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OBESITY – THE EPIDEMIC OF THE 21ST CENTURY

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Abstract. *Obesity is a major global public health challenge, with a continuously increasing prevalence across all age groups and a substantial burden of comorbidities, premature mortality and healthcare-system costs. This review summarises contemporary definitions, epidemiological trends, clinical assessment, comorbidities, pathogenesis—including metabolic adaptation—and fundamental principles of obesity management, emphasising the need for a long-term, individualised approach. A narrative review of guidelines, position statements, large epidemiological analyses and recent review articles addressing obesity definition, assessment, pathophysiology and treatment was performed. Particular emphasis is placed on the limitations of body mass index (BMI), the clinical utility of the Edmonton Obesity Staging System (EOSS), metabolic adaptation and contemporary pharmacotherapeutic options. The World Health Organization defines obesity as a chronic, progressive disease with adverse effects on health and life expectancy. Global projections indicate further growth in prevalence by 2035, including a concerning rise in paediatric populations. Although BMI is useful at the population level, individual risk is determined by fat distribution, ectopic adiposity and associated clinical factors; therefore, combining BMI and waist circumference with comprehensive clinical assessment improves risk stratification. EOSS predicts all-cause mortality more accurately than BMI alone. Obesity is associated with more than 200 diseases, predominantly cardiometabolic disorders, MASLD/MASH, mechanical and psychiatric complications and increased malignancy risk. Mortality increases by approximately 30% for every 5 kg/m² rise in BMI. Pathogenesis is multifactorial, involving genetic susceptibility and neuroendocrine regulation of appetite, strongly influenced by environmental and behavioural factors. Metabolic adaptation after weight loss promotes weight regain, confirming obesity as a chronic relapsing disease.*

Management requires a long-term, multimodal strategy focused on health outcomes, including lifestyle interventions, psychological support, evidence-based pharmacotherapy (GLP-1/GIP-related mechanisms) and bariatric procedures when indicated. Weight stigma remains a major barrier to effective care.

Key words: *obesity; comorbidities; metabolic adaptation; EOSS; pharmacotherapy; stigma*

Introduction

Obesity is one of the most important public health threats in contemporary society. The obesity epidemic, which began in the mid- 1970s, has to date affected more than two billion people worldwide and shows a continuous upward trend across all age groups, including children and adolescents [1–2]. The contemporary concept of obesity goes beyond viewing this condition solely as a consequence of unhealthy lifestyle habits and clearly defines it as a complex, chronic and relapsing disease.

Definition and epidemiology of obesity

The World Health Organization (WHO) defines obesity as a chronic disease in which abnormal or excessive accumulation of adipose tissue impairs health, increases the risk of numerous chronic complications and shortens life expectancy [1]. According to the World Obesity Federation, the prevalence of obesity is projected to rise from about 14% in 2020 to approximately 24% by 2035, affecting nearly two billion adults, children and adolescents [2]. Particularly concerning is the accelerated rise in paediatric obesity, with prevalence doubling in both sexes during 2020–2025 [2]. Obesity as a disease was formally recognised in 1948, classified among chronic diseases in 1997, and in the last decade has been further reaffirmed through statements of the American Medical Association and the European Union as a disease with complex pathophysiological mechanisms [3–5].

Assessment and classification of obesity

In addition to anthropometric measures, contemporary clinical assessment includes targeted identification of complications and functional limitations: blood pressure, glycaemic control (fasting plasma glucose/HbA1c), lipid profile, liver enzymes and assessment of risk for MASLD/MASH, kidney function (eGFR, albuminuria), as well as screening for obstructive sleep apnoea, osteoarthritis and psychiatric comorbidities. In practice, assessment may be complemented by body composition measurements (e.g., bioimpedance, DXA) and identification of sarcopenic obesity in older adults, which can meaningfully influence treatment choice and goals.

In epidemiological studies, obesity is most commonly defined using body mass index (BMI; body weight/height^2), which enables population- level risk estimation. However, BMI does not reflect fat distribution, the degree of visceral and ectopic adiposity or an individual's metabolic profile. At the individual level, complications arise due to excess adiposity, the location and distribution of fat and many other factors, including environmental, genetic, biological and socioeconomic determinants. Although BMI is widely used to assess and classify obesity, it is not a precise tool for identifying obesity- related complications. Waist circumference is independently associated with cardiovascular risk, but alone does not provide precise individual assessment of visceral fat. Combined use of BMI and waist circumference improves identification of high- risk phenotypes, particularly in people with lower BMI. Beyond BMI and waist circumference, comprehensive history taking to identify causes of obesity, physical examination and relevant laboratory testing are essential.

Traditional obesity assessment based exclusively on BMI has substantial limitations because it does not account for clinical heterogeneity, comorbidities and a person's true health risk.

In this context, the Edmonton Obesity Staging System (Edmonton Obesity Staging System – EOSS) was developed as a clinically oriented model for risk stratification in people with excess weight and obesity. EOSS represents an important advance because it integrates metabolic, functional and psychological parameters and has proven to be a better predictor of all- cause mortality than BMI or waist circumference alone [6]. EOSS classifies patients into five stages (0–4) based on the presence and severity of metabolic abnormalities, end- organ damage, functional limitations and psychological consequences of obesity. Unlike BMI, which quantifies the degree of adiposity, EOSS enables assessment of the actual health burden and prognosis.

Stage 0 includes individuals without metabolic risk factors, with preserved physical and psychological function. Stages 1 and 2 include patients with subclinical and clinically manifest comorbidities such as type 2 diabetes, hypertension, dyslipidaemia and obstructive sleep apnoea. Stages 3 and 4 are characterised by severe, often irreversible end- organ damage, significant functional impairment and marked psychiatric disorders, with a high risk of morbidity and mortality. The clinical value of EOSS lies in the fact that it is a stronger predictor of all- cause and cardiovascular mortality than BMI, independently of the degree of obesity. Application of EOSS supports an individualised approach, rational selection of lifestyle measures, pharmacotherapy and bariatric surgery, and identification of patients with so- called metabolically healthy obesity. EOSS has been proposed to guide clinical decision- making across all BMI categories; population studies have shown it predicts all- cause mortality better than BMI or waist circumference alone [6].

Obesity comorbidities

The clinical spectrum of obesity complications includes metabolic, cardiovascular, renal, hepatic, respiratory, mechanical and psychological consequences. Cardiovascular risk increases through a combination of insulin resistance, dyslipidaemia, hypertension, chronic inflammation and changes in myocardial structure and function, including heart failure with preserved ejection fraction (HFpEF) [7]. From a renal perspective, obesity is associated with hyperfiltration, obesity- related glomerulopathy, progression of chronic kidney disease and increased risk of nephrolithiasis [8,9]. At the hepatic level, ectopic fat accumulation contributes to the development of MASLD/MASH, with contemporary nomenclature and diagnostic approaches being harmonised through multisociety consensus processes.

In addition, obesity affects reproductive health (e.g., polycystic ovary syndrome and gestational diabetes) [10,11], the musculoskeletal system (osteoarthritis, pain, functional limitation), the respiratory system (obstructive sleep apnoea) and mental health (anxiety, depression), with a substantial reduction in quality of life. Therefore, in clinical assessment it is important to identify dominant complications and

therapeutic priorities and to set goals that are not limited to kilograms, but focus on improved function and reduced risk of complications.

Obesity is associated with more than 200 different diseases and conditions. Excess adipose tissue leads to dysfunction of multiple organs and systems, and adipose tissue is now regarded as an active endocrine and immune organ [7–8]. Ectopic fat accumulation and increased secretion of adipocytokines and pro- inflammatory mediators contribute to insulin resistance, lipid metabolism disturbances, chronic inflammation and increased cardiometabolic and oncological risk. It is estimated that around 20% of cancers may be attributable to obesity, independent of dietary factors.

The most common metabolic comorbidities include prediabetes, type 2 diabetes, MASLD/MASH, dyslipidaemia, hypertension, coronary disease and HFpEF. Mechanical complications (obstructive sleep apnoea, osteoarthritis, gastro- oesophageal reflux disease, functional muscle weakness) and mental disorders such as anxiety and depression with reduced quality of life are also present [7–8]. Studies have shown that increased BMI correlates positively with calcium nephrolithiasis, gestational diabetes, polycystic ovary syndrome, metabolic syndrome and osteoporosis [9–13].

In some individuals with obesity, ‘metabolically healthy obesity’ (MHO) can be identified. This is a heterogeneous and often transient state strongly linked to fat distribution, ectopic lipids and subsequent development of cardiometabolic disease. Mechanisms are not fully elucidated, but recent data point to the importance of genetic factors, lower visceral adiposity and a more favourable waist- to- hip ratio. Longitudinal evidence indicates that MHO is frequently transient and still associated with increased long- term risk of type 2 diabetes and cardiovascular disease compared with metabolically healthy normal- weight individuals [14].

Obesity has a strong negative impact on life expectancy, which is shortened with increasing BMI by approximately 6 to 14 years. It is estimated that almost 80% of people with normal BMI at age 35 will reach 70 years of age; however, this decreases to about 70% for BMI 30–35 kg/m², ~62% for BMI 35–40 kg/m², and ~50% for BMI 40–50 kg/m². For BMI 40–45 kg/m², median survival is reduced by 8–10 years. Each 5 kg/m² increase in BMI is associated with ~30% higher mortality [15].

Etiology and pathogenesis of obesity

Obesity results from a complex interaction of genetic, epigenetic, neuroendocrine and environmental factors. More than 1,000 genetic loci involved in body weight regulation have been identified, with predominant expression in the central nervous system. Studies demonstrate rich expression of obesity- associated loci not only in the hypothalamus and pituitary—considered key sites for central appetite regulation—but even more prominently in the hippocampus and limbic system, tissues involved in learning, cognition, emotions and memory [16–17].

The brain plays a central role in regulating energy homeostasis through integration of homeostatic (hypothalamus), hedonic (mesolimbic system) and executive (prefrontal

cortex) neural networks. These networks are influenced by peripheral signals from adipose tissue, the pancreas and the gastrointestinal tract.

An increasing body of evidence highlights the importance of inadequate lifestyle patterns in the development of obesity. Modern civilisation, through an unhealthy lifestyle, drives the obesity pandemic. Lifestyle changes arise under strong social, cultural and economic forces. Key lifestyle elements affecting body weight change: physical activity decreases, sleep duration shortens and dietary structure changes [18].

Physical workload in modern occupations has declined, while leisure- time physical activity is often neglected. Advances in food industry technology and distribution expose people to increasing intake of excess energy. This creates an imbalance between energy intake and expenditure. Therefore, changes in daily time organisation and lifestyle and awareness of the importance of health behaviours are crucial. Only then are sustainable changes in dietary structure possible, resulting in durable reductions in energy intake [19].

Socioeconomic and cultural factors also influence control of energy homeostasis, underscoring the need for greater societal impact on the drivers of the obesity pandemic [20–21].

Metabolic adaptation in obesity

Metabolic adaptation is a key mechanism explaining the chronic and relapsing nature of obesity. Its main feature is a disproportionate reduction in total energy expenditure relative to the loss of body weight and lean mass. After weight loss, basal metabolic rate falls beyond what would be expected based on changes in body composition, making the organism more energy- efficient and metabolically 'thrifty'.

This adaptive response includes reduced resting energy expenditure, reduced diet- induced thermogenesis, decreased spontaneous physical activity and diminished adaptive thermogenesis in brown and white adipose tissue. The consequence is persistently reduced energy expenditure, even after weight stabilisation.

Metabolic adaptation is strongly regulated by central mechanisms, primarily at the level of the hypothalamus, through integration of peripheral hormonal signals of energy availability. Reduced fat mass leads to lower leptin concentrations, resulting in increased appetite and decreased energy expenditure, while ghrelin concentrations increase and further stimulate hunger. At the same time, changes occur in insulin signalling and in the hypothalamic–pituitary–thyroid axis, with reduced peripheral conversion of thyroxine to triiodothyronine, further lowering metabolic rate.

In people with long- standing obesity, metabolic adaptation manifests as a form of 'biological memory' of body weight, whereby the organism actively defends a higher level of body weight. This phenomenon, described by the concepts of 'set- point' and 'settling- point', explains why obesity is a chronic, relapsing disease and why short- term dietary interventions most often do not lead to sustained therapeutic success.

Understanding metabolic adaptation has key clinical significance because it points to the need for a long- term, individualised and multimodal approach to obesity management that includes lifestyle change, strategies to preserve lean mass and, when indicated, pharmacological therapy targeting central and peripheral mechanisms of energy balance regulation [22–24].

Obesity therapy

The modern goal of obesity management is not exclusively weight loss, but improvement of health outcomes and quality of life. Therapy must be long- term, individualised and multimodal [25, 26]. Nonetheless, more research is needed to shift the focus of obesity treatment towards patient- centered outcomes rather than weight loss alone.

In clinical practice, treatment choice should be aligned with disease stage (e.g., by EOSS), dominant comorbidities and individual barriers (psychological, social and therapeutic). In EOSS 0–1, the emphasis is on intensive lifestyle interventions and prevention of progression; in EOSS ≥2, there is often a clear need for early pharmacotherapy and/or consideration of bariatric- metabolic procedures according to criteria and comorbidities.

The foundation of obesity management consists of medical nutrition therapy, physical activity and psychological support, with the importance of cognitive behavioural therapy highlighted [26]. Pharmacotherapy is particularly important in patients for whom lifestyle modification alone is insufficient for a clinically meaningful and sustainable response, given the biological basis of relapse (metabolic adaptation). In all cases, success depends on continuous multidisciplinary support (nutritional, psychological, physiotherapy and medical) and on active reduction of stigma within healthcare.

Weight loss achieved through lifestyle change alone generally yields a modest effect that is not sustained long- term, as evidenced by numerous studies. The ACTION- IO study, which included 14,502 individuals, showed that 81% had made one or more serious attempts to lose weight, yet only 11% maintained ≥5% weight loss for one year or longer [27]. Healthy lifestyle change typically achieves 3–5% weight reduction, which is not maintained in most individuals. Therefore, pharmacotherapy is needed because it increases the likelihood of maintaining reduced body weight, which in turn improves obesity- related comorbidities.

Pharmacotherapy is indicated for individuals with BMI ≥30 kg/m² or BMI ≥27 kg/m² with comorbidities such as type 2 diabetes, hyperlipidaemia or hypertension. It should ideally be initiated before severe complications develop. Treatment should be long- term, as many studies demonstrate weight regain when therapy is discontinued [28].

Given the complex pathogenesis of obesity, optimal pharmacotherapy requires action on key signalling pathways: receptors for GLP- 1 (glucagon- like peptide- 1), GIP (glucose- dependent insulinotropic polypeptide) and glucagon [29–30]. GLP- 1 and GIP receptors are present in the hypothalamus and brainstem and mediate reduced

food intake and weight loss. Glucagon receptors are primarily in the liver, while GIP receptors are found in adipose tissue and bone [30].

Contemporary anti- obesity drugs target central and peripheral mechanisms of appetite and energy balance control, including GLP- 1 receptor agonists and dual/triple agonists, with implications for cardiometabolic outcomes [31]. Ongoing research explores doses and combinations (e.g., clinical trials with semaglutide). Long- term strategies require planned follow-up, assessment of response and tolerability, and timely adjustment or switching.

Anti- obesity drugs can be classified by mechanism: agents acting on gastrointestinal absorption (orlistat); centrally acting appetite modulators (phentermine–topiramate; naltrexone–bupropion); and agents mimicking entero- pancreatic hormones affecting central appetite regulation and providing multiple favourable cardiometabolic effects mediated by weight loss (liraglutide, semaglutide, tirzepatide) [32–33]. Novel agents in various phases of preclinical and clinical development include dual/triple agonist combinations: semaglutide 2.4 mg with cagrilintide 2.4 mg (a long- acting amylin analogue), survodutide (dual glucagon/GLP- 1 receptor agonist) and retatrutide (triple GIP/GLP- 1/glucagon receptor agonist) [34]. Oral semaglutide 50 mg achieved 12.7% weight loss [35]. Bimagrumab is an antibody blocking activin type II receptors, producing substantial fat mass reduction with concomitant increases in lean mass [36–37].

When selecting pharmacological agents, comorbidities are crucial—especially type 2 diabetes, cardiovascular disease, MASLD/MASH and chronic kidney disease [38]. Modern agents acting via GLP- 1, GIP and glucagon receptors can achieve 5–20% or greater weight loss, with favourable effects on type 2 diabetes, cardiovascular disease, MASLD and other comorbidities. Semaglutide has shown a particularly favourable effect on psoriatic lesions in people with obesity and type 2 diabetes [39]. It should be emphasised that comorbidities often overlap and substantially influence mortality among people living with obesity. Cardiovascular disease is the cause of death in about two- thirds of people with elevated BMI [40].

The beneficial effect of weight loss on comorbidities depends on the percentage of weight lost and the specific comorbidity. A 5% reduction is generally beneficial across comorbidities. Prevention of type 2 diabetes often requires >10% loss; for sleep apnoea 10–15%; for improved physical functioning up to 20%; and >30% for resolution of fatty liver disease or remission of recently developed type 2 diabetes [41–42]. Up to 35% weight reduction may be needed to prevent adverse cardiovascular events and reduce cancer risk. An individualised approach is essential because all options, including bariatric surgery, have responders and non- responders.

Bariatric- metabolic procedures are the most effective interventions for long- term weight reduction and comorbidity improvement in carefully selected patients, particularly in severe obesity and/or type 2 diabetes [43].

A realistic, sustainable treatment plan is necessary to avoid the ‘yo- yo’ phenomenon. Pharmacotherapy, combined with lifestyle change and used chronically, may lead to

sustainable weight loss and improved health. Selecting the right drug requires consideration of contraindications, risks, adverse effects, comorbidities and medication availability.

Obesity phenotypes and a personalised approach

Identification of dominant phenotypes enables more rational therapy selection and greater treatment success, supporting the need for precision, personalised medicine in obesity care. Four phenotypes are commonly described: 'hungry brain' (higher caloric intake needed to achieve satiety), 'hungry gut' (satiety achieved but short- lived), 'emotional eating' (food intake in both positive and negative emotional states), and 'slow burn' (often physically inactive with sarcopenia). These four phenotypes may cover most patients living with obesity; distribution is similar (approximately 12–18%), and ≥1 phenotype is present in about 85% of patients. For each phenotype, a corresponding therapy is suggested: for the 'hungry brain' phenotype, phentermine–topiramate; for the 'hungry gut' phenotype, liraglutide; for emotional overeating, naltrexone–bupropion; and for 'slow burners', phentermine combined with resistance training [44].

Stigma and challenges in management

Weight stigma can delay help- seeking, reduce adherence, diminish trust in healthcare professionals and worsen outcomes. In practice, this requires neutral, non- judgemental language, a focus on health goals and recognition and management of implicit bias within care teams. At the system level, educational and organisational measures are needed to ensure access to longterm obesity care, including pharmacotherapy and psychological support, with clear follow- up protocols. Despite strong evidence, obesity remains under- recognised and under- treated. Stigma and biased beliefs negatively affect the quality of healthcare and treatment outcomes, underscoring the need for education and systemic change [45].

Conclusion

Obesity is a chronic, progressive and relapsing disease with complex pathogenesis and serious health consequences. Effective management requires integration of contemporary assessment concepts, understanding of metabolic adaptation and a long- term, individualised therapeutic approach.

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GOJAZNOST DANAS – PANDEMIJA 21. STOLJEĆA

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Sažetak. *Gojaznost predstavlja jedan od najvećih globalnih izazova za javno zdravlje, sa stalno rastućom prevalencijom u svim starosnim grupama i značajnim opterećenjem u vidu komorbiditeta, prevremene smrtnosti i troškova zdravstvenog sistema. Ovaj pregled sumira savremene definicije, epidemiološke trendove, kliničku procjenu, komorbiditete, patogenezu — uključujući metaboličku adaptaciju — i osnovne principe liječenja gojaznosti, sa naglaskom na potrebu za dugoročnim, individualizovanim pristupom. Izvršen je narativni pregled smjernica, stavova stručnih udruženja, velikih epidemioloških analiza i nedavnih pregleda literature koji se bave definicijom, procjenom, patofiziologijom i liječenjem gojaznosti. Poseban akcenat stavljen je na ograničenja indeksa tjelesne mase (BMI), kliničku korisnost Edmontonskog sistema za stadijume gojaznosti (EOSS), metaboličku adaptaciju i savremene farmakoterapijske opcije. Svjetska zdravstvena organizacija definiše gojaznost kao hroničnu, progresivnu bolest sa štetnim efektima po zdravlje i životni vijek. Globalne projekcije ukazuju na dalji rast prevalencije do 2035. godine, uključujući zabrinjavajući porast u pedijatrijskoj populaciji. Iako je BMI koristan na populacionom nivou, individualni rizik zavisi od raspodijele masnog tkiva, ektopične adipoznosti i pridruženih kliničkih faktora; stoga kombinovanje BMI-ja i obima struka sa sveobuhvatnom kliničkom procjenom poboljšava stratifikaciju rizika. EOSS preciznije predviđa ukupnu smrtnost u poređenju sa samim BMI-jem. Gojaznost je povezana sa više od 200 bolesti, pretežno kardiometaboličkim poremećajima, MASLD/MASH, mehaničkim i psihijatrijskim komplikacijama i povećanim rizikom od maligniteta. Smrtnost raste za približno 30% na svakih 5 kg/m² povećanja BMI-ja. Patogeneza je multifaktorska, uključujući genetsku predispoziciju i neuroendokrinu regulaciju apetita, snažno pod uticajem faktora iz okruženja i ponašanja. Metabolička adaptacija nakon gubitka težine podstiče ponovno dobijanje na težini, potvrđujući gojaznost kao hroničnu, recidivirajuću bolest. Liječenje zahtijeva dugoročnu, multimodalnu strategiju usmjerenu na ishode po zdravlje, uključujući promjene načina života, psihološku podršku, farmakoterapiju zasnovanu na dokazima (GLP-1/GIP-mehanizmi) i barijatrijske procedure kada su indikovane. Stigma vezana za tjelesnu težinu i dalje predstavlja veliku prepreku za efikasnu njegu.*

Ključne riječi: *gojaznost; komorbiditeti; metabolička adaptacija; EOSS; farmakoterapija; stigma*