipokines, it communicates with other organ systems in a paracrine and endocrine manner, acting both locally and systemically (12). Although adipose tissue is composed of numerous cells with different functions, adipocytes occupy the largest part of the tissue and are traditionally classified into two groups: white, most important as an energy reservoir, but also having a significant role in the pathogenesis of insulin resistance, and brown, which are responsible for maintaining the body temperature and are of vital importance in the postnatal period (13). A disruption in any of these most important functions of adipose tissue can lead to severe metabolic diseases (14). The process of thermogenesis, which is a feature of brown adipose tissue, is mediated by the function of a proton channel in the inner membrane of adipocyte mitochondria, designated as uncoupling protein-1 (UCP-1). The role of this transporter is to redirect part of the energy generated in the electron transport chain during beta-oxidation of fatty acids or glycolysis into heat formation, that is, for body temperature maintenance (15). Two more types of adipose tissue cells have recently been defined. One are beige cells (16), morphologically between white and brown adipocytes, formed in response to exposure to low temperatures. The other are the recently described pink adipocytes, alveolar epithelial cells of the mammary glands, which play a role in milk production during lactation in mammals (17). These two subclasses of adipocytes can conjure up all the flexibility of adipose tissue: not only are they created by the proliferation and differentiation of stem cells, but different types of adipocytes can also be created by the trans differentiation of fully mature adipocytes promoted by the action of different signals. Thus, it was determined that exercise, diet, hormonal status, some drugs, and adipokines can change the “nuance” of adipose tissue cells. These phenotype changes can widen the spectrum of therapeutic possibilities in the treatment of diseases related to fat metabolism, but also of some malignancies, such as breast cancer (18).

Lipogenesis and lipolysis

During the enlargement of adipose tissue, adipocytes become either hyperplastic, where their number increases through the process of adipogenesis, or hypertrophic, where their size increases through lipogenesis. Hyperplastic adipocytes are usually metabolically healthy, while hypertrophic adipose tissue has the characteristics of dysfunctional adipocytes, with a high risk of insulin resistance, hypoxia and chronic inflammation, because the large fat cells are highly inflammatory and adipocyte volume correlates with adipocytokine secretion (19). Adipocytes store fat in the form of triglycerides, through the process of lipogenesis, at a time when nutritional intake exceeds the real needs of the body. As expected, in conditions of high energy needs (starvation,

physical activity, exposure to cold), this reserve is mobilized by the catabolic process of lipolysis to provide the necessary energy in the periphery (20). The balance between lipogenesis and lipolysis is presented in Figure 1 (21).

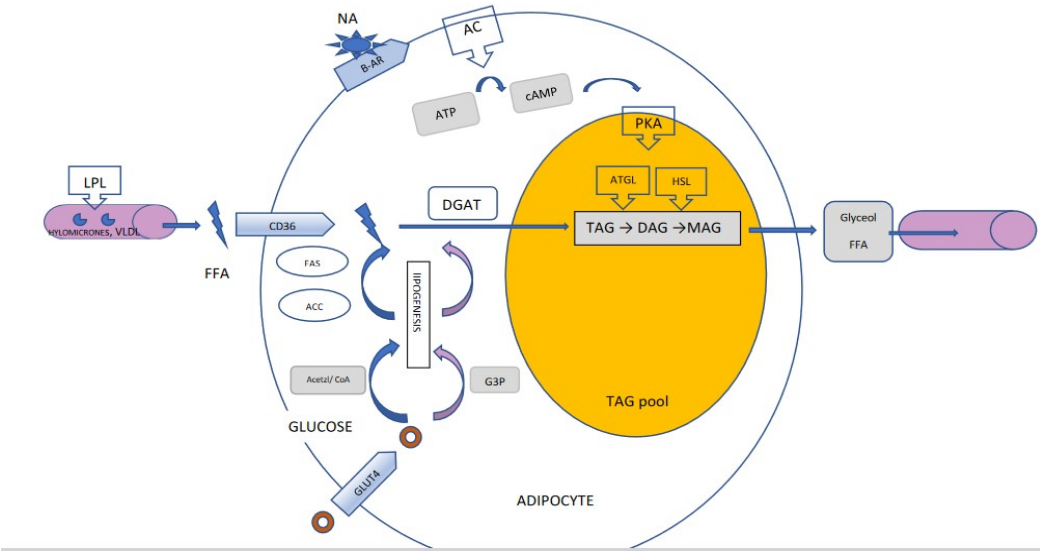

Figure 1. Balance between lipogenesis and lipolysis (adapted from (21))

Slika 1. Ravnoteža između procesa lipogeneze i lipolize (prema (21))

Abbreviations: TG, triglyceride; VLDL-TG, triglyceride- containing very low density lipoprotein; FFA, free fatty acid; CD36, cluster of differentiation 36; LPL, lipoprotein lipase; GLUT4, glucose transporter 4; ACC, acetyl-CoA carboxylase 1; FAS, fatty acid synthase; G3P, glycerol 3 phosphate; DGAT, diacylglycerol acyltransferase; β-AR, β-adrenergic receptor; NA, noradrenaline; AC, adenylyl cyclase; PKA, protein kinase A; ATGL, adipocyte triglyceride lipase; HSL, hormone sensitive lipase; TAG, triacyl glyceride; DAG, diacylglycerol; MAG, monoacylglycerol.

Skraćenice: TG, trigliceridi; VLDL-TG, trigliceridi koji sadrže lipoproteine veoma niske gustine; FFA, slobodne masne kiseline; CD36, klaster diferencijacije 36; LPL, lipoprotein lipaza; GLUT4, glukoza transporter 4; ACC, acetil-CoA karboksilaza; FAS, sintaza masnih kiselina; G3P, glicerol 3 fosfat; DGAT, diacilglicerol aciltransferaza; β-AR, β-adrenergički receptor; NA, noradrenalin; AC, adenilil ciklaza; PKA, protein kinaza A; ATGL, adipocit triglicerid lipaza; HSL, hormon sensitivna lipaza; TAG, triacilglicerid; DAG, diacilglicerol; MAG, monoacilglicerol.

Under normal food intake conditions, there are two ways of storing fat. The action of the enzyme lipoprotein lipase (LPL) in the circulation leads to the breakdown of triglycerides from lipoproteins rich in triglycerides, such as chylomicrons from the cells of the intestinal mucosa or VLDL particles synthesized in hepatocytes, and the free fatty acids produced by this hydrolysis enter the adipocyte via the CD36 receptor. On the other hand, adipocytes take up glucose via GLUT 4 transporter. Glucose is further metabolized to glycerol, which is necessary as a basis for the re-esterification of triglycerides by the enzyme diacylglycerol acyltransferase (DGAT) (22). However, under conditions of

starvation, lipolysis is induced due to the reduced concentration of circulating insulin in white adipose tissue. Insulin inhibits lipolysis by the activation of phosphodiesterase, which leads to a decrease in the intracellular cyclic adenosine monophosphate (cAMP) level, which is an important signal molecule in the hydrolysis of triglycerides (23). When the level of insulin is low, the availability of glucose to provide glycerol-3-phosphate is limited. Then an alternative pathway, the so-called *glyceroneogenesis*, is activated, where glycerol is synthesized from intermediates such as lactate, pyruvate or some amino acids (e.g., alanine) (24). Furthermore, fatty acids represent a structural component of cell membranes and are signaling molecules, and therefore essential for survival. Therefore, cells have evolved mechanisms for either taking up fatty acids from circulation or synthesizing them from other sources, if reserves are unavailable, and this process is called *de novo lipogenesis* (25). During the processes of glycolysis and of the cycle of tricarboxylic acids, there is an increase in the concentration of citrate in the mitochondria, which is then transported into cytosol via a transporter labeled as the mitochondrial citrate/isocitrate carrier (CIC) (Figure 2).

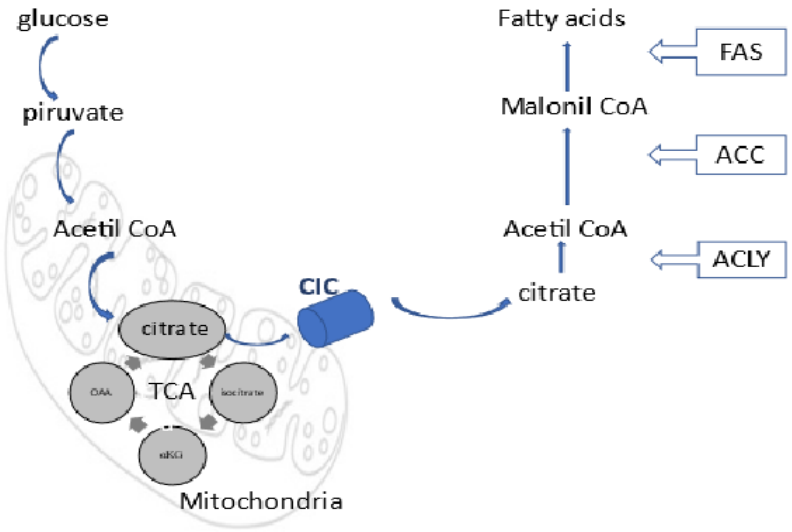

Figure 2. Mechanism of *de novo* lipogenesis (adapted from (26))

Slika 2. Mehanizam *de novo* lipogeneze (prema (26))

Abbreviations: TCA, tricarboxylic acid cycle; OAA, oxaloacetate; CIC, citrate/isocitrate carrier; αKG, α-ketoglutarate; ACLY, ATP-citrate lyase; CoA, Coenzyme A; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase.

Skraćenice; TCA, ciklus trikarboksilnih kiselina; OAA, oksaloacetat; CIC, citrate/izocitrat nosač; αKG, α-ketoglutarat; ACLY, ATP-citrat liaza; CoA, koenzim A; ACC, acetil-CoA karboksilaza; FAS, sintaza masne kiseline.

The cytoplasmic form of citrate is further converted into fatty acids by a series of biochemical reactions catalyzed by various enzymes. The process primarily occurs in adipocytes and hepatocytes; however, evidence speaks of the reactivation of this process in cancer cells as well, in order to open an alternative pathway of energy generation that

is increasingly consumed by malignantly altered cells (26). Enzymes that participate in these biochemical processes: ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), can be new sites of therapeutic approach for the treatment of both malignant diseases and benign pathologies, e.g. non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (T2DM), neurodegenerative or autoimmune diseases. The expression and activity of these enzymes are also determined by post-translational modifications, which are related to the nutritional status, that is, the availability of substrates for synthesis (27).

Lipolysis is hormonally regulated, and the best explanation is the effect of the sympathetic nervous system, i.e. noradrenaline (28). Noradrenaline stimulates β-adrenergic receptors, which, mediated by adenyl cyclase, respond with increased production of cyclic adenosine monophosphate (cAMP), which further activates protein kinase A (PKA). This enzyme leads to phosphorylation and consequent activation of enzymes involved in the breakdown of triglycerides into energy-useful fatty acids and glycerol, which can be further recycled or used in the gluconeogenesis process. While hormone sensitive lipase (HSL) is activated directly by phosphorylation, the activation of adipose triglyceride lipase (ATGL) has a more complex pathway: it is necessary to break down the complex of cofactors comparative gene identification-1 (CGI-58) and perilipin 1 (PLIN1), protein modulators on the membrane of lipid drops (Figure 3) (29).

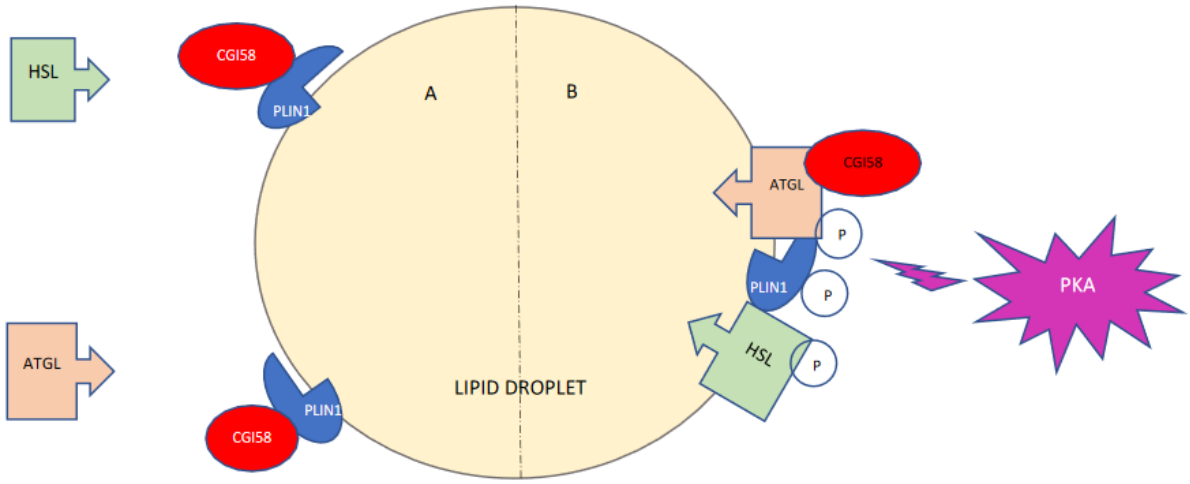

Figure 3. **Activation of protein modulators on lipid droplet membrane during lipolysis: A. In a steady state; B. During β- adrenergic activation by the PKA enzyme (adapted from (30))**

Slika 3. **Aktivacija proteinskih modulatora na membrani lipidne kapi tokom lipolize: A. U stanju ravnoteže; B. β- adrenergička stimulacija preko enzima PKA (prema (30))**

Abbreviations: ATGL, adipose triacylglyceride lipase; CGI-58, comparative gene identification 58 protein; HSL, hormone sensitive lipase; P, phosphate; PKA, protein kinase A; PLIN1, perilipin 1.

Skraćenice; ATGL, adipozna triacilglicerid lipaza; CGI-58, komparativna identifikacija gena 58 protein; HSL, hormon sensitivna lipaza; P, fosfat; PKA, protein kinaza A; PLIN1, perilipin 1.

CGI-58 is constitutively bound to PLIN1 on the lipid droplet membrane. After the activation of PLIN1 by PKA, the dissociation of CGI-58 from PLIN1 occurs. CGI-58 then interacts with ATGL and stimulates the activity of this enzyme (30). The latest research demonstrated the importance of the perilipin family both in the treatment of obesity and diseases associated with increased body mass. PLIN1 is also one of the recommended biomarkers of liposarcoma (30). Impaired expression of PLIN1 has been found in several cancers, such as hepatocellular or breast cancer, where, depending on the cell type, the level of PLIN1 may have prognostic significance: in cells that have the capacity to deposit fat (adipocytes or to some extent hepatocytes), overexpression of PLIN1 may favor tumorigenesis, while generally reduced expression of PLIN1 may lead to reduced availability of fatty acids produced by lipolysis for nutrition of cancer cells (30, 31).

Insulin resistance

Immune system activity and metabolic regulation in adipose tissue are closely related processes. A loss of balance on this axis causes numerous disorders associated with obesity, and the basis of these disorders is *insulin resistance* (32). Obesity is the cause of activation of the innate immune system, and in this process the key role is that of adipose tissue macrophages (ATM) (21). In states of normal nutrition, adipose tissue, primarily visceral, contains numerous cells of the immune system, and the most abundant are macrophages and T regulatory cells (Treg lymphocytes), with a primary role in removing aged adipocytes and removing excess fat (33). However, in obese people, chronic inflammation is a constant state in which these ATMs change their phenotype from the M2 (regenerative macrophages) to M1 type (proinflammatory macrophages). These macrophages secrete pro-inflammatory cytokines (TNF-α, IL-1, IL-6), which will exert their negative effect at the level of the insulin receptor in the cells that possess this receptor: skeletal muscles and smooth muscles of the heart, hepatocytes and, of course, adipocytes (34).

Insulin receptor is a protein tetramer with tyrosine kinase activity which consists of 2 extracellular subunits and 2 transmembrane domains, each with a specific function (35). In normally fed individuals, after the binding of insulin to the receptor, conformational changes occur that lead to the phosphorylation of tyrosine residues on the receptor intracellular part in positions 1162, 1158 and 1163, and finally in position 972. This last phosphorylation stimulates the synthesis and activation of the membrane protein GLUT 4, a glucose transporter. At the cell membrane, GLUT4 allows the facilitated diffusion of circulating glucose down its concentration gradient into adipocytes. This protein is normally found in vesicles in the cytoplasm of insulin-sensitive cells, and after activation it is transferred to the membrane. In obese people, in the states of chronic inflammation described earlier, the influence of pro-inflammatory cytokines and the excess of palmitic acid changes the response of the insulin receptor to insulin binding: instead of tyrosine phosphorylation, the serine residue in position 307 is phosphorylated and there is no activation signal for GLUT 4 (34, 36).

In people with insulin resistance, the process does not stop at this level, unfortunately. Because glucose cannot enter the cell due to insulin resistance, it becomes an unexploited energy source. The cell needs another source of energy for survival, so lipolysis takes precedence and the creation of an increased amount of free fatty acids occurs. Their β-oxidation produces acetyl-CoA, which is consumed in the cycle of tricarboxylic acids, and ketone bodies are formed in excess, mainly acetoacetate and β-hydroxybutyrate (37). This condition is called diabetic ketoacidosis (DKA) if all the three criteria are met: "D" – diabetes, that is glucose value over 11.1 mmol/L, "K" - blood ketone concentrations >3.0 mmol/L and in urine ≥+2, and "A" - acidosis, where pH<7.3 or bicarbonate <15.0 mmol/L (38). This definition of the British Diabetes Association has changed since 2009, especially after the introduction of a new therapy for diabetes (a group of drugs that act on the level of sodium-glucose transport, the so-called SGLT2 inhibitors), so the American Diabetes Association ignored the criteria for the level of glycemia and today, it is considered that any ketonemia greater than 0.6 mmol/L with a pH<7.3 can be considered a risk for the development of DKA (39).

When consuming exceptionally large amounts of food, due to disturbances at the level of adipogenesis and the consequent hypertrophy of fat tissue, excess lipids accumulate in other organs, such as the liver, kidneys and muscle tissue. Other forms of lipids or intermediate products, such as diacylglycerols, can be found in these depots, which can further modify insulin receptors and worsen the degree of insulin resistance (40).

Secretory function of adipose tissue

The secretory function of adipose tissue has been studied in detail in recent years, with research showing that adipose tissue is the largest and an extremely active endocrine organ in the human body (41). The dynamics of this tissue are a direct consequence of the presence of the so-called stroma - vascular fraction, which consists of all cells except adipocytes: blood cells, endothelial cells, pericytes, as well as preadipocytes, fibroblasts and others (42). In addition to locally synthesized hormones, adipose tissue also secretes numerous adipocytokines with pro- and anti-inflammatory properties, the balance of which predisposes one to the condition of metabolic syndrome: diabetes mellitus, hyperlipidemia, hypertension, atherosclerosis (43). The main secretory products of adipose tissue and their functions are shown in Table I (44).

Table I Secretory products of adipose tissue (44)

Tabela I Sekretorni produkti masnog tkiva (44)

Molecule	Function
Leptin	Signals to the brain about body fat stores. Regulation of appetite and energy expenditure. Wide variety of physiological functions
Adiponectin	Plays a protective role in the pathogenesis of type 2 diabetes and cardiovascular disease
Resistin	Hypothetical role in insulin resistance
TNF-α	Affects insulin receptor signaling, possible cause of the development of insulin resistance in obesity
IL-6	Pro-inflammatory, lipid and glucose metabolism, regulation of body weight
PAI-1	Inhibitor of the fibrinolytic system by inhibition of activation of plasminogen
Angiotensinogen	Precursor of angiotensin II; regulator of blood pressure and electrolyte homeostasis
FFA	Oxidized in tissues to produce local energy. Serves as a substrate for triglyceride and structural molecular synthesis. Involved in the development of insulin resistance
ASP	Influences the rate of triglycerides synthesis in adipose tissue
VEGF	Stimulation of angiogenesis
Adipsin	Potential relation between the complement pathway and adipose tissue metabolism
Glycerol	Structural component of the major classes of biological lipids and gluconeogenic precursor
IGF-α	Stimulates proliferation of a wide variety of cells and mediates many cells and many of the effects of growth hormone

Abbreviations: TNF-α, tumor necrosis factor; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor 1; FFA, free fatty acids; ASP, acylation stimulating protein; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor 1.

The earliest discovered hormone of adipocyte origin is *leptin*. It got its name from the Greek word “leptos”. which means thin, petite, small (45). Leptin is secreted from adipocytes of white adipose tissue and transported to the central nervous system through circulation. There, it binds to its receptors in the arcuate nucleus of the hypothalamus, where it exerts its basic effect: creating a feeling of satiety and increasing energy consumption. During the period of starvation, the action of leptin at the level of the hypothalamus is reduced, so a decrease in energy utilization and the feeling of hunger dominate. However, in obesity, this negative feedback of satiety receptor stimulation and food intake often does not work due to the development of resistance to this hormone,

which occurs due to structural changes in leptin and/or its receptor, or mutations in the genes that encode their synthesis, or due to changes in the blood-brain barrier and impaired leptin transport (46). The binding of leptin to the receptor leads to the production of pro-opiomelanocortin (POMC), which dissociates into two products: adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH). which then binds to the melanocortin-4 receptor (MC4R), which stimulates the basic function of leptin (12, 47). Mutations in the gene encoding MC4R synthesis led to increased nutrient intake, so this receptor is a possible site for pharmacotherapy in the treatment of obesity. Also, agonists of this receptor can influence both the increase in insulin sensitivity and the speeding up of energy expenditure (48). Chronic inflammation, but also acute infections, as well as the effect of glucocorticoids, increase the level of leptin, while exposure to cold, melatonin, thyroid hormones and growth hormone, smoking and some drugs in the treatment of T2DM (thiazolidinediones) reduce leptin concentrations. Leptin synthesis is higher in subcutaneous than in visceral adipose tissue, and the inhibitory effect of androgens, along with the stimulating effect of estrogen, explain the higher levels of leptin in women (44, 49).

Another hormone, called *adiponectin*, the synthesis of which is exclusively attributed to adipose tissue, acts in a completely opposite manner to the action of leptin. It stimulates the appetite and reduces energy consumption (44), and unlike leptin levels, adiponectin levels are lower in obese people. Adiponectin, in its different forms, binds to different receptors, and one of the mechanisms of action is the stimulation of β-oxidation of fatty acids by activating AMP-activated kinase (AMPK), which inhibits Acetyl-CoA carboxylase (ACC), the enzyme that determines the rate of *de novo* lipogenesis. Consequently, energy is provided by consuming existing fatty acids (50). In the liver, adiponectin acts by reducing the release of glucose into the circulation (51), while in skeletal muscles it stimulates glucose uptake, fatty acid oxidation, and increases insulin sensitivity (52). Considering the protective effect of adiponectin in states of disturbed metabolism due to obesity, one of the possible new therapeutic approaches would certainly be adiponectin receptor agonists. One such approach, called “AdipoRon”, is a product of a Japanese research center and is certainly a potential future therapy for obesity-related conditions such as T2DM (53).

The most recently discovered adipose tissue hormone is called *resistin*, named for its ability to induce insulin resistance (54). It is a small peptide, 108 amino acid residues long, with a molecular weight of 12.5 kDa (55), and it is primarily secreted by adipose tissue macrophages. It acts through two types of receptors: adenylyl cyclase-associated protein 1 (CAP1) and Toll-like receptor 4 (TLR4), and both receptors have a pro-inflammatory effect. In obese individuals, resistin levels are high and antagonizing the action of resistin leads to increased insulin sensitivity (53, 56).

Impact of obesity treatment

The treatment of obesity starts with disease recognition, which is generally a problem, as the majority of the physicians focus on the obesity consequences, but not on

a problem of the obesity as it is. The treatment itself should be multidisciplinary and should cover all the important treatment aspects. Usually, it will start with diet and lifestyle modifications. Behavioral therapy also plays an important role, as a primary treatment or complementary with other treatment modalities (57, 58). Pharmacotherapy had been offered to obese patients for a long time; however, with the breakthrough of glucagon-like peptide 1 (GLP-1) agonists it started to show promising results for the first time. There are several mechanisms through which GLP-1 agonists help patients achieve efficient weight loss. Alongside stimulating increased insulin production and therefore improving blood sugar levels, these drugs exhibit several other effects, such as improved hunger control and decreased movement of the stomach, which on the other hand leads to satiety. Sometimes these drugs may cause some side effects such as nausea, vomiting and diarrhea (59, 60). The GLP-1 class of drugs isn't recommended to patients with a family history of medullary thyroid cancer. Special attention should also be paid to patients having a history of pancreatitis and gallstones.

Bariatric surgery (BS) represents by far the most efficient and most sustainable weight loss treatment. As it has proven results upon resolving many of the obesity comorbidities, it is also considered a metabolic surgery. Basically, there are two types of bariatric surgery procedures – restrictive and malabsorptive, which are commonly combined. Two of the most common bariatric surgery procedures are “sleeve” gastrectomy (SG), where the stomach is resected, and the narrow gastric tube alongside the lesser curve preserved, and Roux-en-Y gastric “by-pass” (RYGBP), where a small remnant of the proximal stomach is preserved, and then connected to the jejunum, excluding approximately 200 cm of the jejunum out of resorption. Alongside a decreased amount of food that patients can eat after surgery, in recent years there has been a remarkable explanation of hormonal and molecular changes after BS. For example, fasting serum levels of ghrelin decrease significantly after SG. Moreover, postprandial levels of GLP-1 and polypeptide YY increase significantly after both SG and RYGBP. This leads not only to excellent results in terms of weight loss, but also to positive effects on T2DM and dyslipidemia. This is explained by the fast transport of ingested food to the small intestine, which in return stimulates gut cells to produce these hormones (61-63).

Conclusion

Despite the increasing understanding of the origin of the disease itself, the issue of obesity still persists. Even with constant technological improvements in the surgical treatment of obesity, as well as pharmacotherapy, the percentage of weight regain is extremely high. The problem is not only social, since the same issues as before the operation occur again after weight regain: main metabolic disparities, as well as a decrease in the quality of life, and emotional instability. Although obesity is often seen as a nutritional and endocrinological disturbance, psychosocial imbalances have a huge impact, and therefore a multidisciplinary approach, with knowledge of the molecular basis of obesity, gives hope in finding a solution to this global disease.

Acknowledgements

This work has no financial support.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conceptualization: JB; Investigation: JB, OS; Project administration; JB, OS; Supervision; JB; Validation: JB; Visualization: JB; Roles/Writing - original draft: JB, OS; and Writing - review & editing: JB.

References

1. Fan H, Zhang X. Recent trends in overweight and obesity in adolescents aged 12 to 15 years across 21 countries. Pediatr Obes. 2021;17(1):e12839.
2. Wang K, Wu C, Yao Y, Zhang S, Xie Y, Shi K, et al. Association between socio-economic factors and the risk of overweight and obesity among Chinese adults: A retrospective cross-sectional study from the China Health and Nutrition Survey. Glob Health Res Policy. 2022;7(1):41.
3. Evans A, Tolonen H, Hense H, Ferrario M, Sans S, Kuulasmaa K. Trends in coronary risk factors in the WHO MONICA project. Int J Epidemiol. 2001;30(1):35-40.
4. Ruiz-Hurtado G, Ruilope LM. Hypertension and obesity: correlate with renin-angiotensin-aldosterone system and uric acid. J Clin Hypertens (Greenwich). 2014;16(8):559-60.
5. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease. J Am Coll Cardiol. 2009;53(21):1925-32.
6. Yamada T, Kimura-Koyanagi M, Sakaguchi K, Ogawa W, Tamori Y. Obesity and risk for its comorbidities diabetes, hypertension, and dyslipidemia in Japanese individuals aged 65 years. Sci Rep. 2023;13(1):2346.
7. Tadese K, Ernst V, Weaver AL, Thacher TD, Rajjo T, Kumar S, et al. Association of perinatal factors with severe obesity and dyslipidemia in adulthood. J Prim Care Community Health. 2022;13:21501327211058982.
8. Nova S, Irawan R, Widjaja NA, Irwanto I. Vcam-1 values in obese adolescents with dyslipidemia and insulin resistance. Int J Sci Adv. 2022;3(1):105-10.
9. Talbot CV, Branley-Bell D. #BetterHealth: A qualitative analysis of reactions to the UK government's better health campaign. J Health Psychol. 2022;27(5):1252-8.
10. Dewa LH, Lavelle M, Pickles K, Kalorkoti C, Jaques J, Pappa S, et al. Young adults' perceptions of using wearables, social media and other technologies to detect worsening mental health: A qualitative study. PLoS One. 2019;14(9):e0222655.

11. World Health Organization [Internet]. Obesity and overweight [cited 2024 May 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
12. Sikaris KA. The Clinical Biochemistry of Obesity. Clin Biochem Rev. 2004;25:165-81.
13. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004;84:277-359.
14. Carobbio S, Pellegrinelli V, Vidal-Puig A. Adipose tissue function and expandability as determinants of lipotoxicity and the metabolic syndrome. Adv Exp Med Biol. 2017;960:161-96.
15. Barbatelli G, Murano I, Madsen L, Hao Q, Jimenez M, Kristiansen K, et al. The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. Am J Physiol Metab. 2010;298(6):1244-53.
16. Cinti S. Pink adipocytes. Trends Endocrinol Metab. 2018;29(9):651-66.
17. Giordano A, Smorlesi A, Frontini A, Barbatelli G, Cinti S. Mechanisms in Endocrinology: White, brown and pink adipocytes: the extraordinary plasticity of the adipose organ. Eur J Endocrinol. 2014;170(5):159-71.
18. Saponaro C, Gaggini M, Carli F, Gastaldelli A. The Subtle balance between lipolysis and lipogenesis: A Critical Point in Metabolic Homeostasis. Nutrients. 2015;7:9453-74.
19. Braun K, Oeckl J, Westermeier J, Li Y, Klingenspor M. Non-adrenergic control of lipolysis and thermogenesis in adipose tissues. J Exp Biol. 2018;221:1-14.
20. Fielding BA, Frayn KN. Lipoprotein lipase and the disposition of dietary fatty acids. Br J Nutr. 1998;80(6):495–502.
21. Richard AJ, White U, Elks CM, Stephens JM, Feingold KR, Anawalt B, et al. Adipose Tissue: physiology to metabolic dysfunction. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- [updated 2020 Apr 4; cited 2024 May 27]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555602/
22. Gorin E, Tal-Or Z, Shafrir E. Glyceroneogenesis in adipose tissue of fasted, diabetic and triamcinolone treated rats. Eur J Biochem. 1969;8(3):370-5.
23. Ishibashi K, Fujioka T, Ui M. Insulin increased cAMP phosphodiesterase activity antagonizing metabolic actions of glucagon in rat hepatocytes cultured with herbimycin A. Eur J Pharmacol. 2000;409(2):109-21.
24. Smedley I, Lubrzynska E. The biochemical synthesis of the fatty acids. Biochem J. 1913;7:364-74.
25. Koundouros N. Poulogiannis G. Reprogramming of fatty acid metabolism in cancer. Br J Cancer. 2020;122:4-22.
26. Batchuluun B, Pinkosky SL, Steinberg GR. Lipogenesis inhibitors: therapeutic opportunities and challenges. Nat Rev Drug Discov. 2022;21:283-305.
27. Luo L, Liu M. Adipose tissue in control of metabolism. J Endocrinol. 2016;231(3):77-99.
28. Hansen JS, de Mare S, Jones HA, Goransson O, Lindkvist- Petersson K. Visualization of lipid directed dynamics of perilipin1 in human primary adipocytes. Sci Rep. 2017;7:15011.
29. Bombarda-Rocha V, Silva D, Badr-Eddine A, Nogueira P, Gonçalves J, Fresco P. Challenges in pharmacological intervention in perilipins (PLINs) to modulate lipid droplet dynamics in obesity and cancer. Cancers. 2023;15:4013.

30. Westhoff CC, Mrozinski J, Riedel I, Heid HW, Moll R. Perilipin 1 is a highly specific marker for adipocytic differentiation in sarcomas with intermediate sensitivity. J Cancer Res Clin Oncol. 2017;143:225-32.
31. Ota T. Obesity- induced inflammation and insulin resistance. Front Endocrinol. 2014;5:204.
32. Chawla A, Nguzen KD, Goh YP. Macrophage- induced inflammation in metabolic diseases. Nat Rev Immunol. 2011;11:738-49.
33. Bakarat B, Almeida MEF. Biochemical and immunological changes in obesity. Arch Biochem Biophys. 2021;708:108951.
34. Meyts PD, Sajid W, Palsgaard J, Theede AM, Gauguin L, Aladdin H, et al. Insulin and IGF-1 Receptor Structure and Binding Mechanism. In: Saltiel AR, Pessin JE, editors. Mechanisms of Insulin Action. New York, NY: Springer; 2007; p. 1-32.
35. Scheja L, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease. Nat Rev Endocrinol. 2019;15(9):507-24.
36. Asghar A, Sheikh N. Role of immune cells in obesity induced low grade inflammation and insulin resistance. Cell Immunol. 2017;315:18-26.
37. Dhatariya KK. Defining and characterizing diabetic ketoacidosis in adults. Diabetes Res Clin. 2019;155:107797.
38. Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees JA, Courtney CH, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diab Med. 2011;28(5):508-15.
39. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diab Care. 2017;40(12):1622-30.
40. Yang Q, Vijayakumar A, Kahn BB. Metabolites as regulators of insulin sensitivity and metabolism. Nat Rev Mol Cell Biol. 2018;19:654-72.
41. Costa JV, Duarte JS. Adipose tissue and adipokines. Acta Med Port. 2006;19:251-6.
42. Saetang J, Sangkhathat S. Role of innate lymphoid cells in obesity and metabolic disease. Mol Med Rep. 2018;17(1):1403-12.
43. Matsuzawa Y. The metabolic syndrome and adipocytokines. FEBS Lett. 2006;580:2917-21.
44. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci. 2013;2:192-200.
45. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(6505):425-32.
46. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Leptin resistance: underlying mechanisms and diagnosis. Diabetes Metab Syndr Obes. 2019;12:191-8.
47. Cowley MA, Smart JL, Rubinstein M, Cerdar MG, Diano S, Horvath TL, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature. 2001;411:480-4.

48. Heijboer AC, van den Hoek AM, Pijl H, Voshol PJ, Havekes LM, Romijn JA, et al. Intracerebroventricular administration of melanotan II increases insulin sensitivity of glucose disposal in mice. Diabetologia. 2005;48:1621-6.
49. Kersten S. Mechanisms of nutritional and hormonal regulation of lipogenesis. EMBO Rep. 2001;2:282-6.
50. Combs TP, Marliss EB. Adiponectin signaling in the liver. Rev Endocr Metab Disord. 2014;15(2):137-47.
51. Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest. 2001;108(12):1875-81.
52. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med. 2002;8(11):1288-95.
53. Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, et al. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature. 2013;503(7477):493-9.
54. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature. 2001;409(6818):307-12.
55. Patel SD, Rajala MW, Rossetti L, Scherer PE, Shapiro L. Disulfide-dependent multimeric assembly of resistin family hormones. Science. 2004;304:1154-8.
56. Lee S, Lee HC, Kwon YW, Lee SE, Cho Y, Kim J, et al. Adenylyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes. Cell Metab. 2014;19(3):484-97.
57. Johnson V R, Bowen-Jallow KA, Stanford FC. A call to action: multi-disciplinary care and treatment of obesity in pediatrics. Pediatr Investig. 2021;5(1):1-2.
58. Miguel-Etayo PD, Moreno LA, Santabárbara J, Martín-Matillas M, Julian MCA, Marti Del Moral A, et al. Diet quality index as a predictor of treatment efficacy in overweight and obese adolescents: The EVASYON study. Clin Nutr. 2019;38(2):782-90.
59. Malik IO, Petersen MC, Klein S. Glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and glucagon receptor poly-agonists: A new era in obesity pharmacotherapy. Obesity. 2022;30(9):1718-21.
60. Rogliani P, Matera MG, Calzetta L, Hanania NA, Page C, Rossi I, et al. Long-term observational study on the impact of GLP-1R agonists on lung function in diabetic patients. Respir Med. 2019;154:86-92.
61. Larraufie P, Roberts GP, McGavigan AK, Kay RG, Li J, Leiter A, et al. Important Role of the GLP-1 Axis for Glucose Homeostasis after Bariatric Surgery. Cell Rep. 2019;26(6):1399-408.
62. Costa JMMd, Silva PLdS, Rosalem IDS, Pedroni EG, Pessin LP, Pelissari DF, et al. Integrative review of GLP-1 and PYY intestinal hormones in the regulation of appetite and satiety after Roux-en-Y bariatric surgery: Recent evidence in humans. Int J Health Sci. 2023;3(26):2-7.
63. Lampropoulos C, Mulita F, Alexandrides TK, Kehagias D, Kalavrizioti D, Albanopoulos K, et al. Ghrelin, glucagon-like peptide-1, and peptide YY secretion in patients with and without weight regain during long-term follow-up after bariatric surgery: A cross-sectional study. Prz Menopauzalny. 2022;21(2):97-105.

Upoznaj svog neprijatelja: priroda i biohemija gojaznosti

Jasna Bjelanović[1], Ognjan Skrobić[2]

[1]Centar za medicinsku biohemiju, Univerzitetski klinički centar Srbije,
[2]Klinika za digestivnu hirurgiju, Univerzitetski klinički centar Srbije

*Autor za korespondenciju: Jasna Bjelanović, e-mail: jasna_bjelanovic@yahoo.com

Kratak sadržaj

Gojaznost predstavlja ozbiljno zdravstveno stanje i danas je dostigla razmere pandemije. Komorbiditeti povezani sa gojaznošću su teški i utiču na skoro sve sisteme organa. Masno tkivo ima nekoliko važnih zadataka: da obezbedi skladištenje energije, da održava telesnu temperaturu kroz proces termogeneze i da održava ravnotežu u različitim metaboličkim reakcijama. Masno tkivo je endokrini organ sa brojnim biohemijskim ulogama i kod gojaznih osoba ono postaje ili hipertrofično ili hiperplastično, kada dolazi do oštećenja funkcije samog tkiva. Aktivnost imunog sistema i metabolička regulacija u masnom tkivu su izuzetno povezani procesi. Gubitak ravnoteže ove ose izaziva brojne poremećaje povezane sa gojaznošću, a u osnovi ovih poremećaja je insulinska rezistencija, koja je obeležje gojaznosti. Hormoni koji se skoro isključivo proizvode u adipocitima i proučavaju u različitim biohemijskim procesima su leptin, adiponektin i rezistin. Uspešno lečenje gojaznosti se danas postiže modifikacijom načina života i ishrane, farmakoterapijom, uglavnom glukagonu sličnom peptid-1 agonistima, kao i barijatrijskom hirurgijom, koja ostaje najefikasnija metoda lečenja selektivne populacije teško gojaznih osoba. Pozitivni efekti barijatrijske hirurgije ogledaju se ne samo u ograničenju unosa hrane, već u hormonskim promenama, posebno u hormonima intestinalnog porekla odgovornim za regulaciju gladi i energetski metabolizam.

Ključne reči: gojaznost, masno tkivo, metabolizam, terapijski pristup