OBESITY AS A PREDICTOR OF METABOLIC DEVIATIONS AND THE PURPOSE FOR THE PERSONIFIED IMPACT

Babenko A. Yu., Golikova T. I.

World-Class Research Centre for Personalized Medicine, Saint Petersburg, Russia

Corresponding author:
Babenko Alina Yu.,
World-Class Research Centre for
Personalized Medicine,
Akkuratova str. 2, Saint Petersburg,
Russia, 197341.
E-mail: babenko_ayu@almazovcentre.ru

Received 07 September 2021; accepted
25 October 2021.

ABSTRACT

This review is devoted to a description of the factors that underlie various phenotypes of obesity, their interrelationships, a predictor role in predicting metabolic health, maintaining it, in response to various options for therapeutic interventions.The review covered only key parameters: the role of the localization and morphology of adipose tissue in its metabolic activity and secretome characteristics, the role of the main adipokines and hormones involved in the regulation of nutritional metabolism, regulation of appetite and eating behavior and sensitivity to them in the development of obesity of various phenotypes.The role of unmodifiable factors (age and gender) is outlined, and the prospects for using these data in the fight against the obesity epidemic are briefly described.

Key words: adipokines, adipose tissue, gastrointestinal hormones, obesity, phenotypes, secretom.

For citation: Babenko AYu, Golikova TI. Obesity as a predictor of metabolic deviations and the purpose for the personified impact. Russian Journal for Personalized Medicine. 2021;1(1): 59-94.

Abbreviations: TNF — tumor necrosis factor, AH — arterial hypertension, BP — blood pressure, WAT — white adipose tissue, BAT — brown adipose tissue, VAT — visceral adipose tissue, VO — visceral obesity, GIP — glucose-dependent insulinotropic peptide, GLP1 — glucagon-like peptide 1, HSL — hormone-sensitive lipase, DLP — dyslipidemia, FA — fatty acids, AT — adipose tissue, CHD — coronary heart disease, IL — interleukin, BMI — body mass index, IR — insulin resistance, IGF — insulin-like growth factor, LH — luteinizing hormone, HDL — high-density lipoproteins, LPL — lipoprotein lipase, LR — leptino resistance, MH — metabolic health, MHO — metabolically healthy obesity, MUO — metabolically unhealthy obesity, MS — metabolic syndrome, NAFLD — non-alcoholic fatty liver disease, CMD — carbohydrate metabolism disorder, TV — thigh volume, WC — waist circumference, SAT — subcutaneous adipose tissue, sLR — soluble leptin receptors, DM2 — type 2 diabetes mellitus, FFA — free fatty acids, HF — heart failure, CV — cardiovascular, TG — triglycerides, AF — atrial fibrillation, CKD — chronic kidney disease, CCK — cholecystokinin.

INTRODUCTION

1. Obesity as a problem of modern civilization

Obesity is a heterogeneous condition characterized by excessive accumulation of fat in various fat depots. Normally, fat is deposited mainly in the subcutaneous fat depot. In conditions of excess energy (nutrients), its excess accumulates in white adipocytes of subcutaneous adipose tissue (SAT), becoming both a reserve that can be consumed under conditions of energy deficiency and protection against cooling. Meanwhile, in the conditions of modern life, these functions of SAT have ceased to be relevant for most people, and since the consumption of fat from the depot practically does not occur due to the lack of energy deficiency, its reserves become excessive, exceeding the depositing capacity of cells. The role of genetic predisposition in the spread of the obesity epidemic is significantly inferior to the contribution of lifestyle, since the highest increase in the frequency of obesity has been observed in the last 40 years. As Joslin described a hundred years ago, "genetics probably loads the gun, while lifestyle in our obesogenic environment pulls the trigger for the spreading of the obesity epidemic." In addition to overeating and hypodynamia, a number of additional environmental, behavioral and socio-economic factors affect calorie intake and/or consumption, causing weight gain [1]. Normally, SAT accounts for more than 80% of the entire fat layer, while visceral adipose tissue (VAT) accounts for about 10% in women and 20% in men [2]. However, the continued excess supply of nutrients leads to the fact that energy begins to accumulate in other depots — in the visceral adipose tissue and in the periorgan and intraorgan areas. Undoubtedly, this scheme of the sequence of development of various obesity options is extremely simplified, and this issue should be discussed in more detail.

2. Obesity and metabolic health — what determines the latter?

Different phenotypes of obesity are definitions of metabolically healthy obesity.

Dynamics of understanding

The localization of the accumulation of adipose tissue (AT) in certain areas of the body (gluteofemoral, abdominal) and fat depots (subcutaneous, visceral) is influenced by many factors. The most pronounced shifts in the production of biologically active substances involved in the regulation of metabolic processes are noted in visceral obesity (VO), which is usually metabolically unhealthy. Meanwhile, the differences in the effects on metabolic health (MH) and cardiovascular (CV) risks are not only in VAT and SAT, but also in the localization of SAT (gluteofemoral, abdominal). Adipocytes of abdominal SAT are characterized by rapid capture and conservation of energy after eating, high lipid metabolism rate (lipolysis), whereas fat deposits of the lower body have a low lipid metabolism rate and isolate lipids that would otherwise enter non-fat tissues (ectopia of AT). Thus, SAT of the lower body has a higher ability to deposit and preserve lipids [3]. As the body mass index (BMI) increases, the rate of lipid metabolism slows down. Recent studies have shown that there are differences not only for AT localized in different areas of the body, but also for those located at different depths from the skin. The deeper layers of SAT have structural and functional differences: a higher expression of pro-inflammatory, lipogenic and lipolytic genes, a lower methylation level of DNA PPAR-γ, and contain a higher proportion of small adipocytes. That is, deeper layers of SAT have a greater adipogenic potential. The morphology of AT also affects MH. Although obesity is usually characterized by a combination of hypertrophy and hyperplasia of adipocytes, the prevalence of hypertrophy is associated with an unfavorable cardiometabolic profile [4]. The large size of adipocytes is associated with a low rate of lipid metabolism in them and the presence of negative cardiometabolic changes. At the same time, there are contradictions in the data on which localization of adipocyte hypertrophy (visceral or subcutaneous) determines cardiovascular risks. In some studies, the relationship of hypertrophy of VAT cells with insulin resistance (IR) and cardiovascular

diseases was established [5], in others, hypertrophy of visceral adipocytes was associated with dyslipidemia (DLP), while hypertrophy of subcutaneous adipocytes was associated with insulin resistance [6, 7] and the development of type 2 diabetes mellitus (DM2) [8], and normalization of their volume with weight loss was accompanied by normalization of insulin sensitivity [9].

However, these features are not always taken into account in the assessment of metabolically healthy/unhealthy obesity. Metabolically healthy obesity (MHO) is generally understood as obesity, in which there are no significant metabolic disorders [DLP, carbohydrate metabolism disorders (DOE), hyperuricemia, etc.], arterial hypertension (AH), or there is no more than one such disorder. Additionally, an unfavorable inflammatory profile (CRP level 3 g/l) and insulin resistance (HOMA-IR < 2.5) are included, however, recommendations for MHO criteria are very variable, as well as assessments of its prevalence (from 6% to 40%) [10]. Most studies include the presence of the main components of metabolic syndrome (MS) [blood pressure (BP) ≥ 130/85 mmHg, high-density lipoprotein cholesterol (HDL) 1.04 mmol/L in men, 1.3 in women, triglycerides (TG) ≥ 1.7 mmol/L, fasting plasma glucose ≥ 5.6 mmol/L] in the determination of MHO/MUO. Less than half include an assessment of insulin resistance, usually using a surrogate homeostatic model of insulin resistance (HOMA-IR) [11], in some small studies hyperinsulinemic-eugenemic clamp was used [12-14]. A number of authors believe that hyperinsulinemia, not IR, determines metabolically unhealthy obesity (MUO) [14, 15]. Assessment of the level of other hormones is not included in standard definitions.

However, the current definitions of MHO are not optimal, as recent longitudinal studies have shown that most patients with MHO eventually shift into the metabolically unhealthy category [16—21]. Predictors of MH loss include older age [22] and more "poor" baseline metabolic parameters, including lower HDL level [18, 20], higher TG [20], more "central" obesity [20] and IR [18, 20]. Development of new methods for assessing the number and localization of various types of AT (subcutaneous gluteofemoral or abdominal, visceral, liver, pancreas, epicardial AT, etc.) made it possible to form new components of the MHO — predictors of its preservation. Thus, in a recent prospective study of patients with insulin-sensitive and insulin-resistant obesity (assessment of insulin sensitivity by the method of euglycemic hyperinsulinemic clamp), it was shown that the predictors of the preservation/loss of MH, in addition to normal insulin sensitivity, were the phenotype of obesity identified by the volume of VAT and waist circumference (VC), lean body mass, body mass index, diastolic BP, fasting serum insulin level and fat in the liver [14]. At the same time, the dynamic assessment after 5 years in the group with initially IR-obesity, the fat content in the android region increased significantly ($p = 0.0087$), as did the volume of VAT ($p_{time} < 0{,}001$) [14].

A recent study by Zembic, et al. (2021) showed that only obese patients who did not have AH and CMD [systolic BP = 130 mmHg, without antihypertensive therapy, no diabetes (plasma glucose 110 mg/dL) without antidiabetic therapy] and having peripheral obesity type [WC to thighs volume (TV) ratio < 0.95 for women and 1.03 for men] did not have an increased risk of CV events and mortality, regardless of body weight [23]. Unexpectedly, there was no link between DLP and CV prognosis in this study. Of the interesting features of this work, it is worth noting the evaluation of the WC/TV ratio rather than WC for assessing the obesity phenotype, and the QUICKI index instead if HOMA-IR for the assessment of IR. Although WC allows confirming the central (androidic) nature of obesity by estimating the amount of VAT localized in the abdominal cavity, however, when assessing WC, subcutaneous abdominal fat is also included in the value, which has less adverse effects on metabolism than visceral fat [24]. On the contrary, TV reflects the amount of SAT localized in the lower half of the body, which has at least neutral and possibly protective effects on metabolism [24—26]. Other studies have also shown a higher predictor power of WC/TV compared to WC for assessing the risk of death than WC in obesity [27]. The use of the QUICKI index, which is more strongly associated with metabolic risks than the NOMA index, has also improved the predictor value of the study. This study once again emphasized the high importance of localization of AT in the formation of CV risks. The lack of correlation between DLP and the risk of death (CV and general) in this study may be explained by the fact that among the causes of death in obese patients, heart failure (HF), chronic kidney disease (CKD) and oncology dominate, for which DLP is not a key risk factor.

An important causal factor in the development of various cardiometabolic diseases in obesity is the accumulation of AT in the target organs and periorgan space. AT ectopia in various organs is a significant factor in the formation of obesity phenotypes that are heterogeneous in the consequences. At the same time, each variant of organ ectopia of AT: epicardial, mesenteric (around the intestine), retroperitoneal (including perirenal), gonadal, mental (stomach, spleen), hepatic, pancreatic fat, brings features to the clinical course [28] (Figure 1). Thus, the accumulation of AT in the renal hilum correlates with BP and albuminuria, accumulation in the epicardial region is associated with an increased risk of AH, coronary heart disease (CHD),

atrial fibrillation (AF) and HF, in the gonadal region (in the scrotum) — with impaired testosterone production in men and impaired fertility, the accumulation of fat in the pancreas is inversely correlated with secretory function beta cells, and in the liver is associated with hepatic IR, increased fetuin-A secretion, and the development of non-alcoholic liver disease NAFLD. In addition, liver steatosis also contributes to the disruption of secretory activity of pancreatic endocrinocytes [28] and is another strong determinant of insulin sensitivity in obesity [29]. Concurrently, the accumulation of fat in different sites can vary greatly in different patients. The causal factors of these differences have not been fully established, and their determination is a key task, the solution of which will allow developing a personalized approach to the prevention of a number of metabolic diseases.

The complexity of taking these changes into account when assessing risks in various patients is determined by the high cost of the examination which makes it possible to assess ectopic AT (magnetic resonance imaging, proton spectroscopy, densitometry).

Another type of AT, the assessment of which is little available in routine practice, but the interest in which in scientific research does not weaken, is brown adipose tissue (BAT). Unlike white AT (WAT), BAT generates heat, increasing energy consumption, instead of depositing energy in the form of fat. In humans, it is represented by two types — "true" BAT, which is detected only in infants and is localized in the interscapular region and the "inducible thermogenic" BAT, localized mostly in the supraclavicular region [30]. This AT is also called beige, as it contains both white and brown adiposytes and is characterized by the ability to redifferentiate — "switching" between white and beige adiposytes by activation of uncoupling protein 1 (UCP1). This process (redifferentiation of white adipocytes into brown ones) is called WAT browning. A decrease in both the mass and activity of BAT can play a role in the development of obesity and DM2, and its metabolic activity is inversely proportional to the thickness of the fat layer [31] and positively correlates with insulin sensitivity [32]. An increase in the content of TG in the area of localization of BAT is also a negative metabolic predictor and is associated to a high degree with the development of IR and CMD [33].

IR in obesity is closely related not only to an increase in the amount of VAT, but also to the loss of muscle mass, especially in old age [34], the deficiency of which can be considered as a marker of IR and a predictor of development of MUO [29]. Even with normal

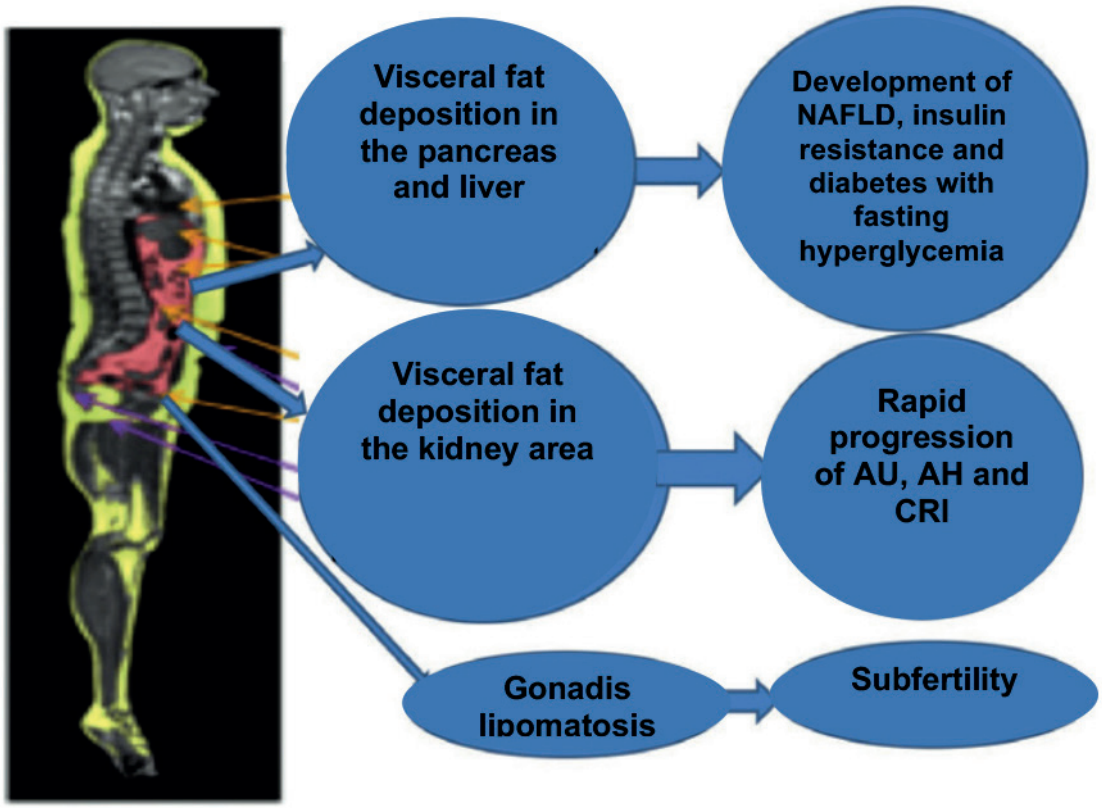

Fig. 1. Examples of the relationship between the localization of the accumulation of ectopic VAT and clinical manifestations

body weight, muscle deficiency leads to the development of IR.

Summing up, the main criteria for determining MHO can be considered an increase in the number of VAT and the ratio of the amount of VAT to lean body weight. The simplest method for estimating the amount of VAT, available in routine practice, is the assessment of WC and the WC/TV ratio. More complex is the targeted determination of the risk of developing individual metabolic disorders and diseases. For the development of CMD, such factors are an increase in the TG content in the liver and pancreas, for cardiovascular diseases (AH, CHD, AF, HF) — thickening of epicardial AT, for development chronic kidney disease — accumulation of AT in the renal hilum. It requires the use of complex, expensive instrumental research methods, therefore, in recent years, research attempts have been made to identify laboratory markers that could become a convenient and affordable alternative to instrumental examination. In addition, the evaluation of biomarkers helps to better understand the mechanisms of the formation of various disorders underlying the transition of MHO to MUO and the basis for the development of individual metabolic disorders.

3. Differences in hormonal and biomarker profiles in different phenotypes of obesity — blood test for predicting metabolic health — myth or reality?

To date, there is no doubt about the presence of endocrine functions in AT, which produces more than 50 hormones (adiposytokines, adipokines) and biologically active substances with various functions [35] (Figure 2). They have effects through paracrine, autocrine and endocrine mechanisms, affecting metabolic processes, inflammation, coagulation, glucose and lipid homeostasis. These include: adiponectin, leptin, free fatty acids (FFA), tumor necrosis factor (TNF)-α, interleukin (IL) -6, interleukin (IL) -8, MCP 1, visfatin, fetuin A, insulin-like growth factor (IGF), plasminogen-I activator inhibitor (PAI-1), angiotensinogen, angiotezin-II, prostaglandins, estrogens, resistin and many others. Changes in the level of hormones and biomarkers — AT products in the blood — to a certain extent reflect the functional imbalance of both AT cells and other organs involved in the formation of typical MUO disorders (liver, kidneys, pancreas, neuroendocrine cells of the gastrointestinal tract).

One of the typical differences noted in visceral obesity (MUO), is the change in the balance of adipocytokines — adiponectin (decrease), leptin (increase) and other secretion products of the fat cell. This is accompanied by modulation of pro-inflammatory and metabolic processes. Physiologically, it is SAT that is designed to deposit excess calories, and its genetically determined high depositing ability allows you to maintain a good MH for a long time. As noted above, it's the SAT of the gluteofemoral region that has the maximum depositing capacity. It is believed that oxygen supply, which is highly determined by angiogenesis, is of great importance in the features of AT secretoma. The main regulators of adipose tissue deposit include components.

AGE

Adipose tissue is a dynamic system, the effects of which on modulation of systemic metabolism and inflammation change at different age periods [36]. In childhood and in young people, AT has high plasticity, adapting to environmental changes and rapidly changing its endocrine, inflammatory and metabolic functions [37]. With age, the ability to differentiate preadipocytes decreases due to a decrease in the expression and activity of the CCAAT/enhancer-binding protein alpha (C/EBPα) and the peroxis-activated gamma proliferator receptor (PPARγ) [38, 39], mainly in SAT, the rate of lipid metabolism slows down and lipids are redistributed in the VAT depot [40]. With age, under the influence of cellular stress reactions caused by lipotoxicity, hypoxia and/or replication disorders [41, 42], gene expression may change with the formation of cellular phenotypes resembling activated macrophages [43]. Aging also contributes to the infiltration of immune cells into AT and leads to an increase in T-cell populations, mainly in VAT [44]. In addition, the progression of AT dysfunction with age is associated with the accumulation of aging cells [45], which are pro-inflammatory and develop a phenotype characterized by a secretion with the production of cytokines, chemokines, matrix metalloproteinases and growth factors that induce inflammatory processes in preadiposytes, inhibit differentiation and stimulate infiltration of immune cells. With increasing age, many hormonal and metabolic changes occur in the body. After 40-50 years, there is a gradual decrease in the level of sex hormones (estradiol, testosterone), growth hormone, thyroxine and, conversely, an increase in the level of leptin and cortisol, a sex steroid-binding protein. These changes reach a peak after 60 years. The main, constantly acting factors underlying these changes are a decrease in both the number of many endocrinocytes due to an increase in apoptosis activity with age and their secretory activity, a decrease in the amplitude of the pulsatory secretion of many hormones, a change in the number and sensitivity of receptors. In particular, an increase in age is a significant factor in increasing the risk of glucose intolerance, since with age, the ratio of proliferation/apoptosis of beta cells increasingly shifts towards a predominance of apoptosis [46]. Due to the increase in apoptosis

of beta cells, the proliferation of alpha cells is disrupted — the percentage of endocrinocytes shifts towards glucagon-producing alpha cells with the development of relative insulin deficiency, which facilitates the development of CMD. Cellular aging can also play a central role in the pathogenesis of age-related resistance to insulin and DM2 [41]. Age-related sarcopenia contributes to the increase in IR with age [34]. It is highly likely that there is a possible link between proinflammatory secretion in age-related dysfunction of AT and skeletal muscles. In addition, with age, the influence of intermittently acting factors grows, such as the development of somatic diseases (chronic renal failure, liver pathology, etc.), nutrition, alcohol, smoking, increasing frequency of obesity, aggravating the changes described above. Thus, age-related changes affect cellularity, insulin response, secre-

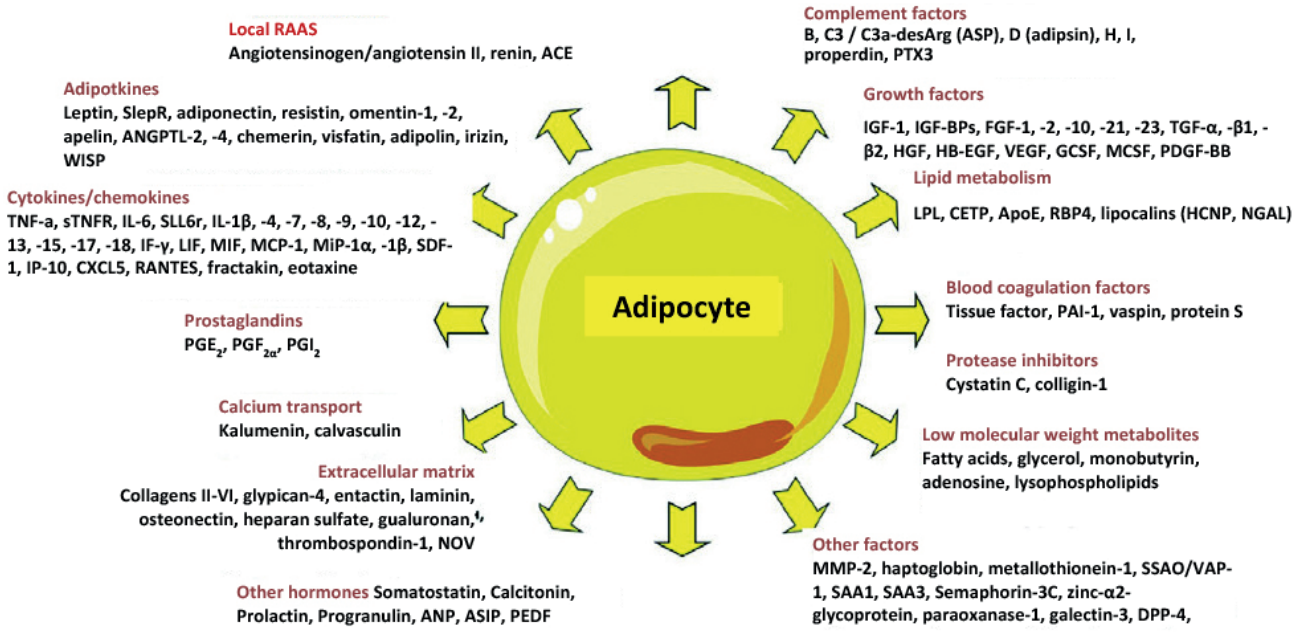

Fig. 2. White adipotocyte secretory activity profile

ACE — angiotensin-converting enzyme; ANGPTL — angiopoietin-like protein; ANP — atrial natriuretic peptide; Apo — apolipoprotein; ASIP — agouti signal protein; ASP — acylation-stimulating protein; CETP — cholesterol ester transmission protein; DPP — dipeptidyl peptidase; FGF — fibroblast growth factor; GCSF — colony-granulocyte stimulating factor; HBEGF — heparin binding epidermal growth factor; HCNP — hippocampal cholinergic neurostimulating peptide; HGF — hepatocyte growth factor; IF — interferon; IGF — insulin-like growth factor; IGF-BP — IGF-binding protein; IL — interleukin; IP-10 — inducing protein 10; LIF — leukemia inhibitory factor; LPL — lipoprotein lipase; MCP — monocyte chemoattractant protein; MCSF — macrophages colony-stimulating factor ; MIF — macrophage migration inhibitory factor; MIP — macrophages inducing protein; MMP — matrix metalloproteinase;

MW — molecular weight; NGAL — neutrophil gelatinase-associated lipocalin;

NOV — renal adenosarcoma superexpressed protein; PAI — profibrinolysin activator inhibitor; PDGF — platelet-derived growth factor; PEDF — pigment epithelial-derived factor; PG — prostaglandin; PTX — pentraxine-bound

protein; RANTES — Regulated on activation normal T-cell expressed and secreted; RAS — renin-angiotensin system; RBP — retinol binding protein; SDF — stromal derived factor; sIL6R — soluble IL-6 receptor;

sLepR — soluble leptin receptor; sTNFR— soluble TNF receptor; SSAO — semicarbazide-sensitive amine oxidase; TGF — transforming growth factor; TNF-a — tumor necrosis factor; VAP — vascular adhesion protein; VEGF — vascular endothelial growth factor; WISP — WNT1-inducible signaling pathway protein

tion and inflammatory status of AT, which leads to its dysfunction. Age determines the shift in fat deposit from the subcutaneous to the visceral depot with the transition of MHO to MUO.

GENDER

The function and predominant localization of AT differ depending on gender, which is determined by differences in the profile of sex hormones. In women, a normal level of estrogen ensures fat deposition in the gluteofemoral region, and a high leptin secretion with a high sensitivity to it. Men accumulate more VAT, which leads to the formation of an android (central) phenotype of obesity, which strongly correlates with an increase in cardiovascular risk. Women of reproductive age accumulate more fat in the subcutaneous depot, but after menopause, estrogen levels decrease and fat deposition shifts to the visceral depot. Thus, the gender effects are determined by differences in the effects of sex hormones, which will be discussed later.

HORMONES

Sex hormones

The effects of sex hormones on the deposit of adipose tissue are largely determined by the genetic sex. Thus, in women, an increased level of androgens is associated with IR, increased fat deposition in the visceral depot, and the development of CMD. At the same time, in men, a high level of testosterone ensures the differentiation of pluripotent progenitor cells into myocytes and a change in body composition towards the predominance of muscle tissue over fatty [48]. In conditions of testosterone deficiency in men, on the contrary, fat deposition in the visceral depot increases and myogenesis decreases. Testosterone normally activates hormone-sensitive lipase (HSL) in adipotytes, activates lipolysis and thus reduces fat mass. The activity of lipoprotein lipase (LPL) limits the rate of fat accumulation, and it is higher in the SAT of the gluteofemoral region as compared to VAT in women, which ensures the gynoid-type accumulation of fat. On the contrary, in men, the activity of LPL is higher in VAT. These gender differences in the distribution of AT are enhanced by the influence of testosterone, which suppresses LPL in the SAT of the gluteofemoral region in men. With obesity, the expression and activity of the aromatase enzyme which provides the conversion of testosterone to estradiol, increases. As a result, the aromatization of testosterone into estradiol increases drastically and its amount decreases. Estradiol inhibits the production of luteinizing hormone (LH) in the pituitary gland, which is accompanied by a decrease in testosterone production in the testicles and a further decrease in its level in the blood [49]. Leptin also inhibits testicular function in adults, but promotes testicular development during puberty [50]. With changes in the production of adipocytokines in AT, IR and insulin levels increase. In conditions of hyperleptinemia and hyperinsulinemia, the level of sex steroid-binding globulin and testosterone decreases even more. Under conditions of testosterone deficiency, lipoprotein lipase in AT is activated and the capture of TG by adipotocytes increases, which contributes to the progression of obesity [49]. At the same time, a high level of testosterone suppresses the production of leptin [50]. Age makes a significant contribution to the nature of the relationship between leptin and gonadal function in men. Thus, in prepubertal period, the level of leptin in boys increases, and this contributes to the development of testicles. During puberty, the level of leptin decreases under the influence of increasing levels of androgens. Accordingly, in adult men, leptin levels are significantly lower than in women, and the increase in leptin levels due to factors, including obesity, inhibits the function of the testicles, leading to decreased testosterone [47, 50].

Estrogens, as already noted, contribute to the deposit of fat in SAT in women, mainly in the gluteofemoral region and in the chest area. This is due to gender-dependent differences in the expression of receptors for leptin and estrogens. Estrogens directly or through the activation of their receptors on adipocytes [estrogen receptors alpha (ERα) and beta (ERβ)] facilitate fat deposition and activate functions of AT. The lipolytic effect of estrogens is mainly mediated through ERa, and ERß can act as a repressor [51, 52]. The distribution of estrogen receptors in different AT depots differs in men and women, making a significant contribution to the sexual dimorphism of obesity phenotypes. In women, a higher ERα/β ratio in VAT limits fat accumulation in this depot, while a lower ERα/ERβ ratio in gluteofemoral SAT ensures its accumulation. In men, the amount of ERa in VAT is significantly lower, and a low ratio of ERa/ERß increases the deposition of fat in the visceral depot [52]. Activation of ERa improves the function of AT by reducing its inflammation and improving insulin sensitivity. Estrogens can regulate (increase) angiogenesis of AT, thereby reducing the severity of hypoxia [53]. Hypoxia is a key inducer of oxidative stress, inflammation and hypertrophy of AT. This allows us to consider the effects of estrogens on angiogenesis as an important mechanism by which estrogens reduce inflammation and fibrosis of AT. Sexual dimorphism also affects the activity and distribution of lipolytic β1-2 and antilipolytic α2-adrenergic receptors. Estradiol increases the number of α2-adreno receptors in SAT, but does not affect them

in VAT [54], differentially increasing sympathetic tone in various AT depots. As a result, the accumulation of lipids in SAT in women and in VAT in men increases [55]. Estrogens can modulate the ability of fat cells to increase volume, strengthening it in the subcutaneous depot and inhibiting it in the visceral. Mammary adipocytes have the highest plasticity. They de-differentiate during pregnancy and remain in a state of de-differentiation during breastfeeding. After stopping feeding, they proliferate and re-differentiate into adiposytes. Estradiol modulates the activity of a number of hormones involved in the regulation of hunger and satiety, increases the effects of anorexigenic substances such as cholecystokinin, apolipoprotein A-IV, leptin, brain-derived neurotrophic factor (BDNF), and reduces the activity of orexigenic hormones, such as melanocortin and ghrelin [55]. Estrogens also protect against weight gain by increasing energy consumption by activating their receptors in the ventral medial nucleus of the hypothalamus [53]. Estrogens increase the metabolic activity of AT and potentiate browning. As a result, the metabolic rate of AT is higher in women due to the greater number of brown AT and higher expression of genes involved in mitochondrial function, including the separating protein (UCP-1) [55].

The female brain is more sensitive to the effects of leptin on regulating food intake and energy consumption, indicating a strong synergy between the obesity hormone leptin and estrogens in the regulation of reproduction and energy homeostasis [53]. There is a two-way relationship between leptin and estrogens. With a decrease in the level of leptin or sensitivity to it, the secretion of kisspeptin is suppressed through it — a decrease in production and a violation of circadian gonadotropin. In addition, leptin stimulates the production of receptors to gonadotropins and gonadotropin-releasing hormone. On the other hand, a high level of estrogens (an increase in their production during the menstrual cycle) stimulates an increase in the level of leptin, which reaches its maximum by the middle of the cycle [50].

Hormones of AT and gastrointestinal tract, involved in depositing energy substances

When discussing the role of hormones such as insulin, adiposytokines, incretins, ghrelin, we should focus on two aspects: changes in the level of these hormones and sensitivity to them. The role of insulin and sensitivity to it in the development of metabolic disorders included in MS is beyond doubt. Although until recently, the indication of IR by various methods has been considered a key method for assessing the risk of metabolic disorders, recent studies have shown that fasting hyperinsulinemia (fasting insulin above 15 pg/ml in normoglycemia) is also a fairly reliable marker [56].

Adipose tissue hormones

Leptin, ат AT hormone that has systemic effects mediated by its binding to a specific receptor. The key effect of leptin is appetite control [57]. Under normal physiological conditions, leptin provides the onset of a feeling of satiety, reducing calorie intake, has a glucose-lowering effect, reduces ectopic fat accumulation through central and peripheral mechanisms, which should have a beneficial effect on metabolic health. The magnitude of leptin effects depends on the tissue, gender and conditions of action [58]. Leptin secretion increases under the influence of a number of hormones (estrogens, growth hormone, thyroxine, glucocorticoids and insulin), changes in glucose, when eating, with obesity, and decreases on an empty stomach, under the influence of catecholamines, iron, FFA, testosterone. It exhibits many metabolic effects on various tissues, and its effects in normal sensitivity to it include: a) in the central nervous system — reducing calorie intake, increasing energy consumption, improving cognitive functions and memory; b) in the liver — reducing the accumulation of lipids and glucose; c) in the pancreas — inhibiting the secretion of glucagon and insulin; d) in muscles — increased oxidation fatty acids and glucose metabolism; e) in AT — in BAT it increases utilization of glucose, in WAT it activates lipolysis and inhibits lipogenesis; e) in bones it accelerates metabolism. The glucose-lowering effects of leptin are partially provided by its direct action in peripheral tissues, but the main effector pathway of leptin is through the central nervous system, mainly through modulation of the activity of neurons of the hypothalamus nuclei. This can be explained by a significantly higher expression of leptin receptors in the central nervous system. Many effects of leptin depend on the presence of insulin and/or sensitivity to it. Thus, under conditions of normoinsulinemia, leptin stimulates lipolysis, reducing the deposit of fat in white AT and increasing energy consumption, however, in conditions of insulin deficiency and/or its effects (IR), on the contrary, inhibits lipolysis. In insulin-resistant patients with type 2 diabetes, leptin administration did not improve glucose homeostasis [59], which may be due to both IR and leptin resistance (LR) [60, 61]. Insulin can act on AT by stimulating the synthesis and secretion of leptin [62, 63], while leptin inhibits insulin secretion. Meanwhile, leptin and insulin, with normal sensitivity of AT to them, act synergistically on it, increasing the browning of white adipocytes and thereby contributing to an increase in energy consumption [64]. In addition to AT, leptin and its receptor were identified in the gastric mucosa [65, 66]. Its secretion in the stomach occurs under the influence of cholecisto kinin (CCK), pentagastrin and secretin [65, 66], as well as adiposytic leptin participates in the regulation of appe-

tite, acting directly in hypothalamus or together with CCK through the vagus [66].

The development of leptin resistance and IR annuls these effects in obesity, changing the direction vector of leptin effects. The relationship between leptin, AT mass and metabolic effects of leptin are complex and are determined by factors such as leptin level, severity of its receptor effects, deterministic sensitivity of leptin receptors and non — receptor effects. Concurrently, leptin's ability to lower glucose and have antilipogenetic effects regardless of leptin regulation of body weight [58]. It is highly probable that the sensitivity to leptin, and not its absolute level, is an indicator of MH. However, no clear criteria for their differentiation have been developed.

Obesity is always characterized by the development of hyperleptinemia, as well as some other pathological conditions. This is confirmed by a laboratory assessment of the level of leptin, which is always higher in obesity than in people with normal weight. However, it is much more difficult to detect the presence of leptin resistance. The term LR can be used to denote a condition in which the level of leptin is chronically high, but its effects are weakened and hyperleptinemia does not cause suppression of hunger and loss of AT mass. The development of LR in obesity is associated with multiple mechanisms: impaired transport through the blood-brain barrier, weakened leptin signaling, endoplasmic reticulum stress, inflammation, autophagy deficiency. It can be assumed that with obesity, the development of LR is a gradual dynamic process, during which, under the influence of excess leptin, the amount of which increases in proportion to the amount of AT, the number of leptin receptors gradually decreases, since the concentration of leptin regulates both their production and their degradation [67, 68]. Accordingly, the method of indicating LR based on the level of this hormone on an empty stomach is inaccurate, since a high level of leptin combines the states of hyperleptinemia and LR. Modern approaches to the detection of LR use an assessment of indices and mathematical models, including, in addition to determining leptin, an assessment of soluble leptin receptors (sLR) in circulation, leptin ratios, sLR and BMI. Meanwhile, the exact method of assessing LR is a matter of future research.

Adiponectin is an adipokine produced almost exclusively in the AT and highly expressed in the cells of WAT in healthy people with normal body weight. In pathological conditions characterized by chronic non-infectious inflammation, including obesity, the level of adiponectin decreases [69]. Morphological and functional changes in WAT that occur during obesity are a highly probable cause. Due to the excessive accumulation of TG, adipocytes in obese people increase in size. The hormonal activity of adipocytes of WAT depends on their size, and larger adipocytes, typical for people with obesity, produce significantly less adiponectin, but significantly more pro-inflammatory cytokines, such as *TNF-α* [70]. At the same time, adiponectin and proinflammatory cytokines (TNF-α and IL-6) mutually inhibit each other's secretion [71, 72]. Negative regulation of adiponectin expression is also the result of hypoxia and oxidative stress [73, 74]. Decreased expression and secretion of adiponectin in AT in obesity can be considered as an inducing factor in the development of inflammation accompanying obesity and entails the activation of a variety of pathological processes, including the development of IR [75]. Thus, adiponectin mediates protective effects in metabolic and vascular diseases associated with obesity, mainly through its anti-inflammatory effect. An interesting experimental finding was that chronic overexpression of adiponectin is accompanied by an increase in the mass of SAT and protects against hypercaloric nutrition-induced resistance to insulin [76]. According to our data, with a sharp decrease in the mass of SAT in patients undergoing bariatric surgery, the expression of adiponectin in SAT, on the contrary, decreases, while its level in circulation increases [77] .

Gastrointestinal hormones

When studying obese patients, we noted not only an imbalance of adiposytokines (leptin and adiponectin), but also an imbalance of incretins [glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic peptide (GIP)] and ghrelin. These hormones are produced by L- and K cells in the intestine in response to stimulation by food. Therefore, normally their level is very low on an empty stomach and increases postprandially. GLP-1 in a glucose-dependent way increases insulin secretion, normalizes glucagon secretion, reduces apoptosis and increases the replication of beta cells. Studying the level of incretins in obesity, we noted an increase in the level of GPP-1 on an empty stomach, which is probably due to resistance to this hormone, since the dynamics of its level in the postprandial status was weakened, and the level of GIP, on the contrary, was significantly reduced both on an empty stomach and postprandially, which indicates its deficiency [77-80].

The role of GIP in the regulation of energy storage in AT and the development of metabolic disorders is not fully defined. GIP has effects on all key tissues that are important for the control of glucose and lipid homeostasis, stimulates the biosynthesis and secretion of insulin and increases the viability of islet cells. In addition, GIP regulates lipid metabolism directly through its receptor (GIPRs) on adipocytes (modulating lipolysis and lipogenesis depending on the level of insulin). The

effect of GIP on adipose tissue is partially regulated by the activation of LPL. Increased insulin secretion after the release of GIP inhibits lipolysis in adipotytes and stimulates adipogenesis while maintaining insulin receptor sensitivity (INSR) [81].

On an empty stomach, GIP stimulates glucagon secretion and lipolysis in SAT. In the post-food status (increased glucose and insulin levels), it inhibits the secretion of glucagon, stimulates insulin secretion and adipogenesis in SAT, and increases the intake of TG in SAT. It is believed that GIP is responsible for depositing excess energy in SAT. Accordingly, a deficiency of GIP can contribute to the redistribution of fat from SAT to visceral. The effects of GIP on LPL are mediated by resistin, which also disrupts insulin signaling and contributes to the development of oxidative stress in human vascular cells. On the other hand, there are studies that have demonstrated that GIP stimulates the expression of pro-inflammatory factors and chemokines, contributing to the deterioration of insulin sensitivity of adipocytes and the formation of AT inflammation. Meanwhile, it cannot be ruled out that these effects were noted in the violation of tissue sensitivity to GIP (GIP-resistance), a phenomenon that is poorly studied at the present time.

The effects of GIP are modulated by the metabolic environment, in particular the level and sensitivity to other hormones involved in the metabolism of AT, glucose and lipid levels in the bloodstream. In healthy people without obesity, the level of GIP is low on an empty stomach, does not change with euglycemia, increases with hypoglycemia, and decreases with hyperglycemia (insulin clamp). In healthy people, GIP increases the secretion of leptin and ghrelin, increases blood flow in AT, reduces blood lipids (LDL and TG) due to their deposition in SAT, and increases HDL in women [82]. That is, normally, the effects of GIP are aimed at preserving MH. In patients with MHO, the level of GIP is low on an empty stomach, but its post-food peak on a high-fat diet is enhanced. As BMI increases, the level of GIP increases [82]. At the same time, with MUO, the level of GIP is also increased on an empty stomach, and its effects are weakened, since the intake of TG into SAT under the influence of GIP is reduced with MUO in comparison with people without obesity. With hyperinsulinemia and IR, the deposit of fat in VAT increases sharply. At the same time, GIP contributes more to the redistribution of TG and fatty acids (FAs) in VAT in men than in women. Despite TG deposition in VAT, high levels of GIP in hyperinsulinemia and hyperglycemia were associated with increased levels of TG in the bloodstream [81]. However, according to other authors, the level of fasting GIP increases only with CMD. Taking into account the revealed differences with MHO and MUO, the level of GIP may depend on IR, and not on BMI. Thus, factors that modulate the level of GIP can be the sensitivity of tissues to insulin, the level of glycemia, and in the post-nutritional status, also the ratio of various nutrients in food. There is a high probability that MUO develops resistance of SAT to GIP primarily in men, since they had twice the higher level of GIP after meals, which was associated with minor fat deposition in SAT and major fat deposition in VAT. In patients with diabetes, the fasting GIP level is elevated and does not change postprandially, and its effects are impaired: with an increased GIP, insulin secretion does not increase, glucagon secretion is not inhibited, and the intake of TG inti SAT is reduced.

In addition to GLP-1 and GIP, a number of other hormones produced by neuroendocrine cells of the gastrointestinal tract (cholecystokinin, peptide YY (PYY), somatostatin) are involved in food metabolism. Almost all of them are characterized by the presence of an anorexigenic effect, except for the orexigenic hormone ghrelin.

Ghrelin

Grelin is a hormone produced mainly by neuroendocrine cells of the gastric fundus (about 65%) [83]. A small number of ghrelin-producing cells were found in the small and large intestine, pituitary gland [84]; α- [85], β- [86], and delta cells [87] of the islets of Langerhans and neurons of the arcuate nucleus of the hypothalamus [88, 89]. Insignificant ghrelin expression was also detected in kidneys, testicles, placenta [90-92] and immunocytes [93]. Ghrelin secretion in the stomach is regulated by nutritional and hormonal factors [94]. It is inhibited by somatostatin, interleikin 1β (IL-1β), STH, high fat food, increased vagal activity, while hunger and low-protein nutrition stimulate ghrelin expression and secretion. Accordingly, ghrelin levels are normally highest on an empty stomach and decrease after eating, unlike other hormones involved in regulating the absorption and deposit of nutrients. Reports on the effects of leptin on ghrelin production are contradictory [95, 96], which can be determined by the preservation of sensitivity to the effects of leptin and the influence of other factors. The associated effects of leptin and ghrelin can provide a regulatory feedback system involving the gastrointestinal tract and central nervous system, and act as an interface between the regulatory appetite centers in the hypothalamus and functions of the gastrointestinal tract in the management of metabolism and growth [97].

This hormone plays an important role both in the regulation of eating behavior and in the regulation of insulin secretion and insulin sensitivity. Ghrelin has been identified as an endogenous ligand for somatotro-

pin receptors (GHS). It functions as an orexigenic (appetite-stimulating) signal from the stomach [98]. The main effects of ghrelin include: an acute decrease in insulin sensitivity; regulation, in an antagonistic manner to leptin, of the synthesis and secretion of several neuropeptides in the hypothalamus, namely increase of appetite through stimulation of the production of neuropeptide Y (NPY) and agouti peptide (AgRP); stimulation of the secretion of counter-regulatory hormones (cortisol, glucagon, catecholamines), mainly through central mechanisms, suppression of adiponectin and insulin secretion; decreased hepatic insulin sensitivity by blocking hepatic transmission of insulin signal at the phosphatidylinositol-3-kinase level; stimulation of fat deposition (adipogenesis); increase of activity of lactotrophs and corticotrophs; increase of gastric motility and hydrochloric acid secretion.

Many researchers note that in obesity, ghrelin level is significantly lower on an empty stomach than in people with normal body weight and negatively correlate with BMI, fat, fasting insulin and leptin levels [99]. Our data, like other studies, indicate a more significant increase in leptin and a lower decrease in ghrelin than in men [47]. When trying to normalize weight, ghrelin prevents weight loss, as weight loss is accompanied by an increase in ghrelin levels, which correlates positively with the degree of weight loss [100] and increases hunger. In the post-food status, most patients with obesity do not have an additional decrease in its level, unlike healthy people, which, firstly, may be a sign of the development of ghrelin resistance, and secondly, may contribute to increased food intake [101].

It is logical to assume that since the first hormonal reaction upon food intake to the quantity and qualitative composition of nutrients is the secretion of incretins and ghrelin, then it is their imbalance that is primary. Meanwhile, with the development of insulin resistance (increased NOMA-IR), a decrease in the sensitivity of GIP receptors in tissues develops. Hypothetically, the sequence of changes can be expressed in the form of a diagram shown in Fig. 3.

GENETIC DETERMINANTS

As it was noted at the beginning, genetic determination has a much smaller contribution to the formation of both obesity itself and its metabolic complications than lifestyle. A very beautiful example of this is the data presented in the article by Ligthart S, et al. (2021), which assessed the polygenic risk of developing type 2 diabetes in patients with normal body weight and obesity in 8,243 individuals enrolled in the ARIC study and 7,428 participants included in the Rotherdam Study (RS) [102], based on a polygenic evaluation of 403 common DNA sequences, identified as risk factors for type 2 diabetes [103]. The authors first assessed the polygenic risk and divided the examinees into groups of low, moderate and high risk. The lifetime risk of developing DM2 in people aged 45 years was 22.8% (95% CI 18.4—27.3) in the low genetic risk category; 30.6% (95% CI 27.9—33.4) in the intermediate genetic risk category and 35.5% (95% CI 30.6—40.5) in the high genetic risk category in the RS cohort and 32.6% (95% CI 27.8—37.4) in the low genetic risk category; 41.1% (95% CI 38.9—43.2) in the intermediate genetic risk category and 47.6% (95% CI 44.3—50.8) in the high genetic risk category in the ARIC cohort. Obese participants had more than twice the risk of developing diabetes compared to people with normal weight in the moderate and high risk categories. At the same time, among participants with a high genetic risk, normal weight was associated with a 56% lower risk of diabetes in the ARIC study and 55% lower risk for RS compared to obesity.

In recent studies, molecular genetic studies of adipose tissue itself have attracted attention. Most studies, like our own earlier findings, show a higher expression of the leptin gene and mRNA in SAT compared to VAT in obese people [77]. In people without obesity, leptin expression in both sites is lower than [104] or comparable [105] to that in obesity. A higher expression of the leptin gene in SAT is observed in women, correlating with its level in the circulation, unlike men, which may be explained by the peculiarities of the formation of obesity: men are characterized by earlier and priority accumulation of fat in VAT with a characteristic imbalance of adipokine production [106]. The expression of adiponectin gene and mRNA is reduced during obesity in AT, but, unlike leptin, changes in its expression are more pronounced in VAT [107]. Finally, a recent study that examined the contribution of expression of various adipokines in individual AT sites (VAT and SAT) to their circulation levels showed that only the expression of the leptin gene in SAT has significant influence on its level in circulation, which means it can determine its systemic effects [108].

Meanwhile, genome-wide studies can reveal new ways to implement the mechanisms for the formation of various phenotypes of obesity, changes in the hormonal and biomarker background, the causes of differences in prognosis and response to therapy. The formation of a huge number of genes, for which a link with the risk of developing obesity and changes in various metabolic parameters has been shown, already today makes it possible to form genetic panels that determine the development of MHO or MUO, CMD and DM, AH, DLP with high accuracy. A detailed description of these studies is a topic for a separate article.

The analysis presented in this review showed that maintaining metabolic health requires the maintenance/restoration of normal sensitivity to leptin, GIP, ghrelin, which is inseparable from normalization of the morphology of AT and insulin sensitivity. Maintaining the level of sex hormones at the level of reproductive age can also significantly restrain the development of changes towards MUO.

An intervention aimed at eliminating causal factors is always optimal. As it was noted at the beginning of this review, the key causal factors of obesity and loss of metabolic health are overeating and inac-

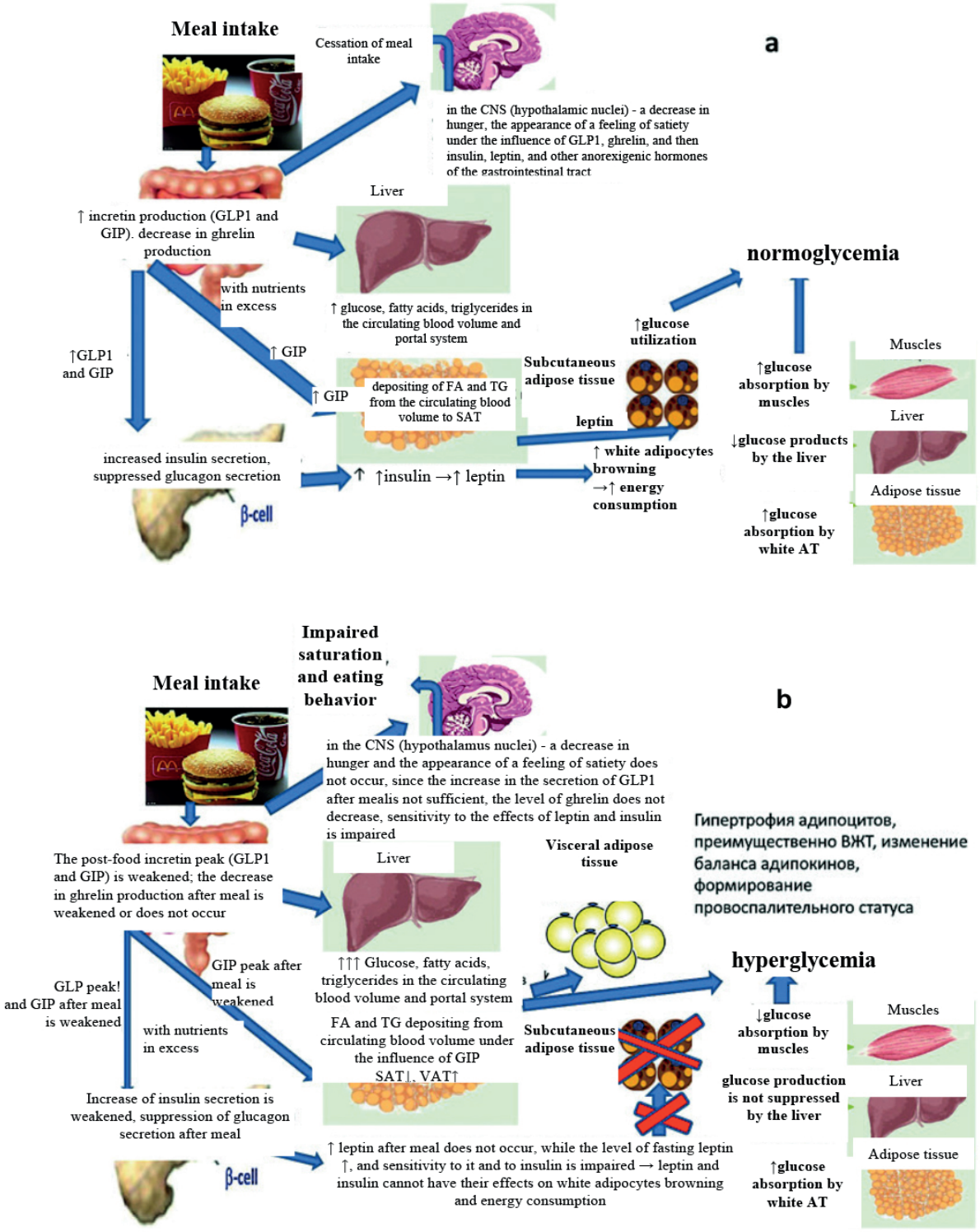

Fig. 3. Regulation of nutrient metabolism in normal (a) and overeating (b)

tivity, which are complemented by sleep disorders, exposure to sociopathogenic environmental factors and stress. However, the differences in impacts can already be personalized based on gender differences: the response to a high-fat diet is radically different in men and women. In men, ketogenic diets cause adverse metabolic changes (an increase in the level of unsaturated FA and inflammatory markers), which are not observed in women [109]. Age also influences the choice of interventions — the choice of therapy in favor of drugs that slow down cellular aging, such as metformin, allows you to modulate the speed of these processes. The involvement of sex hormone replacement therapy can also significantly slow down the rate of age-related changes. The duration of obesity, CMD also determines the response. In patients with a short history of obesity, with a decrease in body weight, normalization of adipocyte volume was noted, while in patients with a long duration, even bariatric interventions did not eliminate hypertrophic changes [2]. Weight loss by 10% or more and a decrease in liver TG in patients with a short history (up to 6 years) of type 2 diabetes made it possible to achieve remission of diabetes [110], while with the duration of the disease (more than 10 years) remission is unlikely even after bariatric interventions.

Future directions of personalization of obesity therapy involve the use of drugs that target the accumulation of fat in VAT and its excessive ectopic accumulation. The use of angiogenesis activity, fibrosis and modulation of receptor activity/hormone levels involved in fat depositing in various fat depots as targets can help in solving these problems. Modulation of sensitivity to GIP seems promising, resistance to which redirects lipids from the subcutaneous to the visceral depot. Activation of browning AT with increased metabolic activity of adipocytes also looks attractive. Already today, the ability to influence its activity is being discussed in a number of drugs (GLP-1 receptor agonists, glyflozins, reduxin), which have demonstrated the ability not only to reduce body weight, but also to improve metabolic parameters. Clarification of molecular genetics pathways for the formation of various obesity phenotypes will help in the development of new drugs for individual choice in therapy.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Keith SW, Redden DT, Katzmarzyk PT, et al. Putative contributors to the secular increase in obesity: exploring the roads less traveled. Int J Obes (Lond). 2006;30(11):1585–1594. DOI: 10.1038/sj.ijo.0803326.
2. Morigny P, Bouche J, Arner P, et al. Lipid and glucose metabolism in white adipocytes: pathways, dysfunction and therapeutics. Nat Rev Endocrinol. 2021;17(5):276–295. DOI: 10.1038/s41574-021-00471-8.
3. Chen GC, Arthur R, Iyengar NM, et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. Eur Heart J. 2019;40(34):2849–2855. DOI: 10.1093/eurheartj/ehz391.
4. Laforest S, Labrecque J, Michaud A, et al. Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. Crit Rev Clin Lab Sci. 2015;52(6):301–313. DOI: 10.3109/10408363.2015.1041582.
5. Tandon P, Wafer R, Minchin JEN. Adipose morphology and metabolic disease. J Exp Biol. 2018;221(Pt Suppl 1):jeb164970. DOI: 10.1242/jeb.164970.
6. Hoffstedt J, Arner E, Wahrenberg H, et al. Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity. Diabetologia. 2010;53(12):2496–2503. DOI: 10.1007/s00125-010-1889-3.
7. Veilleux A, Caron-Jobin M, Noel S, et al. Visceral adipocyte hypertrophy is associated with dyslipidemia independent of body composition and fat distribution in women. Diabetes. 2011;60(5):1504–1511. DOI: 10.2337/db10-1039.
8. Lonn M, Mehlig K, Bengtsson C, et al. Adipocyte size predicts incidence of type 2 diabetes in women. FASEB J. 2010;24(1):326–331. DOI: 10.1096/fj.09-133058.
9. Stenkula KG, Erlanson-Albertsson C. Adipose cell size: importance in health and disease. Am J Physiol Regul Integr Comp Physiol. 2018;315(2):284–295. DOI: 10.1152/ajpregu.00257.2017.
10. Jung CH, Lee WJ, Song KH. Metabolically healthy obesity: a friend or foe? Korean J Intern Med. 2017;32(4): 611–621. DOI: 10.3904/kjim.2016.259.
11. Rey-López JP, de Rezende LF, Pastor-Valero M, et al. The prevalence of metabolically healthy obesity: a systematic review and critical evaluation of the definitions used. Obes Rev. 2014;15(10):781–790. DOI: 10.1111/obr.12198
12. Bo S, Musso G, Gambino R, et al. Prognostic implications for insulin-sensitive and insulin-resistant normal-weight and obese individuals from a population-based cohort. Am J Clin Nutr. 2012;96(5):962–969. DOI: 10.3945/ajcn.112.040006.
13. Kloting N, Fasshauer M, Dietrich A, et al. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab. 2010;299(3):E506–515. doi: 10.1152/ajpendo.00586.2009.
14. Tang A, Coster ACF, Tonks KT, et al. Longitudinal changes in insulin resistance in normal weight, overweight and obese individuals. J Clin Med. 2019;8(5):623. DOI: 10.3390/jcm8050623.
15. Packer M. Differential pathophysiological mechanisms in heart failure with a reduced or

preserved ejection fraction in diabetes. JACC Heart Fail. 2021;9(8):535–549. DOI: 10.1016/j.jchf.2021.05.019.

16. Roos V, Elmståhl S, Ingelsson E, et al. Metabolic syndrome development during aging with special reference to obesity without the metabolic syndrome. Metab Syndr Relat Disord. 2017;15(1):36–43. DOI: 10.1089/met.2016.0082.

17. Zheng R, Liu C, Wang C, et al. Natural course of metabolically healthy overweight/obese subjects and the impact of weight change. Nutrients. 2016;8(7):430. DOI: 10.3390/nu8070430.

18. Khan UI, Wang D, Karvonen-Gutierrez CA, et al. Progression from metabolically benign to at-risk obesity in perimenopausal women: a longitudinal analysis of Study of Women Across the Nation (SWAN). J Clin Endocrinol Metab. 2014;99(7):2516–2525. DOI: 10.1210/jc.2013-3259.

19. Kabat GC, Wu WY-Y, Bea JW, et al. Metabolic phenotypes of obesity: frequency, correlates and change over time in a cohort of postmenopausal women. Int J Obes (Lond). 2017;41(1):170–177. DOI: 10.1038/ijo.2016.179.

20. Hwang Y-C, Hayashi T, Fujimoto WY, et al. Visceral abdominal fat accumulation predicts the conversion of metabolically healthy obese subjects to an unhealthy phenotype. Int J Obes. 2015;39(9):1365–1370. DOI: 10.1038/ijo.2015.75.

21. Bell JA, Hamer M, Sabia S, et al. The natural course of healthy obesity over 20 years. J Am Coll Cardiol. 2015;65(1):101–102. DOI: 10.1016/j.jacc.2014.09.077.

22. Appleton SL, Seaborn CJ, Visvanathan R, et al. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care. 2013;36(8):2388–2394. DOI: 10.2337/dc12-1971.

23. Zembic A, Eckel N, Stefan N, et al. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. JAMA Netw Open. 2021;4(5):e218505. DOI: 10.1001/jamanetworkopen.2021.8505.

24. Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. Lancet Diabetes Endocrinol. 2020;8(7):616–627. DOI: 10.1016/S2213-8587(20)30110-8.

25. Lotta LA, Wittemans LBL, Zuber V, et al. Association of genetic variants related to gluteofemoral vs abdominal fat distribution with type 2 diabetes, coronary disease, and cardiovascular risk factors. JAMA. 2018;320(24):2553–2563. DOI: 10.1001/jama.2018.19329.

26. Neeland IJ, Poirier P, Despres JP. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation. 2018;137(13):1391–1406. DOI: 10.1161/CIRCULATIONAHA.117.029617

27. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008;359(20):2105–2120. DOI: 10.1056/NEJMoa0801891

28. Haring HU. Novel phenotypes of prediabetes? Diabetologia. 2016;599):1806–1818. DOI: 10.1007/s00125-016-4015-3.

29. Lee MJ, Kim E-H, Bae SJ, et al. Protective role of skeletal muscle mass against progression from metabolically healthy to unhealthy phenotype. Clin Endocrinol (Oxf). 2019;90(1):102–113. DOI: 10.1111/cen.13874.

30. Lidell ME, Betz MJ, Dahlqvist LO, et al. Evidence for two types of brown adipose tissue in humans. Nat Med. 2013;19(5):631–634. DOI: 10.1038/nm.3017.

31. Matsushita M, Yoneshiro T, Aita S, et al. Impact of brown adipose tissue on body fatness and glucose metabolism in healthy humans. Int J Obes (Lond) 2014;38(6):812–817. DOI: 10.1038/ijo.2013.206.

32. Orava J, Nuutila P, Noponen T, et al. Blunted metabolic responses to cold and insulin stimulation in brown adipose tissue of obese humans. Obesity (Silver Spring). 2013;21(11):2279–2287. DOI: 10.1002/oby.20456.

33. Raiko J, Holstila M, Virtanen KA, et al. Brown adipose tissue triglyceride content is associated with decreased insulin sensitivity independent of age and obesity. Diabetes Obes Metab. 2015;17(5):516–519. DOI: 10.1111/dom.12433.

34. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. J Endocrinol. 2016;229(2):R67–R81. DOI: 10.1530/JOE-15-0533.

35. Gerst F, Wagner R, Oquendo MB, et al. What role do fat cells play in pancreatic tissue? Mol Metab. 2019;25:1–10. DOI: 10.1016/j.molmet.2019.05.001.

36. Stout MB, Tchkonia T, Kirkland JL. The aging adipose organ: lipid redistribution, inflammation, and cellular senescence. In: Adipose Tissue and Adipokines in Health and Disease, edited by Fantuzzi G, Braunschweig C. New York: Humana.2014;69–80.

37. Mourkioti F, Kratsios P, Luedde T, et al. Targeted ablation of IKK2 improves skeletal muscle strength, maintains mass, and promotes regeneration. J Clin Invest. 2006;116(11): 2945–2954. DOI: 10.1172/JCI28721.

38. Karagiannides I, Tchkonia T, Dobson DE, et al. Altered expression of C/EBP family members results in decreased adipogenesis with aging. Am J Physiol Regul Integr Comp Physiol. 2001;280(6):R1772–1780. DOI: 10.1152/ajpregu.2001.280.6.R1772.

39. Schipper BM, Marra KG, Zhang W, et al. Regional anatomic and age effects on cell function of human adipose-derived stem cells. Ann Plastic Surg.2008;60(5):538–544. DOI: 10.1097/SAP.0b013e3181723bbe.

40. Stout MB, Justice JN, Nicklas BJ, et al. Physiological aging: links among adipose tissue dysfunction, diabetes, and frailty. Physiology (Bethesda). 2017;32(1):9–19. DOI: 10.1152/physiol.00012.2016.

41. Mack I, BelAiba RS, Djordjevic T, et al. Functional analyses reveal the greater potency of preadipocytes

compared with adipocytes as endothelial cell activator under normoxia, hypoxia, and TNFalpha exposure. Am J Physiol Endocrinol Metab. 2009;297(3):735–748. DOI: 10.1152/ajpendo.90851.2008.

42. Tchkonia T, Morbeck DE, Von Zglinicki T, et al. Fat tissue, aging, and cellular senescence. Aging Cell. 2010;9(5):667–684. DOI: 10.1111/j.1474-9726.2010.00608.x.

43. Zhu Y, Tchkonia T, Stout MB, et al. Inflammation and the depot-specific secretome of human preadipocytes. Obesity (Silver Spring).2015;23(5):989–999. DOI: 10.1002/oby.21053.

44. Lumeng CN, Liu J, Geletka L, et al. Aging is associated with an increase in T cells and inflammatory macrophages in visceral adipose tissue. J Immunol. 2011;187(12):6208–6216. DOI: 10.4049/jimmunol.1102188.

45. Xu M, Palmer AK, Ding H, et al. Targeting senescent cells enhances adipogenesis and metabolic function in old age. 2015;4:e12997. DOI: 10.7554/eLife.12997.

46. Lee PG, Halter JB. The pathophysiology of hyperglycemia in older adults: clinical considerations. Diabetes Care. 2017;40(4): 444–452. DOI: 10.2337/dc16-1732.

47. Babenko AY, Matveev GA, Alekseenko TI, et al. Interrelations of components of metabolic syndrome with the level of the hormones involved in regulation of adipose tissue metabolism. Arterial Hypertension. 2019;25(6):639–652. DOI: 10.18705/1607-419X-2019-25-6-639-652.

48. Singh R, Artaza JN, Taylor WE, et al. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. Endocrinology. 2003;144(11):5081–5088. DOI: 10.1210/en.2003-0741.

49. Buvat J, Maggi M, Guay A, et al. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med. 2013;10(1):245–284. DOI: 10.1111/j.1743-6109.2012.02783.x.

50. Childs GV, Odle AK, MacNicol MC, et al. The importance of leptin to reproduction. Endocrinology. 2021;162(2):bqaa204. DOI: 10.1210/endocr/bqaa204.

51. Gavin KM, Cooper EE, Raymer DK, et al. Estradiol effects on subcutaneous adipose tissue lipolysis in premenopausal women are adipose tissue depot specific and treatment dependent. Am J Physiol Endocrinol Metab. 2013;304(11):1167–1174. DOI: 10.1152/ajpendo.00023.2013.

52. Clegg DJ, Brown LM, Woods SC, et al. Gonadal hormones determine sensitivity to central leptin and insulin. Diabetes. 2006;55(4):978–987. DOI: 10.2337/diabetes.55.04.06.db05-1339.

53. Musatov S, Chen W, Pfaff DW, et al. Silencing of estrogen receptor alpha in the ventromedial nucleus of hypothalamus leads to metabolic syndrome. Proc Natl Acad Sci USA. 2007;104(7):2501–2506. DOI: 10.1073/pnas.0610787104.

54. Petersen EW, Carey AL, Sacchetti M, et al. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. Am J Physiol Endocrinol Metab. 2005;288(1):E155–E162. DOI: 10.1152/ajpendo.00257.2004.

55. Nookaew I, Svensson P-A, Jacobson P, et al. Adipose tissue resting energy expenditure and expression of genes involved in mitochondrial function are higher in women than in men. J Clin Endocrinol Metab. 2013;98(2):E370–E378. DOI: 10.1210/jc.2012-2764.

56. Kolb H, Kempf K, Röhling M, et al. Insulin: too much of a good thing is bad. BMC Medicine. 2020;18(1):224. DOI: 10.1186/s12916-020-01688-6.

57. Schnurbein J, Manzoor J, Brandt S, et al. Leptin is not essential for obesity-associated hypertension. Obes Facts. 2019;12(4):460–475. DOI: 10.1159/000501319.

58. Pereira S, Cline DL, Glavas MM, et al. Tissue-specific effects of leptin on glucose and lipid metabolism. Endocr Rev. 2021;42(1):1–28. DOI: 10.1210/endrev/bnaa027.

59. Mittendorfer B, Horowitz JF, DePaoli AM, et al. Recombinant human leptin treatment does not improve insulin action in obese subjects with type 2 diabetes. Diabetes. 2001;60(5):1474–1477. DOI: 10.2337/db10-1302.

60. Caro JF, Kolaczynski JW, Nyce MR, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet. 1996;348(9021):159–161. DOI: 10.1016/s0140-6736(96)03173-x.

61. Sinha MK, Ohannesian JP, Heiman ML, et al. Nocturnal rise of leptin in lean, obese, and non-insulin-dependent diabetes mellitus subjects. J Clin Invest. 1996;97(5):1344–1347. DOI: 10.1172/JCI118551.

62. Barr VA, Malide D, Zarnowski MJ, et al. Insulin stimulates both leptin secretion and production by rat white adipose tissue. Endocrinology. 1997;138(10):4463–4472. DOI: 10.1210/endo.138.10.5451.

63. Saladin R, De Vos P, Guerre-Millo M, et al. Transient increase in obese gene expression after food intake or insulin administration. Nature. 1995;377(6549):527–529. DOI: 10.1038/377527a0.

64. Dodd GT, Descherf S, Loh K, et al. Leptin and insulin act on POMC neurons to promote the browning of white fat. Cell. 2015;160(1-2):88–104. DOI: 10.1016/j.cell.2014.12.022.

65. Sobhani I, Bado A, Vissuzaine C, et al. Leptin secretion and leptin receptor in the human stomach. 2000;47(2):178–183. DOI: 10.1136/gut.47.2.178.

66. Sobhani I, Buyse M, Goiot H, et al. Vagal stimulation rapidly increases leptin secretion in human stomach. Gastroenterology. 2002;122(2):259–263. DOI: 10.1053/gast.2002.31385.

67. Martin RL, Perez E, He YJ, et al. Leptin resistance is associated with hypothalamic leptin receptor mRNA and protein downregulation. Metabolism. 2000;49(11):1479–1484. DOI: 10.1053/meta.2000.17695.

68. Zhang Y, Olbort M, Schwarzer K, et al. The leptin receptor mediates apparent autocrine regulation of leptin gene expression. Biochem Biophys Res Commun.1997;240(2):492–495. DOI: 10.1006/bbrc.1997.7622.

69. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257(1):79–83. DOI: 10.1006/bbrc.1999.0255.

70. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005;96(9):939–949. DOI: 10.1161/01.RES.0000163635.62927.34.

71. Fasshauer M, Kralisch S, Klier M, et al. Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes. Biochem Biophys Res Commun. 2003;301(4):1045–1050. DOI: 10.1016/s0006-291x(03)00090-1.

72. Engeli S, Feldpausch M, Gorzelniak K, et al. Association between adiponectin and mediators of inflammation in obese women. Diabetes. 2003;52(4):942–947. DOI: 10.1507/endocrj.K07-032.

73. Hattori Y, Akimoto K, Gross SS, et al. Angiotensin-II-induced oxidative stress elicits hypoadiponectinaemia in rats. Diabetologia. 2005;48(6):1066–1074. DOI: 10.1007/s00125-005-1766-7.

74. Hosogai N, Fukuhara A, Oshima K, et al. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. Diabetes. 2007;56(4):901–911. DOI: 10.2337/db06-0911.

75. Maeda N, Shimomura I, Kishida K, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med. 2002;8(7):731–737. DOI: 10.1038/nm724.

76. Kim J-Y, Van De Wall E, Laplante M, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007;117(9):2621–2637. DOI: 10.1172/JCI31021.

77. Vasileva LB, Artemyeva MS, Ma Y, et al. The effect of obesity, impaired carbohydrate metabolism and bariatric surgery on adiponectin and leptin mRNA levels in different adipose tissue depots. Arterial Hypertension. 2019;25(5):568–576. DOI: 10.18705/1607-419X-2019-25-5-568-576.

78. Anandhakrishnan A, Korbonits M. Glucagon-like peptide-1 in the pathophysiology and pharmacotherapy of clinical obesity. World J Diabetes. 2016;7(20):572–598. DOI: 10.4239/wjd.v7.i20.572.

79. Yamaoka-Tojo M, Tojo T, Takahira N, et al. Elevated circulating levels of an incretin hormone, glucagon-like peptide-1, are associated with metabolic components in high-risk patients with cardiovascular disease. Cardiovasc Diabetol. 2010;9:17. DOI: 10.1186/1475-2840-9-17.

80. Cho YM, Fujita Y, Kieffer TJ. Glucagon-like peptide-1: glucose homeostasis and beyond. Annu Rev Physiol. 2014;76:535–559. DOI: 10.1146/annurev-physiol-021113-170315.

81. Møller CL, Vistisen D, Færch K, et al. Glucose-Dependent Insulinotropic Polypeptide Is Associated With Lower Low-Density Lipoprotein But Unhealthy Fat Distribution, Independent of Insulin: The ADDITION-PRO Study. J Clin Endocrinol Metab. 2016;101(2):485–493. DOI: 10.1210/jc.2015-3133.

82. Gasbjerg LS, Gabe MBN, Hartmann B, et al. Glucose-dependent insulinotropic polypeptide (GIP) receptor antagonists as anti-diabetic agents. Peptides. 2018;100:173–181. DOI: 10.1016/j.peptides.2017.11.021.

83. Ariyasu H, Takaya K, Tagami T, et al. Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans. J Clin Endocrinol Metab. 2001;86(10):4753–47538. DOI: 10.1210/jcem.86.10.7885.

84. Korbonits M, Bustin SA, Kojima M, et al. The expression of the growth hormone secretagogue receptor ligand ghrelin in normal and abnormal human pituitary and other neuroendocrine tumors. J Clin Endocrinol Metab. 2001;86(2):881–887. DOI: 10.1210/jcem.86.2.7190.

85. Date Y, Nakazato M, Hashiguchi S, et al. Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. Diabetes. 2002;51(1):124–129. DOI: 10.2337/diabetes.51.1.124.

86. Volante M, Allia E, Gugliotta P, et al. Expression of ghrelin and of the GH secretagogue receptor by pancreatic islet cells and related endocrine tumors. J Clin Endocrinol Metab. 2002;87(3):1300–1308. DOI: 10.1210/jcem.87.3.8279.

87. Wierup N, Svensson H, Mulder H, et al. The ghrelin cell: a novel developmentally regulated islet cell in the human pancreas. Regul Pept. 2002;107(1-3):63–69. DOI: 10.1016/s0167-0115(02)00067-8.

88. Kojima M, Hosoda H, Date Y, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature. 1999;402(6762):656–660. DOI: 10.1038/45230.

89. Inui A, Asakawa A, Bowers CY, et al. Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. FASEB J. 2004;18(3):439–456. DOI: 10.1096/fj.03-0641rev.

90. Mori K, Yoshimoto A, Takaya K, et al. Kidney produces a novel acylated peptide, ghrelin. FEBS Lett. 2000;486(3):213–216. DOI: 10.1016/s0014-5793(00)02308-5.

91. Tena-Sempere M, Barreiro ML, Gonzalez LC, et al. Novel expression and functional role of ghrelin in rat testis. Endocrinology. 2002;143(2):717–725. DOI: 10.1210/endo.143.2.8646.

92. Gualillo O, Caminos J, Blanco M, et al. Ghrelin, a novel placental-derived hormone. Endocrinology. 2001;142(2):788–794. DOI: 10.1210/endo.142.2.7987.

93. Hattori N, Saito T, Yagyu T, et al. GH, GH receptor, GH secretagogue receptor,and ghrelin expression in human T cells, B cells, and neutrophils. J Clin Endocrinol Metab. 2001;86(9):4284–4291. DOI: 10.1210/jcem.86.9.7866.

94. Pinkney J, Williams G. Ghrelin gets hungry. Lancet. 2002;359(9315):1360–1361. DOI: 10.1016/S0140-6736(02)08387-3.

95. Lee H-M, Wang G, Englander EW, et al. Ghrelin, a new gastrointestinal endocrine peptide that stimulates insulin secretion: enteric distribution, ontogeny, influence of endocrine, and dietary manipulations. Endocrinology. 2002;143(1):185–190. DOI: 10.1210/endo.143.1.8602.

96. Toshinai K, Mondal MS, Nakazato M, et al. Upregulation of ghrelin expression in the stomach upon fasting, insulin-induced hypoglycemia, and leptin administration. Biochem Biophys Res Commun. 2001;281(5):1220–1225. DOI: 10.1006/bbrc.2001.4518.

97. Lindqvist A, Erlanson-Albertsson C. Fat Digestion and its Role in Appetite Regulation and Energy Balance -The Importance of Enterostatin and Tetrahydrolipstatin. Curr Med Chem — Central Nervous System Agents. 2003;3:157–175. DOI: 10.2174/1568015033477712.

98. Inui A. Ghrelin: an orexigenic and somatotrophic signal from stomach. Nat Rev Neurosci. 2001;2(8):551–560. DOI: 10.1038/35086018.

99. Tschop M, Weyer C, Tataranni PA, et al. Circulating ghrelin levels are decreased in human obesity. Diabetes. 2001;50(4):707–709. DOI: 10.2337/diabetes.50.4.707.

100. Hansen TK, Dall R, Hosoda H, et al. Weight loss increases circulating levels of ghrelin in human obesity. Clin Endocrinol (Oxf). 2002;56(2):203–206. DOI: 10.1046/j.0300-0664.2001.01456.x.

101. English PJ, Ghatei MA, Malik IA, et al. Food fails to suppress ghrelin levels in obese humans. J Clin Endocrinol Metab. 2002:87(6):2984–2987. DOI: 10.1210/jcem.87.6.8738.

102. Ligthart S, Hasbani NR, Ahmadizar F, et al. Genetic susceptibility, obesity and lifetime risk of type 2 diabetes: The ARIC study and Rotterdam Study. Diabet Med. 2021;38(10):e14639. DOI: 10.1111/dme.14639.

103. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet. 2018;50(11):1505–1513. DOI: 10.1038/s41588-018-0241-6.

104. Tinahones FJ, Coín-Aragüez L, Mayas MD, et al. Obesity-associated insulin resistance is correlated to adipose tissue vascular endothelial growth factors and metalloproteinase levels. BMC Physiol. 2012;12:4. DOI: 10.1186/1472-6793-12-4.

105. Tsiotra PC, Boutati E, Dimitriadis G, et al. High insulin and leptin increase resistin and inflammatory cytokine production from human mononuclear cells. Biomed Res Int. 2013;2013:487081. DOI: 10.1155/2013/487081.

106. Pereira-Fernandes A, Dirinck E, Dirtu AC, et al. Expression of obesity markers and Persistent Organic Pollutants levels in adipose tissue of obese patients: reinforcing the obesogen hypothesis? PLoS One. 2014;9(1):e84816. DOI: 10.1371/journal.pone.0084816.

107. Cano-Martínez LJ, Marroquín C, Coral-Vázquez RM, et al. Expression of adipokines and their receptors in adipose tissue of women with class 3 obesity with or without hypertension. Gene. 2019;702:148–152. DOI: 10.1016/j.gene.2019.03.070.

108. Konigorski S, Janke J, Drogan D, et al. Prediction of circulating adipokine levels based on body fat compartments and adipose tissue gene expression. Obes Facts. 2019;12(6):590–605. DOI: 10.1159/000502117.

109. Morselli E, Fuente-Martin E, Finan B, et al. Hypothalamic PGC-1α protects against high-fat diet exposure by regulating ERα. Cell Rep. 2014;9(2):633–645. DOI: 10.1016/j.celrep.2014.09.025.

110. Taylor R. Calorie restriction for long-term remission of type 2 diabetes. Clin Med (Lond). 2019;19(1):37–42. DOI: 10.7861/clinmedicine.19-1-37.

Author information:

Babenko Alina Yu., MD, Dr. Sc., Head of the Research Institute of Genetic Risks and Personalized Personal Prevention, World-Class Research Centre for Personalized Medicine;

Golikova Tatyana Igorevna, Junior Researcher, Research Laboratory of Prediabetes and Other Metabolic Disorders, Research Institute of Genetic Risks and Personalized Prevention, World-Class Research Centre for Personalized Medicine.