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Biochemistry and laboratory diagnosis of obesity

Neda Milinković, Nataša Bogavac-Stanojević, Jelena Vekić, Snežana Jovičić, Jelena Kotur-Stevuljević

Department of Medical Biochemistry, University of Belgrade – Faculty of Pharmacy

Corresponding author: Neda Milinković, e-mail: nedan@pharmacy.bg.ac.rs

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Abstract

Until now, a lot of research has been carried out which significantly helped in understanding and solving the problem of obesity. Despite this, there has been an upward in obesity trend at the global level. The role of laboratory diagnostics in the field of obesity is of great importance to doctors for establishing a diagnosis and monitoring the effects of therapy. Determining biochemical parameters also contributes to practical usefulness in the prevention of this disease, and prevention of consequent complications. Routinely available biochemical analyses are usually used to diagnose and monitor the effects of obesity therapy. The initial association related to laboratory analyses refers to parameters of lipid status, but there are a variety of routine laboratory parameters that can help in understanding and monitoring obesity from different angles. Timely and adequate management of obesity is also of interest from an economic aspect. For this reason, the topic of this research is to summarize the latest aspects of the concept of obesity, specifically from the point of view of biochemistry and laboratory diagnostics. Taking into account the complexity of this disease, it is important to point out the future perspectives and challenges that inevitably arise before both laboratory professionals and healthcare providers in general.

Key words: obesity, laboratory diagnostic, biochemical parameters, new biomarkers

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Introduction

Obesity represents a chronic disorder that develops due to an imbalance between energy intake and expenditure. Individuals are classified as obese if their body mass index (BMI) is over 30 kg/m^2, while overweight people fall into the BMI range of 25–30 kg/m^2 (1). Obesity is an important public health problem as it increases the risk of developing a wide range of non-communicable diseases: diabetes, cardiovascular disease (CVD), liver disease and various cancers (2, 3).

According to the World Health Organisation (WHO), in 2022 there were 2.5 billion overweight adults older than 18, with over 890 million obese adults. This accounts for 43% of adults older than 18 (43% of men and 44% of women) who were overweight, marking an increase from 1990, when only 25% of adults in the same age group were overweight. The prevalence of overweight by regions varied significantly, from 31% in South-East Asia and African regions to 67% in the Americas. In 2022, approximately 16% of adults aged 18 years and older worldwide were classified as obese. The global prevalence of obesity more than doubled between 1990 and 2022 (1). The prevalence of obesity in Serbia (data from 2016) was 17.6% for men and 18.0% for women. The WHO predicts an increase to 18% for men and 21% for women by 2025 (2).

According to an OECD analysis, obese people use 2.4 times more healthcare services, undergo more surgery, stay in hospital longer and require more expensive and complex treatments than health-conscious people. Obesity accounts for more than 70% of all treatment costs for diabetes, almost a quarter of treatment costs for cardiovascular disease, and 9% of cancers. Between 2020 and 2050, obesity and related diseases will reduce work productivity and gross domestic product, as well as reducing life expectancy by three years in the EU and other industrialised countries (4).

In countries with lower gross domestic product per capita, lower income and greater gender inequality, the prevalence of obesity tends to be higher in women than in men (5). Current evidence shows that women have a higher risk of developing obesity. Key mechanisms that alter the risk between men and women include differences in the hormonal, metabolic and inflammatory milieu, the insulin/insulin-like growth factor-1 axis and the emerging role of adipocytokines (6, 7). Obesity-related malignancies are more common in women and include endometrial, ovarian and postmenopausal breast cancer. Oesophageal cancer, on the other hand, is more common in men. In addition to hormone-related malignancies, other obesity-related comorbidities such as non-alcoholic fatty liver disease, type 2 diabetes mellitus, obesity hypoventilation syndrome and mental disorders are more common in women than in men (8, 9).

However, up to 30% of obese patients are metabolically healthy and do not have the “typical” complications associated with obesity (10). In these patients, the increase in adipose tissue is achieved by the recruitment and differentiation of adipose progenitor cells and not by the infiltration of fat into mature adipocytes. In contrast, subcutaneous adipose tissue (SAT) becomes dysfunctional in obese patients with impaired metabolic homeostasis, as progenitor cells fail to form properly, leading to adipocyte hypertrophy,

reduced adipogenesis and angiogenesis. When the storage capacity of SAT is exceeded, further caloric overload leads to fat accumulation in ectopic tissues and visceral depots (11, 12). In addition, fat accumulation is associated with an increased local inflammatory response and oxidative stress, which is gradually transmitted to the systemic level via the endocrine effects of adipocyte-derived molecules (adipokines), leading to impaired glucose metabolism, dyslipidaemia, elevated blood pressure and the development of metabolic syndrome (MS) (13). It is therefore clear that more concrete and practical indicators are needed in the real clinical setting that can be translated from research into daily practice and used as predictors of intervention outcomes.

The importance of laboratory diagnostics in the examination of obesity

Laboratory diagnostics play a central role in helping doctors assess obesity, establish a diagnosis and monitor the effects of therapy. Although lipid status parameters are used centrally as routine tests, there are a large number of biochemical analyzes that are related to this multifactorial disease.

Basic biochemistry and lipid status

Several routine biochemical parameters could deviate from the normal range in obese subjects, indicating adverse metabolic changes and/or organ dysfunction. The most obvious is the increase of fasting glucose levels, due to the development of insulin resistance, a common feature of obesity (14). Furthermore, obese subjects often exhibit hyperinsulinemia, as a consequence of increased insulin secretion in an attempt to maintain glucose homeostasis. The changes in the sensitivity to insulin may ultimately lead to impaired glucose tolerance, a metabolic disorder characterized by elevated serum glucose level during the oral glucose tolerance test (OGTT). Finally, in the conditions of prolonged insulin resistance, coupled with hyperinsulinemia and impaired glucose tolerance, the risk of developing type 2 diabetes mellitus is significantly increased (15).

Another detrimental consequence of insulin resistance is dyslipidemia. Insulin resistance is characterized by increased release of free fatty acids from adipose tissue, which is followed by enhanced hepatic production and secretion of very-low density lipoproteins (VLDL). Elevated circulating free fatty acids additionally impair plasma clearance of VLDLs, resulting in hypertriglyceridemia, the main feature of lipid profile in obese subjects (16). The level of high-density lipoprotein cholesterol (HDL-C) in obese subjects is generally decreased, which is associated with altered distribution and function of HDL subfactions (17-19). On the other side, the level of low-density lipoprotein cholesterol (LDL-C) is usually normal or slightly elevated, although the quality of LDL particles can be considerably altered. Indeed, obese subjects are characterised by a preponderance of small, dense LDL particles in the plasma, which are the most proatherogenic LDL species (20). These alterations in the lipid profile are being increasingly recognised in obese subjects as atherogenic dyslipidemia, based on the firm association with high CVD risk (21).

Obesity is characterized by a chronic low-grade inflammation, mainly driven by the dysfunctional adipose tissue and the consequent activation of immunological mechanisms. Briefly, dysfunctional adipose tissue is characterised by the production of proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The inflammatory milieu within adipose tissue is further exacerbated by increased production of adipokines, the most important being leptin and resistin, as well as by the infiltration of immune cells, particularly macrophages (22). Expectedly, the bulk of proinflammatory species released from adipose tissue consequently contribute to the development of systemic inflammation. At this point it should be stressed that the evaluation of low-grade inflammation requires the use of assays with high precision and accuracy in order to measure very low concentrations of inflammatory biomarkers. In this manner, a high-sensitivity C-reactive protein (hsCRP) test enables accurate measurement of CRP levels below detection limits of conventional tests, which is particularly important for cardiovascular risk assessment in subjects without known CVD or diabetes (23, 24). It is also important to note that the use of hsCRP in the contexts of CVD risk assessment requires the absence of inflammation and other chronic diseases.

Lastly, obesity is often associated with impaired renal function, reflected by altered glomerular filtration rate (GFR). In general, the extent of kidney function decline in obese subjects depends on the presence of other co-morbidities. Insulin resistance and diabetes may cause changes in the structure and function of the glomeruli, thus impairing glomerular filtration, while hypertension and lipid accumulation might induce damage of renal arteries and consequently reduce renal blood flow (25). Indeed, obesity accompanied by insulin resistance, diabetes, dyslipidemia or hypertension, is associated with decreased GFR and an increased risk of chronic kidney disease (26). Taking all into account, estimating GFR in obese subjects is of critical importance for monitoring kidney function decline. Yet, there is still no consensus on the best equation for GFR estimation in obese subjects (27).

Obesity-related metabolic changes can lead to numerous complications, including type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), CVD and certain types of cancer (28, 29), which significantly impact the quality of life and life expectancy (30). Therefore, regular monitoring of routine biochemical parameters is paramount to prevent and timely recognise obesity-related health issues and improve long-term outcomes.

Changes in enzymes activity in obesity

It is well known that there is an increased activity of glycolytic and enzymes involved in fatty acid synthesis in the adipose tissue of obese persons, thus promoting lipogenesis. This may be a result of both genetic and adaptive enzyme alterations. In their study, Belfiore et al. (31) investigated several enzymes related to lipogenesis in the adipose tissue in obese subjects who were on a controlled dietary and physical activity regimen. They found significantly increased both activity and protein concentration of hexokinase (EC 2.7.1.1), biphosphofructokinase (EC 2.7.1.11), and ATP citrate lyase (EC

4.1.3.8). These results indicated that the activity of enzymes related to glycerol 3-phosphate and fatty acid synthesis are increased in the adipose tissue of obese subject, enabling the enhanced triglyceride formation.

Fatty acids biosynthesis is vital in cell physiology in general, but especially in adipose tissue physiology. It depends on renowned enzyme-regulated processes. Today it is well recognized that adipose tissue can account for up to 40% of whole-body lipogenesis in a high carbohydrate diet (32, 33). The main enzymes in lipid synthesis which may be linked to the development of obesity are fatty acid synthase (FAS, EC 2.3.1.85) and acetyl-CoA carboxilase (ACC, EC 6.4.1.2) (34–36). By catalyzing the conversion of malonyl-CoA into palmitate, FAS represents the central enzyme in de novo lipogenesis (37). ACC catalyzes the formation of malonyl-CoA, an essential substrate for FAS and the chain elongation systems (38). Several studies have demonstrated lower adipose tissue mRNA, protein or activity levels of FAS and ACC genes in overweight and obese subjects compared with lean individuals, thus suggesting that, at the gene expression levels, the lipogenic pathway is downregulated in obesity (39–42). Others have reported the opposite – that the FAS and ACC genes are significantly increased in both subcutaneous and visceral fat samples from overweight and from obese subjects (regardless of the presence of type 2 diabetes) (43). A possible explanation of such contradictory findings may be that during the dynamic phase of obesity, in which the fat depos are growing, there is an increase in the lipogenic capacity of adipose tissue. On the other hand, with a large and continuing fat excess, the adaptive process aiming to limit further development of fat mass decreases the expression of lipogenic genes (44). Studies on rodents have demonstrated that the pharmacological inhibition of the activity of FAS blocks adipocyte differentiation and leads to a reduction of the adipocyte number (45). Therefore, the induction of lipogenesis catalyzed with FAS may contribute to obesity, and this process would be active during the development of obesity and insulin resistance. At one point, adipose tissue may reach an offset point, reversing the process and downregulating it through the natural inhibitory feedback process. Apparently, once the storage capacity of adipocytes is reached, the cells reduce their ability to synthesize additional fatty acids (46). Most probably obesity, insulin resistance and type 2 diabetes downregulate lipogenesis in adipose tissue through this suppression of lipogenic enzymes genes when visceral obesity augments to inappropriate levels (42).

Several studies have reported increased levels of circulating kynurenines in individuals with obesity (46, 47). One of the first enzymes of the kynurenine pathway (the main route of tryptophane degradation), indoleamine-2,3-dioxygenase (IDO1, EC 1.13.11.42), is induced by inflammation and expressed in many tissues, including adipose tissue (48). Moreover, it has been demonstrated that its gene expression is enhanced in the adipose tissue of people with obesity (49). Kynurenines are the group of metabolites that can be metabolized in three different ways: with kynurenic acid, xanthurenic acid, and quinolinic acid and nicotinamide adenine dinucleotide (NAD) as final products. Kynurenines are involved in immune regulation, tolerance mechanisms, and some are neuroactive (50, 51). Products of the quinolinic acid route are neuroprotective, while the

xanthurenic acid is a predisposing factor to insulin resistance and its levels are increased in diabetes (52, 53). Favenec et al. (54) investigated the kynurenine pathway regulation in relation to obesity in humans. They compared the expression of the genes of kynurenine pathway enzymes in subcutaneous and visceral adipose tissues from women with obesity and lean controls. In addition, they investigated whether these enzymes and kynurenines were associated with the BMI, inflammatory markers, as well as the contribution of adipocytes and macrophages to their relative expression. Their results showed that the expression of genes for IDO1, kynureninase (KYNU, EC 3.7.1.3), kynurenine aminotransferase III (CCBL2, EC 4.4.1.13), and kynurenine 3-monooxygenase (KMO, EC 1.14.13.9) is increased in the visceral adipose tissue of obese women. This expression in human primary adipocytes was induced by the proinflammatory cytokines for KYNU, CCBL2 and IDO1. As for the expression of KMO, which is not expressed in adipocytes, the authors hypothesized that its promotion was probably due to its presence in resident macrophages. The expression of all of these enzymes was higher in M1 proinflammatory than in M2 anti-inflammatory macrophages. Therefore, the conclusion was that the inflammation was causing the overall activation of the kynurenine pathway in adipose tissue. The observed activation of KMO, which has the central role in this metabolic cascade, controls the synthesis of bioactive kynurenines by directing the kynurenine pathway from the formation of NAD to the production 3-hydroxykinurenine and xanthurenic acid (55).

Increased caloric intake in obesity increases the load on glucose metabolism and other metabolic pathways. Thiamine and magnesium play an important role in glucose metabolism, where magnesium is essential for the activation of thiamine to its active form thiamine-diphosphate (TDP). Magnesium is also necessary for the activation of TDP dependent enzymes – transketolase (TK, EC 2.2.1.1), pyruvate dehydrogenase (PDH, EC 1.2.4.1), and α-keto glutaric acid dehydrogenase (AKGDH, EC 1.2.4.2). The deficiency of thiamine and magnesium, often seen in obesity, leads to the accumulation of lactate, as an anaerobic metabolite, due to a discrepancy between caloric burden and underfunctioning of thiamine dependent enzymes. (56). This lactate produced in adipocytes, due to the activation of the anaerobic pathway of glucose metabolism, precedes the onset of insulin resistance in obese patients (57). Lactate accumulation is a direct consequence of the loss of responsiveness of PDH to insulin that may be mediated by the compromised activity of PDH due to thiamine deficiency (58, 59). Additionally, the quantities of the accumulated lactate are proportionate to the mass of adipocytes, and the rate of lactate production is in correlation with the age of the adipocyte, thus indicating the extent and duration of the obesity condition (60, 61).

Endocrinological aspect of obesity

The current knowledge about obesity increasingly confirms that there is an inextricable link between this disorder, the resulting complications and endocrinological imbalance (62). The latest recommendations of the European Society of Endocrinology Clinical Guideline on the Endocrine Work-up in Obesity emphasize the importance of

determining the parameters of hormonal status in obese patients (63). Special importance is attached to the monitoring of thyroid function, and it is recommended as mandatory, given the high prevalence of hypothyroidism in these persons. However, only in the case of clinical suspicion of endocrine disorder hypercortisolism, male hypogonadism and female gonadal dysfunction is the determination of specific hormones recommended. A two-sided concept of the connection between endocrinological imbalance, obesity and consequent complications has been proposed (63). On the one hand, we can talk about obesity as a consequence of an endocrinological disease. By treating endocrinological disorders, obesity would be controlled. On the other hand, the treatment of obesity itself and the loss of fat tissue can be crucial to the restoration of hormonal imbalances.

Table I shows all the so-far described pathophysiological mechanisms of hormones that are directly related to obesity (63).

The confirmed connection between changes in the level of individual hormones and obesity has facilitated the management of the endocrinological aspect of obesity, in terms of determining specific hormones. For example, in the case of central obesity, irregular menstruation and hirsutism, which is a frequent consequence of excess androgens in women, it is important to determine LH, FSH, oestradiol, and testosterone. Most hormones are secreted by various tissues, but their target actions directly or indirectly change the adipose tissue metabolism. The endocrinological aspect of obesity and its consequences have been intensively investigated in terms of type 2 diabetes mellitus and the development of atherosclerosis, in which case an extremely common fatty tissue pathology has been confirmed (64). The results of a large number of studies explain in detail the effect of insulin on lipid metabolism in adipose tissue, and indicate the importance of insulin resistance in the development of obesity (65-68). The more frequent presence of obesity in women highlights the significant effect of sex hormones on obesity, as well as on the metabolic changes and inflammation inherent in obesity (69-72). Thyroid dysfunction has been observed as a common component of central obesity, although studies suggest a mutual association between obesity and thyroid imbalance, with the additional existence of impaired sensitivity of adipose tissue to thyroid hormones (73-75). The latest research indicates that severe obesity is associated with pituitary corticotroph hyperplasia and neoplasia (76). From animal to human studies, the negative effect of obesity on bone metabolism has been confirmed, as well as the complex relationship between bone and adipose tissue, given their distinct endocrinological activity (77-79). Some studies suggest a significant role of the renin angiotensin aldosterone system in the management of obesity and metabolic syndrome, and its potential clinical utility in addition to its confirmed association with blood pressure and heart failure (80-81).

Additionally, adipose tissue in itself represents an important endocrinological organ (82-84). Until recently, it was thought that only white adipose tissue had a significant endocrinological role, due to the secretion of leptin and a number of pro-inflammatory cytokines. (85). Recent research points to a significant endocrinological role of brown adipose tissue, given the numerous endocrine cytokines that have been

identified (86). However, further studies should be carried out to confirm and explain the functional targets of endocrine action of brown adipose tissue to pathophysiological processes.

Table I Hormones and associated mechanisms involved in the pathogenesis of obesity

Tabela I Hormoni i udruženi mehanizmi uključeni u patogenezu gojaznosti

Hormone	Levels in obesity	Proposed pathophysiologic mechanism
TSH	N or I	I of leptin, and insulin; I of peripheral T4 disposal
fT4	N or slightly D	I of disposal
Cortisol (blood, urine, saliva)	N or I Altered suppression tests	I of CRH, and adipose 11-HSD; D of CBG; Hyperactivity of the HPA axis
ACTH	N or I	I of CRH
GH	N or D	D of GHRH and ghrelin; I of GH-BP, insulin, and somatostatin
IGF-1	N or D	I of GH sensitivity; Increased intrahepatic triglyceride content
Testosterone (M)	D	D of SHBG, and GnRH; I of aromatase
Testosterone (F)	I	Insulin resistance (PCOS); D SHBG
LH/FSH (M)	D	I oestrogens/androgens
LH/FSH (F)	I	Insulin resistance in female
25-OH vitamin D	D	Trapping in adipose tissue, D sun exposure, 25-OH DBP; D liver synthesis
PTH	N or I	Secondary due to vitamin D deficiency
Insulin	I	Insulin resistance
Renin	I	I Sympathetic tone
Aldosterone	I	I Adipokines, renin- angiotensin, leptin
GLP-1	D	I FFA, microbiota
Leptin	I	Increased adipose mass, Leptin resistance
Ghrelin	D	Lack of ghrelin decrease after meals

Abbreviation: 11-HSD, 11β-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropic hormone; CBG, corticosteroid-binding globulin; CRH, corticotropin-releasing hormone; D; decrease levels; DBP, vitamin D binding hormone; FFA, free fatty acids; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH-BP, growth hormone-binding protein; GHRH, growth hormone releasing hormone; GLP, glucagon-like peptide; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal axis; I, increase levels; IGF, insulin-like growth factor; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; PTH, parathyroid hormone; SHBG, sex hormone-binding globulin; T4, Thyroxine; TSH, thyroid-stimulating hormone.

Skraćenice: 11-HSD, 11β-hidroksisteroid dehidrogenaza; ACTH, adrenokortikotropni hormon; CBG, globulin koji vezuje kortikosteroide; CRH, kortikotropin oslobađajući hormon; D; smanjenje nivoa; DBP, hormon koji vezuje vitamin D; FFA, slobodne masne kiseline; FSH, folikul stimulirajući hormon; FT4, slobodni tiroksin; GH-BP, protein koji vezuje hormon rasta; GHRH, hormon koji oslobađa hormon rasta; GLP, peptid sličan glukagonu; GnRH, gonadotropin oslobađajući hormon; HPA, osovina hipotalamus-hipofiza-nadbubrežna žlezda; I, povećanje nivoa; IGF, faktor rasta sličan insulina; LH, luteinizirajući hormon; PCOS, sindrom policističnih jajnika; PTH, paratiroidni hormon; SHBG, globulin koji vezuje polne hormone; T4, tiroksin; TSH, hormon koji stimuliše štitnu žlezdu.

The field of obesity research and medicine is growing faster and faster as obesity reaches pandemic proportions. Considering that hormonal and metabolic imbalances are the key factors that lead to obesity, Kaira et al. (7) have proposed a new terminology in the medical literature. The name “barocrinology” would focus on the endocrine and metabolic domains of the physiology and pathology of the adipose tissue metabolism that significantly contribute to the management of the endocrine perspective of obesity.

Obesity and inflammation

Obesity has been connected with chronic low-grade inflammation, which is one of the common pathological pathways for insulin resistance development and several non-communicable diseases such as cancers, atherosclerosis and CVD (87). If we consider obesity biochemistry, we may focus on many recently evolved inflammatory cytokines, such as: IL-6, IL-18, tumor necrosis factor alpha, CRP, adipokines (resistin, visfatin, leptin, adiponectin, apelin) (88). This means that these biomarkers are in stronger correlation in obese people compared to lean subjects, with a higher correlation with body fat measures than with the BMI (89).

Adipose tissue in obese subjects is consisted of hypertrophic adipocytes, which are characterized by a constant production of inflammation markers, mainly fibrinogen, CRP, interleukins (IL-6, IL-34) and TNF-α (90), which could be measured in systemic circulation. As a general mechanism of the inflammatory biomolecules influence on endothelium, a plethora of adhesion molecules and chemokines are produced which induce monocyte migration into the blood vessel intima, and subsequent transformation into macrophages (91). All these features stimulate insulin resistance (92). Proinflammatory cytokines IL-1 and IL-6, as well as TNF-α, induce CRP synthesis, so that constant production of any of these inflammatory biomolecules will cause the synthesis of the others, leading to a vicious circle of constant low-grade inflammation (93). The severity of obesity is in correlation with the TNF-α level, since in obese subject there is no negative feedback by a high TNF-α concentration (94). There are many TNF-α connected deleterious effects whereby it enforces IR: lipolysis enhancement, and as a consequence circulatory free fatty acids increase and NF-κB activation. TNF-α also induce vascular adhesion molecules activation, one of the conditions for atherosclerosis generation (95). CRP is a well-known risk factor and biomarker of the risk for cardiovascular disease development, especially for the hsCRP values above 3 mg/L. It is also reported that CRP is in direct correlation with obesity measured through the BMI, and in indirect correlation with HDL-cholesterol concentration (96).

The role of CRP in atherosclerosis is explained through its capability for complement and endothelial cells activation, and inhibition of nitric oxide synthase (97). IL-6 is a glycoprotein whose structure consists of a 185 aminoacids polypeptide chain, which is arranged in 4 helices. It is well-known as a major inflammatory mediator with a very low concentration in the circulation of healthy people, while in an inflammatory disease this IL-6 reaches much higher values. It is important to emphasize the dual role

of this IL-6: proinflammatory and anti-inflammatory. White adipose tissue also produces, among many other inflammatory cytokines, 15-35% of blood IL-6. All kind of cells present in adipose tissue could produce IL-6. The systemic circulation's release of IL-6, particularly heightened in obese subjects, suggests a potential novel function for IL-6 as a regulator of body weight and lipid metabolism on a systemic level (98). Adipose tissue expressed large amounts of IL-34, which is in correlation with increased concentration of this IL-34 in obese compared to lean subjects, and also in T2DM patients compared to healthy people. This IL-34 is also in a positive correlation with the BMI, blood pressure, plasma insulin, HOMA-IR and several cytokines and inflammatory markers. The function of IL-34 is revealed as a secondary ligand for colony-stimulating factor-1 receptor, which could rationalize IL-34 role in monocyte differentiation and proliferation, processes also involved in early atherogenesis. The expression of IL-34 in tissues is markedly increased during the adipogenesis process (99).

Obesity and oxidative stress

In several of our articles, we have analyzed the mutual involvement of inflammation and oxidative stress, especially in cardiovascular disease patients. We have found a generally significant positive correlation between markers of inflammation and oxidative stress parameters (100-103). It has been documented that obesity is linked to low-grade chronic systemic inflammation within adipose tissue, a condition driven by innate immune system activation in adipose tissue, fostering a pro-inflammatory environment and oxidative stress (OS), which in turn instigates a systemic acute-phase response (104).

Considering that reactive oxygen species (ROS) are generated through TNF-α induction of NF-κB signaling, and that ROS further stimulate the release of pro-inflammatory cytokines, expression of adhesion molecules and growth factors, such as platelet-derived growth factor and vascular cell adhesion molecule-1, their mutual involvement in obesity becomes evident. This creates a vicious cycle of deleterious effects governed by redox-sensitive transcription factors, notably NF-κB, and the NADPH oxidase pathway (NOX) (105). Mitochondria serve as targets for ROS produced by NOX and act as a significant source of ROS themselves, thereby potentially amplifying NADPH oxidase activity. Additionally, mitochondria can influence several antioxidants, thereby inhibiting ROS production and reducing NOX activity. All the above-mentioned mechanisms are even more pronounced in obese subjects, because their antioxidant defense is already exhausted (106). If we want to define the term “oxidative stress” or “redox imbalance”, we must take into consideration two possibilities: general increase in ROS production or overwhelming decrease in antioxidative protection elements. However, in reality, in chronic conditions like obesity the two processes run simultaneously. Endogenous antioxidant defense consists of antioxidative enzymes (superoxide-dismutase, catalase, glutathione peroxidase), peroxiredoxins, and the non-enzymatic part (antioxidant vitamins (A, C, E), small molecules with reducing capacity (bilirubin, uric acid, ceruloplasmin, albumin, flavonoids, glutathione) (107, 108). Antioxidants may partially restore redox imbalance, typically under physiological

conditions. However, in circumstances marked by heightened oxidative stress, as seen in various pathological conditions, one or more components of this system may become impaired over time. Consequently, oxidative stress becomes predominant, as observed in obesity (109).

Hematological changes in obesity

A large number of previous studies indicate a significant impact of obesity on immune function and alteration of hematological indices (110-115). Although obesity is considered a low-grade inflammation condition, inflammation is chronic and these changes are noticeable and reflected in elevated leukocyte and lymphocyte subset counts, suppressed mitogen-induced lymphocyte proliferation, higher monocyte and granulocyte phagocytosis, and oxidative burst activity (116). The main inducers of these changes are pro-inflammatory cytokines in association with adipokines, of which the influence of leptin and resistin has been studied to the greatest extent (117). In addition to increased granulocytopoiesis in the bone marrow and accelerated release of neutrophils, demargination of intravascular neutrophils occurs. The results of the study confirm the positive correlation of the number of leukocytes with the BMI, but also the predictive significance of the neutrophil/lymphocyte ratio for certain complications of obesity (118, 119). In addition, a significant influence of gender in obese persons on changes in the number and function of leukocytes was observed in women, due to an amplified inflammatory state and associated comorbidities, such as polycystic ovarian syndrome and obstructive sleep apnea (117).

The first study to report low serum iron levels and a negative correlation with body mass index was conducted more than seven decades ago (120). The results of subsequent tests confirmed that anemia is inextricably linked with obesity (118-121). Low serum iron is the main cause of sideropenic anemia, and the first parameter used to diagnose and assess the status of anemia and oxygenation of the body is hemoglobin. This indicates that in obese people it is of particular importance to determine the parameters of the complete blood count, with special emphasis on the red blood line. Recent research indicates a clear association of increased hepcidin levels with impaired iron metabolism in obesity (122). The results of one study (123) indicate that obesity is an independent risk factor for plasma lipid peroxidation and depletion of erythrocyte cytoprotective enzymes in humans. Although the interrelationship between inflammation, hematological changes and obesity has not been frequently investigated, it is important to emphasize that it exists, and the assumed interplay is shown in Figure 1.

Additionally, recent studies indicate that obesity and aging leave an apparent metabolic imprint on the metabolomic profile of red blood cells by up/down-regulating the specific pathways associated with these cells (124, 117). Altered erythrocyte metabolism is associated with increased glucose concentration in obese individuals, increased levels of creatine and phosphocreatine, as a consequence of increased food intake in obese individuals (125). Domingo-Orti et al. (125) suggest that obesity could have a significant negative effect on the natural evolution of erythrocytes and adaptation

of the organism to natural changes such as senescence. In obese people, a significant specific association of the body shape and anthropometric characteristics with erythrocyte and reticulocyte parameters was confirmed (121). The results of this study indicate that erythrocyte count, hematocrit, hemoglobin, and reticulocyte count and proportions were highest for the “apple” and lowest for the “pear” phenotype, without the influence of gender. Moreover, general and abdominal obesity uncomplicated with diabetes are associated with increased erythropoiesis and reticulocyte immaturity (121). Future studies should elucidate the specific association and changes in obesity with the specific type of anemia.

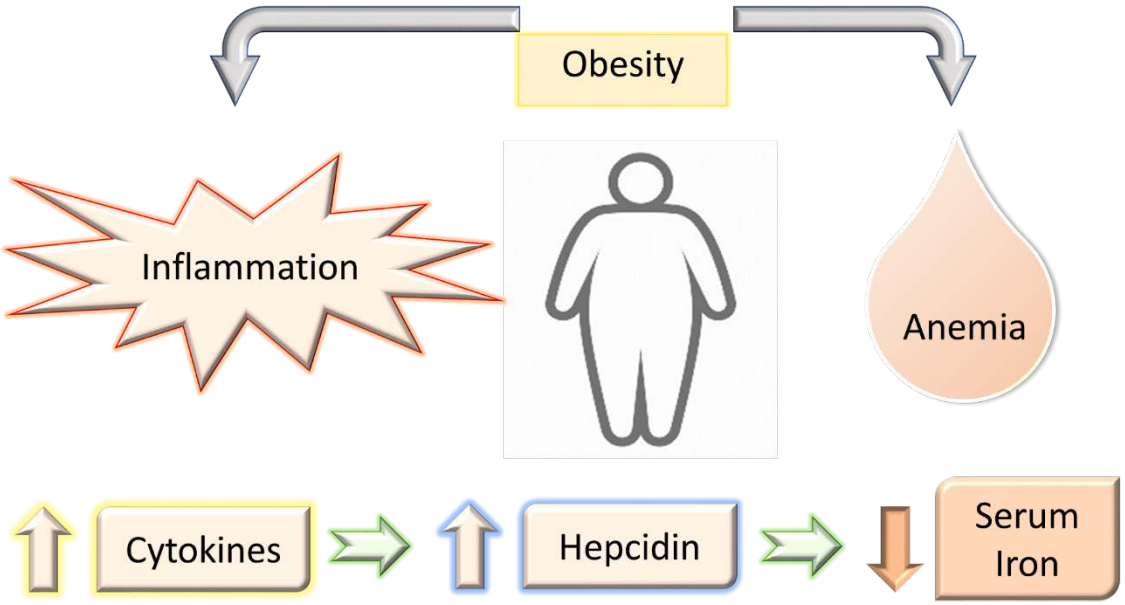

Figure 1. Interrelationship between inflammation, hematological changes and obesity
Slika 1. Međusobna povezanost inflamacije, hematoloških promena i gojaznosti

The effect of obesity on the platelet metabolism and consequent hemostasis disorders is explained elsewhere in this text.

Changes in hemostasis in obesity

In addition to the above-mentioned haematological disorders, obesity is also characterized by changes in hemostasis (Figure 2). These changes are mainly reflected in the disrupted balance between procoagulant and anticoagulant factors, which further predispose obese subjects to thrombotic events. Indeed, obese individuals have approximately twofold higher risk of venous thromboembolism (VTE) than normal-weight subjects (117).

Several interconnected mechanisms are responsible for the observed prothrombotic state in obese subjects, including chronic low-grade inflammation, insulin resistance and dysfunction of adipose tissue. In brief, proinflammatory cytokines are able to increase

fibrinogen and factor VIII levels by the stimulation of acute-phase proteins synthesis in the liver (126). In addition, they can upregulate endothelial expression of tissue factor, the main activator of coagulation, as well as the synthesis of plasminogen activator inhibitor 1 (PAI-1), a major inhibitor of fibrinolysis (127). Another contributor is insulin resistance, through a complex interplay between metabolic and hemostatic abnormalities. Namely, insulin resistance is intimately linked to endothelial dysfunction, reflected in the reduced bioavailability of nitric oxide (NO), increased production of endothelin-1, and enhanced expression of adhesion molecules, such as soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1), which impairs vasodilation, but promotes adhesion and aggregation of the platelets (128). While the specific effects of adipocyte tissue-derived hormones, such as leptin and resistin, on hemostasis in obese subjects are still being elucidated, emerging evidence suggests that these mediators may contribute to the prothrombotic state through the effects on endothelial and platelet function and fibrinolysis. For instance, both leptin and resistin have been shown to upregulate the expression of PAI-1 in endothelial and adipose tissue cells (129, 130). Similarly, resistin may promote endothelial dysfunction by reducing NO bioavailability and increasing the expression of adhesion molecules (131). Although experimental data suggest that leptin can stimulate ADP-mediated platelet aggregation, this effect can be compromised in obese subjects due to leptin resistance (132).

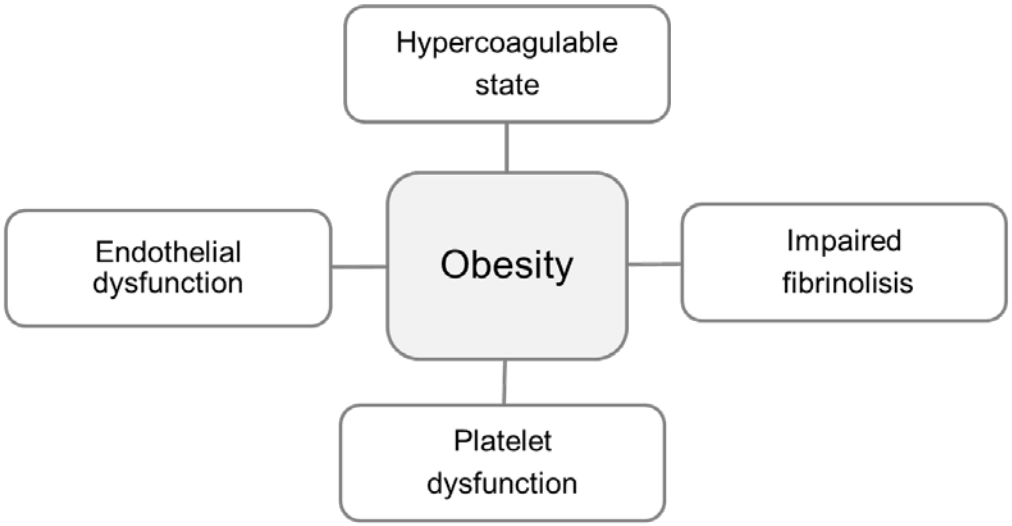

Figure 2. Disorders of hemostasis in obese subjects
Slika 2. Poremećaj hemostaze kod gojaznih osoba

Taken together, the presence of atherogenic dyslipidemia and chronic low-grade inflammation predispose obese subjects to atherosclerosis, while the disrupted balance in the hemostasis system in favour of procoagulant factors increases the risk for thrombus formation. Collectively, these are the main mechanisms responsible for the increased risk

for developing CVD in obese subjects. At present, effective weight management represents the main strategy to correct underlying metabolic abnormalities and improve hemostasis disorders in obese individuals (133). Importantly, careful consideration is needed when managing thromboprophylaxis in obese patients undergoing bariatric surgery (134).

Laboratory assessment of hemostasis biomarkers can help in the evaluation of the hypercoagulable state in obese individuals, and guide clinical management strategies aimed at reducing thrombotic risk. Furthermore, in recent years there has been a considerable interest in identifying hemostasis biomarkers that might improve CVD risk prediction in obese subjects, beyond traditional risk factors. Yet, the assessment of a single marker could not provide complete insight into the processes of hemostasis activation and fibrinolysis. Accordingly, several studies have compared different biomarkers of hemostasis disorders between obese individuals and normal-weight subjects, and their main findings are summarised in Table II.

Table II Hemostasis biomarkers in obese subjects

Tabela II Biomarkeri hemostaze kod gojaznih osoba

Disorder of hemostasis	Biomarkers that are altered in obese subjects
Hypercoagulable state	Fibrinogen, factors VIII, IX, X and XII, TAT, F1+2, D-dimer, protein S, protein C, antithrombin III
Impaired fibrinolysis	PAI-1
Platelet dysfunction	Platelet count, MPV
Endothelial dysfunction	t-PA, vWF

Abbreviations: t-PA, tissue plasminogen activator; vWF, von Willebrand factor; TAT, thrombin-antithrombin complexes; F1+2, prothrombin fragment F1+2; PAI-1, plasminogen activator inhibitor 1; MPV, mean platelet volume.

Skraćenice: t-PA, tkivni aktivator plazminogena; vWF, von Willebrand faktor; TAT, thrombin-antitrombin kompleksi; F1+2, protrombin fragment F1+2; PAI-1, inhibitor aktivatora plazminogena 1; MPV, prosečna zapremina trombocita.

The results of routine coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), generally show no differences between obese subjects and controls (135). However, some authors reported a shortened aPTT, which corresponds to the increased levels of coagulation factors of the intrinsic pathway, observed in obese individuals (136, 137). In a more recent population-based study, the authors investigated the levels of coagulation markers across different BMI categories. They reported that obese subjects had the highest concentrations of factor VIII, fibrinogen, protein S and D-dimer, while having lowest level of anticoagulant protein antithrombin III (138). It is important to note that although normal D-dimer represents a useful tool to exclude VTE, its level is often increased in obesity (139), which limits the

utility of this assay in subjects with increased body weight. Regarding biomarkers of platelet dysfunction, the most readily available indices are platelet count and mean platelet volume (MPV). In addition to increased platelet count, increased MPV is also observed in obese individuals (140), indicating the larger size of the platelets and their higher reactivity, and thus greater thrombotic potential. Other platelet indices, such as platelet distribution width (PDW) and plateletcrit (PCT), as well as MPV/PCT and PDW/PCT ratios, are considered to be emerging biomarkers of prothrombotic state in obese individuals, although their clinical significance is uncertain (141). At present, these indices remain research tools until their potential to be included in routine clinical practice is firmly established.

Future perspectives and challenges

Since obesity is a complex disorder, its management is challenging and far from having reached the desired success. From a medical biochemistry perspective, several important aspects of obesity deserve further research efforts. These include, but are not limited to, the investigation of metabolic pathways in adipose tissue, the role of hormones and adipokines in the regulation of lipid and glucose homeostasis, as well as genetic and epigenetic factors that predispose individuals to obesity and affect the response to environmental factors, such as physical activity and dietary interventions. Recently, the concept of metabolically healthy obesity (MHO) has emerged to denote obese individuals who do not exhibit the typical metabolic abnormalities and do not meet the criteria for metabolic syndrome. In particular, MHO individuals often have normal blood pressure and serum levels of glucose, insulin and lipid parameters, despite increased body weight. Consequently, MHO subjects are considered to be at a lower risk of developing cardiometabolic diseases (142). It is important to note that the concept of MHO is still controversial, and further research is needed to better understand the underlying mechanisms and long-term health outcomes associated with this phenotype.

Medical biochemistry laboratories play an important role in the management of obesity and associated comorbidities. Indeed, evidence-based clinical practice guidelines include specific recommendations for assessing laboratory parameters in obese subjects to evaluate their metabolic health, as well as to identify potential complications and guide treatment decisions. In recent years, the need for a more personalized approach in obesity management, based on the patient's specific health status and therapeutic goals, has been increasingly recognized (28). Implementing such specific interventions, tailored to individual needs, requires an integrative approach by a multidisciplinary team of healthcare providers from different specialties, where medical biochemistry professionals have an indispensable role to play.

Novel biomarkers of obesity

The new “omics” technologies have enabled the discovery of novel biomarkers of obesity, which could clarify its etiology and its role in the pathophysiology of chronic diseases, contribute to the characterization of obesity phenotypes, and be a potential target

for specific prevention and therapy strategies. The research in this area involves genomics (identification of genes), transcriptomics (mRNA and miRNAs), proteomics (proteins), and metabolomics (metabolites), as well as epigenomics (regulation of gene expression and phenotype by epigenetic markers, such as DNA methylation) and microbiomics (143). The overview of these emerging biomarkers is presented in Table III.

Table III "Omics" biomarkers in obesity

Tabela III „Omics" biomarkeri gojaznosti

Genomics	Epigenomics	Transcriptomics	Proteomics	Metabolomics	Glycomics	Microbiome
• DNA sequence • Gene polymorphisms • Polygenic risk scores	• DNA methylation • DNA methylation patterns	• Protein-coding RNAs (mRNAs) • Non-coding RNAs (miRNAs; lncRNAs)	• Proteins • Post-translational modifications	• Low-molecular weight metabolites (e.g. amino-acids, peptides, organic acids, carbohydratesand lipids)	• Glycans • Protein-glycosylation patterns	• Gut microbiota (composition and function)

Genomic studies involving genome-wide association studies (GWAS) have identified 941 near-independent single-nucleotide polymorphisms (SNPs) associated with the BMI (144). Genes at different loci interact and determine pathways and networks that reflect biological processes underlying the fat accumulation and distribution (145). Therefore, there have been many attempts to develop multi-locus profiles of genetic risk scores for obesity (146).

Epigenetic regulation involves DNA and histones modifications, as well as the non-coding RNAs that may influence the DNA processes without changing the DNA sequence. Studies have shown that DNA methylation of cytosines in cytosine-guanine dinucleotides (CpG) defines changes in response to environmental factors, which causes the association of early-life exposures to stress, under- or overnutrition during gestation or lactation, with overweight or obesity in later adulthood (147). This may be explained with DNA methylation of genes involved in growth, inflammation, lipid metabolism, glycolysis, and adipogenesis (148, 149).

The analysis of transcriptomic biomarkers (protein-coding and non-coding RNAs) in adipocytes revealed that the expression of more than a thousand genes was altered in obese individuals compared to lean persons. Transcriptomic biomarkers in obesity can also be identified by analyzing the peripheral blood transcriptome (150).

Serum or plasma proteome represents a useful resource for studying pathophysiological changes in obesity (151). In the study by Cominetti et al., proteomic measurements demonstrated statistically significant associations of complement factor B (CFAB), complement factor H (CFAH), complement factor I (CFAI), C-reactive protein (CRP), proline-rich acidic protein 1 (PRAP1), and calprotectin complex formed by proteins S100-A8 and S100-A9 with the BMI (152).

Metabolomic studies found specific metabolic changes in obese persons compared to lean ones in different populations, which included higher levels of branched-chain (BCAA) and aromatic amino acids, acylcarnitines, fatty acids, and certain phospholipids, and lower levels of glycine in the plasma. Some of these changes, i.e., higher BCAA and aromatic aminoacids and lower glycine, were also linked to insulin resistance and higher risk of type 2 diabetes (153–155).

Glycomics could provide important information for understanding systematic connections between obesity and metabolic diseases. For example, recent studies have demonstrated that changes in IgG N-glycosylation pattern, e.g. low galactosylation, correlate with measures of obesity and central obesity. In addition, IgG galactosylation decreases its proinflammatory activity, thus contributing to chronic inflammation in obesity (156).

Advanced bioinformatic methods, such as deep learning and artificial neural networks, are necessary to analyse complex “omics” data, especially in analyzing combinations of “omics” datasets. Furthermore, integrated multi-“omics” emerged as a tool to better clarify the complexity and interactions of the biological processes that predispose obesity. There are a lot of limitations and challenges in this field, including bias generated from different study design, sample collection protocols, data analysis methods, etc. This implies further endeavors to develop analytical protocols capable of generating, analyzing and interpreting multi-“omics” data that will be a solid basis for guiding personalized prevention and therapy strategies in obesity (143).

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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, JKS and NM; Investigation, NBS, JKS, JV, SJ, NM; Project administration JKS and NM; Supervision, NM; Validation, NM; Roles/Writing - original draft, NBS, JKS, JV, SJ, NM; and Writing - review & editing, NM.

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Biohemija i laboratorijska dijagnostika gojaznosti

Neda Milinković, Nataša Bogavac-Stanojević, Jelena Vekić, Snežana Jovičić, Jelena Kotur-Stevuljević

Katedra za medicinsku biohemiju, Univerzitet u Beogradu – Farmaceutski fakultet

*Autor za korespondenciju: Neda Milinković, e-mail: nedan@pharmacy.bg.ac.rs

Kratak sadržaj

Do sada je sprovedeno dosta istraživanja koja su značajno pomogla u sagledavanju i rešavanju problema gojaznosti. I pored toga, gojaznost ima trend porasta na globalnom nivou. Uloga laboratorijske dijagnostike u oblasti gojaznosti je od velikog značaja lekarima za postavljanje dijagnoze i praćenje efekata terapije. Određivanje biohemijskih parametara takođe doprinosi praktičnoj korisnosti u prevenciji ovog oboljenja, kao i predupređenju posledičnih komplikacija. Obično se za postavljanje dijagnoze i praćenje efekata terapije gojaznosti određuju rutinski dostupne biohemijske analize. Prvobitna asocijacija vezana za laboratorijske analize odnosi se na parametre lipidnog statusa, ali jako je veliki broj rutinskih analiza koje mogu pomoći u sagledavanju i praćenju gojaznosti iz različitih uglova. Dodatno, pravovremeno i adekvatno upravljanje gojaznošću je od interesa i sa ekonomskog aspekta. Iz tog razloga, tema ovog istraživanja je sumiranje najnovijih aspekata koncepta gojaznosti, posebno sa stanovišta biohemije i laboratorijske dijagnostike. Uzimajući u obzir složenost ove bolesti, važno je ukazati na buduće perspektive i izazove koji se neizbežno javljaju kako pred laboratorijskim stručnjacima, tako i pred zdravstvenim radnicima uopšte.

Ključne reči: gojaznost, laboratorijska dijagnostika, biohemijski parametri, novi biomarkeri