Biološke poveznice poremećaja hranjenja u djetinjstvu i adolescenciji

/ Biological Correlates of Eating Disorders in Childhood and Adolescence

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Cilj ovog narativnog pregleda je prikazati biološke mehanizme (genetske, neurobiološke i hormonalne) koji bi mogli biti uključeni u etiopatogenezu poremećaja hranjenja. Rad se temelji na pretraživanju literature provedenom putem baza *PubMed* i *Google Scholar* u zadnjih desetak godina. Istaknuti su važni dijagnostički i klinički laboratorijski nalazi kod poremećaja hranjenja (PH). Nađene su razlike u nalazima kod anoreksije nervoze (AN) u odnosu na bulimiju nervozu (BN) zbog prisutne pothranjenosti i mogućeg opasnijeg metaboličkog i elektrolitskog disbalansa i opasnijih kardioloških posljedica. Nađene su i razlike između AN i BN u genetskim čimbenicima na što ukazuju studije blizanaca, obiteljske studije te GWAS studija. Najčešći neurobiološki čimbenici koje se povezuje s poremećajima hranjenja su prefrontalni korteks, limbički sustav, hipotalamus, od neurotransmitera dopamin i serotonin, visoki kortizol, disfunkcija spolnih hormona te promjene leptina i grelina. S njima se nalazi i povezanost sa simptomima kao što su restriktivni trend, kognitivna rigidnost, emocionalne reakcije, impulzivnost, nedostatak kontrole. Potvrđena je važnost bioloških čimbenika kod poremećaja hranjenja uz vjerojatnu interakciju s drugim čimbenicima. Navedena etiopatogenetska biološka saznanja mogla bi dati veće uvide u nove integrativne i multidisciplinarne dijagnostičke i terapijske intervencije.

/ The aim of this narrative review is to present the biological mechanisms (genetic, neurobiological, and hormonal) that may be involved in the etiopathogenesis of eating disorders (ED). This review is based on a literature search conducted through the PubMed and Google Scholar databases in the past ten years. The findings highlight important diagnostic and clinical laboratory parameters in ED. Differences are found between anorexia nervosa (AN) and bulimia nervosa (BN) owing to the presence of malnutrition and a potentially more dangerous metabolic and electrolyte imbalance, as well as more serious cardiac consequences in AN. Differences between AN and BN are also found in genetic factors, as demonstrated by twin studies, family studies, and GWAS studies. The most frequent neurobiological factors associated with ED are the prefrontal cortex, limbic system, hypothalamus, neurotransmitters dopamine and serotonin, elevated cortisol, dysfunction of sex hormones, and changes in leptin and ghrelin. These are further associated with clinical symptoms such as a restrictive tendency, cognitive rigidity, emotional reactivity, impulsivity, lack of control, and others. This work confirms the importance of biological factors in ED, with a probable interaction with other factors. These etiopathogenetic biological findings could provide greater insights into novel integrative and multidisciplinary diagnostic and therapeutic interventions.

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UVODNI ASPEKTI

Klasifikacija, klinička slika, epidemiologija

Prema petom, revidiranom, izdanju Dijagnostičkog i statističkog priručnika za duševne poremećaje (DSM-5-TR) te 11. reviziji Međunarodne klasifikacije bolesti (MKB-11), poremećaji hranjenja (PH) obuhvaćaju anoreksiju nervozu (AN), bulimiju nervozu (BN), poremećaj prejedanja (PP), izbjegavajući/restriktivni poremećaj unosa hrane (ARFID), piku, poremećaj preživanja (ruminacije) te kategorije drugih specificiranih i nespecificiranih poremećaja hranjenja i jedenja (1,2). Dvije su klasifikacije velikim dijelom usklađene, uz manje razlike (2). AN možemo podijeliti na anoreksiju nervozu - restriktivni tip (AN-RT), te na anoreksiju nervozu - tip s prejedanjem i čišćenjem (AN-PČ) (3). Zbog boljeg fokusa ovog rada i najčešćih poremećaja u dječjoj i adolescentnoj dobi detaljnije ćemo se usredotočiti samo na AN i BN, dok će se PP navesti u manjem opsegu.

Kriteriji kliničke slike AN-RT prema DSM-5 su restrikcija energetskog unosa, uz pothranjenost, poremećaj tjelesne sheme, strah od dobivanja na masi, što je često udruženo s ekscesivnim vježbanjem. Kriteriji AN-PČ su slični AN-RT uz pothranjenost te dodatno povremena prejedanja obično manjih količina hrane, a može postojati i ponašanje čišćenja. BN se oči-

INTRODUCTORY ASPECTS

Classification, Clinical Presentation, Epidemiology

According to the fifth, text-revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) and the 11th revision of the International Classification of Diseases (ICD-11), eating disorders (ED) encompass anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), avoidant/restrictive food intake disorder (ARFID), pica, rumination disorder, and the categories of other specified and unspecified feeding and eating disorders (1,2). The two classifications are largely harmonized, with minor differences (2). AN can be divided into anorexia nervosa – restricting type (AN-R) and anorexia nervosa – binge-eating/purging type (AN-BP) (3). For the sake of a clearer focus of this paper and of the disorders most common in childhood and adolescence, the text will focus in greater detail only on AN and BN, while BED will be addressed to a lesser extent.

The clinical criteria for AN-R according to DSM-5 are restriction of energy intake, accompanied by undernutrition, disturbance of body image, fear of weight gain, and frequently associated excessive exercise. The criteria for AN-BP are similar to AN-R, with undernutrition, plus additional occasional binge-eating episodes usually involving smaller amounts of food, and purging

tuje slično AN s poremećajem tjelesne sheme, strahom od dobivanja na tjelesnoj masi (TM), međutim uz abnormalno jedenje (koje tipično uključuje prejedanje, ali može uključivati i manje restriktivne epizode) uz moguće kompenzatorne mehanizme: ekscesivno vježbanje te ponašanja čišćenja, uz normalnu TM. PP je obilježen abnormalnim jedenjem, prejedanjem, povremenom restrikcijom, TM je normalna ili postoji pretilost, nema kompenzatornih ponašanja ili vježbanja, nema straha od dobivanja na TM niti poremećaja tjelesne sheme, mada povremeno može i to postojati (1,3).

PH su među najčešćim kroničnim stanjima u adolescenata, a učestalost je u porastu (4). Sustavni pregledi pokazuju da se procijenjena prevalencija poremećaja hranjenja u općoj populaciji više nego udvostručila: s 3,4 % u razdoblju 2000.–2006. na 7,8 % u razdoblju 2013.–2018. (5). U reprezentativnom uzorku američkih adolescenata (13–18 godina) cjeloživotna prevalencija iznosila je 0,3 % za AN, 0,9 % za BN i 1,6 % za PP (6). Sličan trend porasta se vjerojatno nalazi i u Hrvatskoj. AN i BN znatno su češći u djevojaka nego u dječaka (omjer približno od 2:1 do 10:1), dok je kod PP spolna razlika manje izražena (približno 3:1) (6,7). AN najčešće započinje peripubertalno, dok tipično BN počinje pri kraju adolescencije (3,7).

O PH u Hrvatskoj u zadnjim dekadama ima malo publikacija (8-12), što je začuđujuće s obzirom na povećanu incidenciju ovog poremećaja u svijetu i u Hrvatskoj.

Biopsihosocijalni model etiopatogeneze poremećaja hranjenja

Važno je naglasiti da biološke predispozicije same po sebi ne objašnjavaju razvoj PH; one djeluju u interakciji s osobnim, okolišnim i sociokulturnim čimbenicima (3). Begovac i suradnici su predstavili model koji objašnjava etiopatogenezu PH (3) u kojem pojedinačni

behavior may also be present. BN is manifested similarly to AN, with disturbance of body image and fear of gaining body weight (BW), but with abnormal eating (typically including binge eating, although it may also include less restrictive episodes), with possible compensatory mechanisms: excessive exercise and purging behaviors, yet with normal BW. BED is characterized by abnormal eating, binge eating, occasional restriction, with normal BW or obesity present; in principle, there are no compensatory behaviors or exercise, and in principle, there is no fear of gaining BW or disturbance of body image, although these may occasionally be present (1,3).

EDs are among the most common chronic conditions in adolescents, and their frequency is increasing (4). Systematic reviews show that the estimated prevalence of eating disorders in the general population has more than doubled — from 3.4% in the period 2000–2006 to 7.8% in the period 2013–2018 (5). In a representative sample of American adolescents (13–18 years), the lifetime prevalence was 0.3% for AN, 0.9% for BN, and 1.6% for BED (6). A similar upward trend is probably also present in Croatia. AN and BN are considerably more frequent in girls than in boys (ratio approximately 2:1 to 10:1), whereas in BED the sex difference is less pronounced (approximately 3:1) (6,7). AN most often begins peripubertally, while BN typically begins in late adolescence (3,7).

Only a limited number of publications in Croatia in recent decades have addressed ED (8,9,10,11,12), which is surprising given the increased incidence of this disorder worldwide and in Croatia.

The Biopsychosocial Model of the Etiopathogenesis of Eating Disorders

It is important to emphasize that biological predispositions alone do not explain the development of ED; they act in interaction with personal, environmental, and sociocultural factors (3).

čimbenici (zaštitni ili rizični individualni čimbenici) djeluju u interakciji s okolišnim čimbenicima (zaštitnim ili rizičnim okolišnim čimbenicima), koji se dalje dijele na predisponirajuće čimbenike, okidače i čimbenike održavanja. U tom modelu razvoj ličnosti i prilagodba (ranjivost nasuprot otpornosti) imaju ključnu ulogu, kako u biološkom tako i u psihološkom smislu. Pojedinačni čimbenici uključuju genetske i epigenetske utjecaje, osobne psihološke značajke, obrasce privrženosti, psihodinamske aspekte te kognitivno-bihevioralne mehanizme. Okidači unutar tih čimbenika mogu uključivati individualizaciju i separaciju tijekom adolescencije. Okolišni čimbenici mogu uključivati stresore, životne događaje, međuljudske odnose, obiteljsku dinamiku te sociokulturna očekivanja vezana uz mršavost. Dodatni okidači mogu uključivati zadirkivanje od vršnjaka kao precipitirajući čimbenik. Pri usporedbi PH u dječjoj i adolescentnoj psihijatriji s drugim psihijatrijskim poremećajima u toj populaciji može se uočiti uravnoteženo prožimanje somatskih (bioloških) i psihogenih (psiholoških) sastavnica, uz blagu prevagu psiholoških čimbenika. Ta se ravnoteža može mijenjati ovisno o stadiju poremećaja i individualnoj kliničkoj slici pacijenta. Međutim, kada se stanje primjerice kod AN jednom razvije, dugotrajno gladovanje dovodi do niza metaboličkih i hormonalnih promjena, koje potom dodatno pojačavaju i somatske i psihološke promjene. Stoga je u praksi teško razlikovati primarne uzroke poremećaja od posljedica gladovanja (3).

Terapijski aspekti

U svijetu postoje različiti terapijski integrativni i multidisciplinarni algoritmi liječenja ovog poremećaja (3,13). Pojedini autori dijele algoritme liječenja na devet *setting*a (13), odnosno terapijski algoritam se može podijeliti na opće pristupe te na specifične pristupe u četiri dijela: 1. Somatska stabilizacija, nutritivna rehabilitacija i terapija; 2. Psihosocijalne intervencije,

Begovac et al. present a model that explains the etiopathogenesis of ED (3), in which individual factors (protective or risk individual factors) act in interaction with environmental factors (protective or risk environmental factors), which are further divided into predisposing factors, triggers, and maintaining factors. In this model, personality development and adaptation (vulnerability versus resilience) play a key role, both in the biological and psychological senses. Individual factors include genetic and epigenetic influences, personal psychological characteristics, attachment patterns, psychodynamic aspects, and cognitive-behavioral mechanisms. Triggers within these factors may include individuation and separation during adolescence. Environmental factors may include stressors, life events, interpersonal relationships, family dynamics, and sociocultural expectations related to thinness. Additional triggers may include teasing by peers as a precipitating factor. When comparing ED in child and adolescent psychiatry with other psychiatric disorders in this population, a balanced interweaving of somatic (biological) and psychogenic (psychological) components can be observed, with a slight predominance of psychological factors. However, this balance may shift depending on the stage of the disorder and the individual clinical presentation of the patient. Nevertheless, once the condition has developed — for example, in AN — prolonged starvation leads to a series of metabolic and hormonal changes, which then further intensify both somatic and psychological changes. Therefore, it is difficult in practice to distinguish the primary causes of the disorder from the consequences of starvation (3).

Therapeutic Aspects

Various integrative and multidisciplinary treatment algorithms for this disorder exist worldwide (3,13). Some authors divide treatment algorithms into nine settings (13). In other words, the therapeutic algorithm can be divided into general and specific approaches in four parts: 1. somatic stabilization, nutritional

psihoterapija; 3. Rad s roditeljima i obitelji; 4. Psihofarmakoterapija i drugi oblici liječenja (3,14).

Što se tiče psihosocijalnih metoda i rada s roditeljima postoje različiti terapijski algoritmi. Naglašena je uporaba kognitivno-bihevioralnih metoda, kao i specifične vrste liječenja (13,15), ali važne su i psihodinamske metode liječenja (3).

U psihofarmakološkom pristupu liječenju pomažu saznanja o primjeni lijekova kod djece i adolescenata kao i specifičniji radovi kod AN (16). Postoje otvorena i kontroverzna pitanja rane dijagnostike, cjelokupnog multimodalnog integrativnog načina liječenja unutar jednog medicinskog sustava te smanjenja kronifikacije poremećaja u odrasloj dobi (13).

CILJ RADA

Danas je izazovno klinički i znanstveno obuhvatiti moguće biološke etiopatogenetske čimbenike, koji nisu dovoljno istraženi u literaturi (3,17). Zbog boljeg fokusa ovog rada neće se ulaziti detaljnije u opisivanje psiholoških i socijalnih čimbenika. Dakle, cilj ovog narativnog pregleda je prikazati biološke mehanizme (genetske, neurobiološke i hormonalne mehanizme), a koji bi mogli biti uključeni u etiopatogenezu PH. Mogući odgovori na etiopatogenetska biološka saznanja bi nam mogli dati veće uvide u nove integrativne dijagnostičke i terapijske intervencije.

METODE

Strategija pretraživanja i kriteriji odabira

Ovaj se narativni pregledni rad temelji na pretraživanju literature provedenom putem baze *PubMed*, uz dopunsko pretraživanje putem *Google Scholara*. Pretraživanje je provedeno korištenjem sljedećih ključnih riječi: „eating

rehabilitation, and therapy; 2. psychosocial interventions and psychotherapy; 3. work with parents and family; 4. psychopharmacotherapy and other forms of treatment (3,14).

Regarding psychosocial methods and work with parents, various therapeutic algorithms exist. The use of cognitive-behavioral methods is emphasized, as well as specific types of treatment (13,15); however, psychodynamic methods of treatment are also important (3).

Regarding the psychopharmacological approach to treatment, we are aided by knowledge about the use of medications in children and adolescents, as well as more specific papers on AN (16). There remain open and controversial questions regarding early diagnosis, the overall multimodal integrative mode of treatment within a single medical system, and the reduction of chronification of the disorder into adulthood (13).

AIM OF THE PAPER

Today, it is challenging, clinically and scientifically, to encompass the possible biological etiopathogenetic factors, which are insufficiently investigated in the literature (3,17). For the sake of a clearer focus of this paper, the psychological and social factors will not be described in greater detail. Thus, the aim of this narrative review is to present the biological mechanisms (genetic, neurobiological, and hormonal) that may be involved in the etiopathogenesis of ED. Possible answers regarding etiopathogenetic biological findings could provide greater insights into novel integrative diagnostic and therapeutic interventions.

METHODS

Search Strategy and Selection Criteria

This narrative review article is based on a literature search conducted through the PubMed database, with supplementary searching through

disorders" (poremećaji hranjenja), „anorexia nervosa" (anoreksija nervoza), „bulimia nervosa" (bulimija nervoza), „binge-eating disorder" (poremećaj prejedanja), „genetic factors" (genetski čimbenici), „neurobiology" (neurobiologija) te „hormonal regulation" (hormonalna regulacija). Naglasak je stavljen na radove relevantne za dječju i adolescentnu dob u zadnjih desetak godina, uz uključivanje ranijih temeljnih radova i referentnih izvora. Kao kriteriji isključivanja bili su radovi koji nemaju tematsku povezanost s biološkim (genetskim, neurobiološkim i hormonalnim) čimbenicima PH, kao i prikazi slučajeva.

REZULTATI I RASPRAVA

Pojedini dijagnostički i klinički laboratorijski nalazi kod poremećaja hranjenja

U tablici 1 je prikazana diferencijalna dijagnoza glavnih simptoma, te razlika u važnijim dijagnostičkim i kliničkim somatskim nalazima između AN i BN (3,18,19). Kod svih PH laboratorijske nalaze treba tumačiti unutar kliničkog konteksta, jer rezultati mogu varirati ovisno o težini bolesti, trajanju i kompenzacijskim ponašanjima. Rutinski laboratorijski nalazi u pacijenata s PH su važni za dijagnostičko prepoznavanje mogućih medicinskih stanja i komplikacija i usmjeravanje terapijskih intervencija (20).

Laboratorijski nalazi su odraz činjenice da su kod pothranjenosti i AN, a mogu biti i kod BN, zahvaćeni svi organski sustavi u tijelu. Osobito su zabrinjavajuće kardiovaskularne komplikacije (sinusna bradikardija, srčane aritmije, ortostatske promjene srčane frekvencije ili krvnog tlaka, hipotenzija, sinkopa, kardiomiopatija, perikardijski izljev) te metaboličke posljedice. Međutim, značajne su i druge abnormalnosti uključujući gastrointestinalne, endokrine, bubrežne, hematološke, neurološke (npr. atrofija mozga) i dermatološke promjene (3).

Google Scholar. The search was performed using the following keywords: "eating disorders", "anorexia nervosa", "bulimia nervosa", "binge-eating disorder", "genetic factors", "neurobiology" and "hormonal regulation". Emphasis was placed on papers relevant to childhood and adolescence, in the past ten years or so, while also including earlier foundational works and reference sources. The exclusion criteria were papers lacking thematic relevance to the biological (genetic, neurobiological, and hormonal) factors of ED, as well as case reports.

RESULTS AND DISCUSSION

Selected Diagnostic and Clinical Laboratory Findings in Eating Disorders

Table 1 presents the differential diagnosis of the main symptoms, and the differences in more important diagnostic and clinical somatic findings between AN and BN (3,18,19). In all EDs, laboratory findings should be interpreted within the clinical context, as the results may vary depending on the severity of the illness, its duration, and compensatory behaviors. Routine laboratory findings in patients with EDs are important for the diagnostic recognition of possible medical conditions and complications and for guiding therapeutic interventions (20).

Laboratory findings reflect the fact that in undernutrition and AN — and possibly also in BN — all organ systems in the body are affected. Cardiovascular complications (sinus bradycardia, cardiac arrhythmias, orthostatic changes in heart rate or blood pressure, hypotension, syncope, cardiomyopathy, pericardial effusion, etc.) and metabolic consequences are of particular concern. However, other abnormalities are also significant, including gastrointestinal, endocrine, renal, haematological, neurological (e.g. brain atrophy), and dermatological changes (3).

TABLICA 1. Diferencijalna dijagnoza glavnih kliničkih simptoma te razlika važnijih dijagnostičkih i kliničkih somatskih nalaza između anoreksije nervoze i bulimije nervoze.
TABLE 1. Differential Diagnosis of the Main Clinical Symptoms, and the Differences in More Important Diagnostic and Clinical Somatic Findings Between Anorexia Nervosa and Bulimia Nervosa.

	Anoreksija nervoza / Anorexia nervosa	Bulimija nervoza / Bulimia nervosa
Glavni klinički simptomi / Main clinical symptoms	Poremećaj slike tijela, strah od dobivanja na masi, restriktivno hranjenje; ekscesivno vježbanje; pothranjenost / Body image disturbance, fear of weight gain, restrictive eating; excessive exercise; undernutrition	Poremećaj slike tijela, strah od dobivanja na masi; uredan BMI; prejedanje, kompenzatorna ponašanja / Body image disturbance, fear of weight gain; normal BMI; binge eating, compensatory behaviors
Vrsta poremećaja / Type of disorder	Psihijatrijski i potencijalni metabolički poremećaj / Psychiatric and potential metabolic disorder	Psihijatrijski poremećaj / Psychiatric disorder
Dijagnostičke i kliničke somatske komplikacije / Diagnostic and clinical somatic complications		
Opći status / General status	Pothranjenost / Undernutrition	/
Kardiovaskularni učinci / Cardiovascular effects	Kardiovaskularne komplikacije / Cardiovascular complications	Kardiovaskularne komplikacije / Cardiovascular complications
Poremećaji elektrolita / Electrolyte disturbances	Poremećaji elektrolita; hipokalemija / Electrolyte disturbances; hypokalaemia	Hipokloremijska alkaloza, a što dovodi do hipokalemije, osobito u osoba koje se služe samoinduciranim povraćanjem; Hiperkloremična metabolička acidoza može se uočiti u pacijenata koji zloupotrebljavaju laksative / Hypochloraemic alkalosis leading to hypokalaemia, especially in individuals who use self-induced vomiting; hyperchloraemic metabolic acidosis may be seen in patients who abuse laxatives
Poremećaji minerala / Mineral disturbances	Ca, Mg, fosfor i drugi / Ca, Mg, phosphorus and others	Ca, Mg, fosfor i drugi / Ca, Mg, phosphorus and others
Endokrine abnormalnosti i drugi parametri / Endocrine abnormalities and other parameters	Povišene razine kortizola, niske razine hormona štitnjače (T3) i hipogonadotropni hipogonadizam, što doprinosi amenoreji kod djevojaka; hipoglikemija, povišeni jetreni enzimi i niska razina inzulinu sličnog čimbenika rasta 1 / Elevated cortisol levels, low thyroid hormone levels (T3) and hypogonadotropic hypogonadism, contributing to amenorrhoea in girls; hypoglycaemia, elevated liver enzymes and low insulin-like growth factor 1	Oscilacije razine glukoze u krvi, razine amilaze često se bilježe zbog kronične stimulacije parotidne žlijezde / Fluctuations in blood glucose levels; amylase levels are often recorded owing to chronic stimulation of the parotid gland

Osobe s AN mogu pokazivati elektrolitski disbalans (19,21). Elektrolitski poremećaji, osobito niske razine kalija, povećavaju rizik od malignih srčanih aritmija koje su vodeći uzrok smrtnosti kod AN (22,23). Potrebno je pratiti i druge parametre, kao npr. koncentraciju minerala, osobito fosfata (14). Može se uočiti leukopeniju, anemiju i trombocitopeniju, što odražava supresiju koštane srži zbog pothranjenosti (18,19). Endokrine abnormalnosti uključuju povišene razine kortizola, niske razine hormona štitnjače (T3) i hipogonadotropni hipogonadizam, što doprinosi amenoreji kod djevojaka (20,24). Hipoglikemija, povišeni jetreni enzimi i niska razina inzulinu sličnog čimbenika rasta 1 (IGF-1) također su česti, što ukazuje na metaboličku prilagodbu na gladovanje (24,25).

Individuals with AN may show electrolyte imbalance (19,21). Electrolyte disturbances, especially low potassium levels, increase the risk of malignant cardiac arrhythmias, which are the leading cause of mortality in AN (22,23). It is also necessary to monitor other parameters, such as the concentration of minerals, especially phosphate (14). Leukopenia, anemia, and thrombocytopenia may be observed, reflecting bone marrow suppression due to undernutrition (18,19). Endocrine abnormalities include elevated cortisol levels, low thyroid hormone levels (T3), and hypogonadotropic hypogonadism, which contributes to amenorrhea in girls (20,24). Hypoglycemia, elevated liver enzymes, and a low level of insulin-like growth factor 1 (IGF-1) are also common, indicating metabolic adaptation to starvation (24,25).

Kod BN najčešće laboratorijske abnormalnosti posljedica su učestalog povraćanja i kompenzacijskih ponašanja. One uključuju hipokloremijsku alkalozu, što dovodi do hipokalemije, osobito u osoba koje se služe samoinduciranim povraćanjem (22,26). Hiperkloremična metabolička acidoza može se uočiti u pacijenata koji zloupotrebljavaju laksative (22,27). Povišene razine amilaze često se bilježe zbog kronične stimulacije parotidne žlijezde zbog povraćanja, što također može dovesti do njene hipertrofije (26,27). Osim toga, mogu se javiti oscilacije razine glukoze u krvi, doprinoseći vrtoglavici, umoru i pojačanoj žudnji za ugljikohidratima (28).

Kod PP laboratorijski nalazi ponajprije odražavaju metaboličku disregulaciju povezanu s pretilošću (29). Česte abnormalnosti uključuju povišenu glukozu natašte i inzulinsku rezistenciju, čime se povećava rizik od šećerne bolesti tipa 2 (30,31). Dislipidemija, povišeni triglyceridi i niski HDL kolesterol česti su nalazi (30). Povišeni jetreni enzimi (ALT, AST) upućuju na nealkoholnu masnu bolest jetre, čestu komplikaciju dugotrajnog prejedanja (31). Često su prisutni i povišeni biljezi sustavne upale poput C-reaktivnog proteina (CRP), što odražava kronični metabolički stres i povećani rizik od kardiovaskularnih bolesti (30,31).

Mogući etiopatogenetski biološki čimbenici

Genetski čimbenici

Razlike između AN i BN u odnosu na genetske i neurobiološke čimbenike prikazane su u tablici 2 (32-35). PH može imati značajnu genetsku sastavnicu, pri čemu istraživanja upućuju na to da genetski čimbenici doprinose ranjivosti, osobito u kombinaciji s okolišnim utjecajima. Ta se genetska predispozicija može očitovati na dva glavna načina (32,33,36,37). Neki pojedinci nasljeđuju specifične gene koji izravno utječu na regulaciju apetita, kontrolu impulsa

In BN, the most common laboratory abnormalities are a consequence of frequent vomiting and compensatory behaviors. They include hypochloraemic alkalosis, which leads to hypokalemia, especially in individuals who use self-induced vomiting (22,26). Hyperchloraemic metabolic acidosis may be observed in patients who abuse laxatives (22,27). Elevated amylase levels are often recorded owing to chronic stimulation of the parotid gland as a result of vomiting, which may also lead to parotid gland hypertrophy (26,27). In addition, fluctuations in blood glucose levels may occur, contributing to dizziness, fatigue, and increased craving for carbohydrates (28).

In BED, laboratory findings primarily reflect the metabolic dysregulation associated with obesity (29). Common abnormalities include elevated fasting glucose and insulin resistance, which increases the risk of type 2 diabetes mellitus (30,31). Dyslipidemia, elevated triglycerides, and low HDL cholesterol are common findings (30). Elevated liver enzymes (ALT, AST) point to non-alcoholic fatty liver disease, a common complication of long-term binge eating (31). Elevated markers of systemic inflammation, such as C-reactive protein (CRP), are also frequently present, reflecting chronic metabolic stress and an increased risk of cardiovascular disease (30,31).

Possible Etiopathogenetic Biological Factors

Genetic Factors

The differences between AN and BN in relation to genetic and neurobiological factors are presented in Table 2 (32,33,34,35). ED may have a significant genetic component, with research indicating that genetic factors contribute to vulnerability, especially in combination with environmental influences. This genetic predisposition may manifest in two main ways (32,33,36,37). Some individuals inherit specific genes that directly affect appetite regulation, impulse control, and emotional processing, thereby increasing their risk

TABLICA 2. Razlike između anoreksije nervoze i bulimije nervoze u odnosu na genetske i neurobiološke čimbenike.
TABLE 2. Differences Between Anorexia Nervosa and Bulimia Nervosa in Relation to Genetic and Neurobiological Factors.

	Anoreksija nervoza / Anorexia nervosa	Bulimija nervoza / Bulimia nervosa
GENETSKI ČIMBENICI / GENETIC FACTORS		
Studije blizanaca / Twin studies	Od 33 % do 84 % / From 33% to 84%	Od 28 % do 83 % / From 28% to 83%
Obiteljske studije – srodnici prvog stupnja / Family studies – first-degree relatives	Deseterostruko povećan rizik / Ten-fold increased risk	Četverostruko povećan rizik / Four-fold increased risk
Provedena GWAS analiza / GWAS analysis performed	Osam lokusa; psihijatrijski i potencijalni metabolički poremećaj / Eight loci; psychiatric and potential metabolic disorder	Nema podataka / No data
NEUROBIOLOŠKI ČIMBENICI / NEUROBIOLOGICAL FACTORS		
Strukture mozga / Brain structures		
Prefrontalni korteks: donošenje odluka, kontrola impulsa i samoregulacija; kognitivne funkcije i regulacija emocija / **Prefrontal cortex:** decision-making, impulse control and self-regulation; cognitive functions and emotion regulation	Hiperaktivnost; rigidna kontrola hranjenja i pojačana osjetljivost na percipirane nedostatke u slici tijela; kognitivna nefleksibilnost / Hyperactivity; rigid control of eating and heightened sensitivity to perceived flaws in body image; cognitive inflexibility	Hipoaktivnost; impulzivno ponašanje; nedostatak kontrole nad ciklusima prejedanja i čišćenja / Hypoactivity; impulsive behavior; lack of control over binge-purge cycles
Limbički sustav: regulacija emocija i obrada nagrade; pojačane emocionalne reakcije, osobito tjeskoba i strah vezan uz hranu i debljanje / **Limbic system:** emotion regulation and reward processing; heightened emotional reactions, especially anxiety and fear related to food and weight gain	Averzivna reakcija na hranu, vjerojatno potaknuta hiperaktivnošću amigdale; moguća je i hipoaktivacija amigdale i striatuma, što vodi do oslabljene obrade nagrade / Aversive reaction to food, probably driven by amygdala hyperactivity; hypoactivation of the amygdala and striatum is also possible, leading to impaired reward processing	Promijenjena obrada nagrade, osobito u nukleusu akumbensu, glavnom području uključenom u dopaminske putove; učvršćujuće ponašanje prejedanja kao sredstvo za privremeno ublažavanje stresa ili negativnih emocija / Altered reward processing, especially in the nucleus accumbens, a key area involved in dopaminergic pathways; reinforcing binge-eating behavior as a means of temporarily relieving stress or negative emotions
Hipotalamus: upravljanje glađu i energetskom ravnotežom / **Hypothalamus:** management of hunger and energy balance	Oslabljeni signali gladi i neuobičajena otpornost na osjećaj gladi unatoč teškom kaloričnom ograničenju; restriktivno ponašanje / Impaired hunger signals and unusual resistance to the sensation of hunger despite severe caloric restriction; restrictive behavior	Pojačani signali gladi, što često dovodi do epizoda prejedanja / Heightened hunger signals, which often leads to binge-eating episodes
Neurotransmiteri i hormoni / Neurotransmitters and hormones		
Dopamin: obrada nagrade i ponašanje vezano uz hranjenje, motivacija / **Dopamine:** reward processing and eating-related behaviour, motivation	Doprinosi averziji prema hrani i restriktivnom hranjenju; povećana osjetljivost sustava / Contributes to food aversion and restrictive eating; increased sensitivity of the system	Promijenjena obrada nagrade i poremećena signalizacija sitosti olakšavaju ponašanje prejedanja i čišćenja; doprinosi kompulzivnim i impulzivnim ponašanjima / Altered reward processing and impaired satiety signalling facilitate binge-eating and purging behavior; contributes to compulsive and impulsive behaviors
Serotonin: regulacija emocija i impulzivnost / **Serotonin:** emotion regulation and impulsivity	Emocionalna reakcija ili tjeskoba što potencijalno potiče restriktivno hranjenje / Emotional reaction or anxiety, potentially encouraging restrictive eating	Emocionalna reakcija ili tjeskoba; epizode prejedanja kao pokušaj poboljšanja raspoloženja; posljedični ciklusi prejedanja i čišćenja / Emotional reaction or anxiety; binge episodes as an attempt to improve mood; consequent binge-purge cycles
Visoki kortizol: odgovor tijela na stres / **Elevated cortisol:** the body's response to stress	Intenzivna tjeskoba i opsesivno-kompulzivno ponašanje / Intense anxiety and obsessive-compulsive behavior	Ciklusi prejedanja i čišćenja / Binge-purge cycles
Spolni hormoni / Sex hormones	Amenoreja kod djevojaka; smanjenje gustoće kostiju; kardiovaskularno zdravlje / Amenorrhoea in girls; reduced bone density; cardiovascular health	/
Leptin: „hormon sitosti" / **Leptin:** the "satiety hormone"	Vrijednosti su obično niske; mijenja se regulacija apetita, raspoloženje i ponašanje; otežava oporavak od restriktivnog hranjenja / Values are usually low; appetite regulation, mood and behavior are altered; impedes recovery from restrictive eating	/
Grelin: „hormon gladi"; poticanje gladi / **Ghrelin:** the "hunger hormone"; stimulation of hunger	/	Često su vrijednosti povišene; intenzivna glad praćena prejedanjem, osjećajem krivnje i gubitkom kontrole / Values are often elevated; intense hunger accompanied by binge eating, feelings of guilt and loss of control

i obradu emocija čime se povećava njihov rizik od razvoja PH. Drugi pak mogu naslijediti osobine ličnosti poput perfekcionizma, povišene osjetljivosti na stres ili poteškoća u regulaciji emocija, što ih čini podložnijima poremećenoj kogniciji i ponašanju vezanom uz hranjenje u određenim životnim okolnostima. Pri izloženosti značajnim stresorima, poput traume, socijalnih pritisaka ili velikih životnih promjena, te se genetske predispozicije mogu aktivirati, povećavajući vjerojatnost razvoja PH kao neprilagođenog mehanizma suočavanja (38).

Postoje dokazi da genetski čimbenici mogu imati važnu ulogu u razvoju PH (39). Studije blizanaca otkrivaju snažnu nasljednu sastavnicu; za AN procjene nasljednosti kreću se od 33 % do 84 %, što ukazuje na znatan genetski udio u ranjivosti za taj poremećaj (20). BN pokazuje sličan genetski doprinos, s procjenama u rasponu od 28 % do 83 %, što odražava međudjelovanje genetske predispozicije i okolišnih čimbenika poput sociokulturnih utjecaja i psiholoških stresora (40). Čini se da PP ima nešto nižu, ali i dalje značajnu genetsku sastavnicu, s procjenama nasljednosti između 41 % i 57 %, što upućuje na to da, iako genetika ima ulogu, razvoju doprinose i okolišni čimbenici poput prehrambenih navika i regulacije emocija (41).

Obiteljske studije dodatno potkrepljuju te nalaze pokazujući da srodnici prvog stupnja osoba s PH imaju deseterostruko povećan rizik od razvoja AN i četverostruko povećan rizik od BN, što upućuje na to da nasljeđivanje znatno doprinosi tim poremećajima (36). Taj povišeni rizik naglašava ulogu nasljednih čimbenika, koji vjerojatno djeluju u interakciji s okolišnim i psihološkim okidačima u pokretanju i održavanju poremećene emocionalne regulacije, kognicije i ponašanja vezanog uz hranjenje.

Studije asocijacije na razini cijeloga genoma (GWAS) otkrile su specifične lokuse povezane s PH, osobito s AN. Jedan zapažen nalaz jest preklapanje genetskih lokusa povezanih s AN i

of developing ED. Others, in turn, may inherit personality traits such as perfectionism, heightened sensitivity to stress, or difficulties in emotion regulation, which makes them more susceptible to disordered cognition and eating-related behavior under certain life circumstances. When exposed to significant stressors, such as trauma, social pressures, or major life changes, these genetic predispositions may become activated, increasing the likelihood of developing ED as a maladaptive coping mechanism (38).

There is evidence that genetic factors may play an important role in the development of ED (39). Twin studies reveal a strong heritable component; for AN, heritability estimates range from 33% to 84%, indicating a substantial genetic contribution to vulnerability for this disorder (20). BN shows a similar genetic contribution, with estimates ranging from 28% to 83%, reflecting the interplay between genetic predisposition and environmental factors, such as sociocultural influences and psychological stressors (40). BED appears to have a somewhat lower but still significant genetic component, with heritability estimates between 41% and 57%, suggesting that although genetics plays a role, environmental factors such as dietary habits and emotion regulation also contribute to its development (41).

Family studies further corroborate these findings, showing that first-degree relatives of individuals with ED have a ten-fold increased risk of developing AN and a four-fold increased risk of BN, suggesting that heredity contributes substantially to these disorders (36). This increased risk underscores the role of hereditary factors, which probably act in interaction with environmental and psychological triggers in initiating and maintaining disordered emotional regulation, cognition, and eating-related behavior.

Furthermore, genome-wide association studies (GWAS) have revealed specific loci associated with ED, particularly AN. One notable finding is the overlap of genetic loci associated with AN

onih uključenih u metaboličke procese (32). Ti lokusi uključuju gene povezane s energetskom homeostazom, poput onih koji reguliraju metabolizam glukoze i prijenos lipida, što upućuje na to da pojedinci s genetskom predispozicijom za AN mogu imati metaboličke razlike koje utječu na njihov odgovor na unos hrane i potrošnju energije.

Najveća dosad provedena GWAS meta-analiza AN (16 992 oboljelih i 55 525 kontrolnih ispitanika iz inicijative ANGI, konzorcija PGC-ED i baze UK Biobank) identificirala je osam lokusa povezanih s AN na razini cijeloga genoma ($P<5\times10^{-8}$). Vodeći signali nalaze se na kromosomu 3 (multigensko područje od 111 gena, najbliži gen NCKIPSD, te zasebni lokusi u blizini gena FOXP1 i NSUN3), kromosomu 11 (gen CADM1, čija varijanta nije specifična za AN i dijelom se preklapa s onom povezanom sa šećernom bolešću tipa 2), kromosomu 2 (područje gena ASB3 i ERLEC1), kromosomu 10 (gen MGMT), kromosomu 1 (gen PTBP2) te kromosomu 5 (u blizini gena CDH10) (32). Osim toga, AN pokazuje značajne genetske korelacije s psihijatrijskim fenotipovima (opsesivno-kompulzivni poremećaj, depresija, anksioznost i shizofrenija) te s metaboličkim, glikemijskim, lipidnim i antropometrijskim obilježjima: negativne genetske korelacije s indeksom TM, postotkom masti tijela, inzulinom natašte, inzulinskom rezistencijom, šećernom bolešću tipa 2 i leptinom, a pozitivna s HDL kolesterolom, neovisno o učincima varijanti povezanih s indeksom TM. Upravo su ti nalazi temelj za rekonceptualizaciju AN kao „metaboličko-psihijatrijskog" poremećaja (32,42). Ovi konkretni lokusi odnose se na AN; za BN i PP zasada ne postoje studije asocijacije na razini cijeloga genoma usporedive veličine, pa pojedinačni značajni lokusi još nisu pouzdano utvrđeni, a dosadašnji su nalazi ograničeni na pojedine gene kandidate (npr. serotoninski i dopaminski sustav) (kasnije u tekstu o dopaminu i serotoninu) (41,43).

and those involved in metabolic processes (32). These loci include genes associated with energy homeostasis, such as those that regulate glucose metabolism and lipid transport, suggesting that individuals with a genetic predisposition to AN may have metabolic differences that affect their response to food intake and energy expenditure.

The largest GWAS meta-analysis of AN conducted to date (16,992 affected individuals and 55,525 control subjects from the ANGI initiative, the PGC-ED consortium, and the UK Biobank) identified eight loci associated with AN at the genome-wide level ($P < 5 \times 10^{-8}$). The leading signals are located on chromosome 3 (a multigenic region of 111 genes, the nearest gene being NCKIPSD, and separate loci near the FOXP1 and NSUN3 genes), chromosome 11 (the CADM1 gene, whose variant is not specific to AN and partly overlaps with one associated with type 2 diabetes mellitus), chromosome 2 (the region of the ASB3 and ERLEC1 genes), chromosome 10 (the MGMT gene), chromosome 1 (the PTBP2 gene), and chromosome 5 (near the CDH10 gene) (32). In addition, AN shows significant genetic correlations with psychiatric phenotypes (obsessive-compulsive disorder, depression, anxiety, and schizophrenia) and with metabolic, glycemic, lipid, and anthropometric traits: negative genetic correlations with body-mass index, body fat percentage, fasting insulin, insulin resistance, type 2 diabetes mellitus, and leptin, and a positive correlation with HDL cholesterol, independent of the effects of variants associated with body-mass index. It is precisely these findings that form the basis for reconceptualising AN as a "metabo-psychiatric" disorder (32,42). It should be noted that these specific loci pertain to AN; for BN and BED, there are as yet no genome-wide association studies of comparable size, so individual significant loci have not yet been reliably established, and the findings to date are limited to certain candidate genes (e.g. the serotonergic and dopaminergic systems) (see later in the text on dopamine and serotonin) (41,43).

Istraživanja također ukazuju na ulogu epigenetike u PH, gdje okolišni čimbenici mogu utjecati na ekspresiju gena bez promjene same sekvence DNA. Epigenetske promjene mogu dodatno doprinositi održavanju PH pojačavanjem neprilagođenih neuronskih krugova povezanih s poremećenim emocijama, kognicijom i ponašanjem vezanim uz hranjenje, što bi moglo objasniti zašto neki pojedinci doživljavaju recidiv čak i nakon liječenja (43). Primjerice, stres i trauma - poznati rizični čimbenici za PH - mogu pokrenuti epigenetske modifikacije u genima uključenima u odgovor na stres i neuroplastičnost potencijalno povećavajući podložnost PH (25).

Neurobiološki čimbenici

Strukture mozga. Vjerojatno su sve regije mozga složenim vezama uključene kod PH. Neurobiologija može biti važno područje u razumijevanju PH, budući da se čini da su abnormalnosti u moždanim krugovima povezane s temeljnim simptomima poput iskrivljene slike tijela, tjeskobe povezane s hranom i narušene kontrole impulsa (34). Brojne neuroradiološke studije utvrdile su strukturne i funkcionalne abnormalnosti u određenim moždanim područjima uključenima u PH, u prvom redu u prefrontalnom korteksu, limbičkom sustavu i hipotalamusu (tablica 2) (34,35). Ta područja mogu biti uključena u regulaciju gladi, sitosti, obradu nagrade i regulaciju emocija - ključne funkcije koje su kod PH često poremećene.

Prefrontalni korteks, uključen u izvršne funkcije poput donošenja odluka, kontrole impulsa i samoregulacije, također pokazuje abnormalnu aktivnost kod PH. Pacijenti s AN, primjerice, često pokazuju hiperaktivnost prefrontalnog korteksa, što može doprinositi njihovoj rigidnoj emocionalnoj kontroli hranjenja i pojačanoj osjetljivosti na percipirane nedostatke u slici tijela (45,46), kao i tome da se takvi pacijenti teško prilagođavaju u svojem ponašanju čak i kada prepoznaju štetne zdrav-

Research also points to a role of epigenetics in ED, in which environmental factors may affect gene expression without altering the DNA sequence itself. Epigenetic changes may further contribute to the maintenance of ED by reinforcing maladaptive neural circuits associated with disordered emotions, cognition, and eating-related behavior, which could explain why some individuals experience relapse even after treatment (43). For example, stress and trauma — known risk factors for ED — may trigger epigenetic modifications in genes involved in the stress response and neuroplasticity, potentially increasing susceptibility to ED (25).

Neurobiological Factors

Brain structures. Probably all brain regions are involved in ED through complex connections. Neurobiology may be an important area in understanding ED, since abnormalities in brain circuits appear to be associated with core symptoms such as distorted body image, food-related anxiety, and impaired impulse control (34). Numerous neuroimaging studies have identified structural and functional abnormalities in certain brain areas involved in ED, primarily in the prefrontal cortex, limbic system, and hypothalamus (see Table 2) (34,35). These areas may be involved in the regulation of hunger, satiety, reward processing, and emotion regulation — key functions that are often disturbed in ED.

The **prefrontal cortex** is involved in executive functions such as decision-making, impulse control, and self-regulation, and it also shows abnormal activity in ED. Patients with AN, for example, often show hyperactivity of the prefrontal cortex, which may contribute to their rigid emotional control of eating and heightened sensitivity to perceived flaws in body image (45,46), as well as to their difficulty in adapting their behavior even when they recognize the harmful health consequences of restriction (47). In contrast, individuals with BN often show hypoactivity of the prefrontal cortex, which may

stvene posljedice restrikcije (47). Nasuprot tome, osobe s BN često pokazuju hipoaktivnost prefrontalnog korteksa što može biti u podlozi njihova impulzivnog ponašanja povezanog s hranjenjem i nedostatkom kontrole nad ciklusima prejedanja i čišćenja (48).

Limbički sustav, koji uključuje strukture poput amigdale i hipokampusa, također je povezan s PH zbog svoje uloge u regulaciji emocija i obradi nagrade. Smatra se da kod PH abnormalnosti limbičkog sustava doprinose pojačanim emocionalnim reakcijama, osobito tjeskobi i strahu vezanima uz hranu i debljanje (49). Primjerice, osobe s AN često pokazuju averzivnu reakciju na hranu, vjerojatno potaknutu hiperaktivnošću amigdale na salijentne podražaje (hrana, tijelo) što učvršćuje njihovo restriktivno ponašanje vezano uz hranjenje kao sredstvo kontrole te tjeskobe (50).

Nalazi o amigdali ipak nisu posve jednoznačni i ovise o ispitivanoj paradigmi: dok se pri obradi salijentnih i averzivnih podražaja opisuje hiperaktivacija. Novije neuroradiološke meta-analize u kontekstu obrade nagrade kod AN nalaze hiperaktivaciju prefrontalnog korteksa i prednjega cingularnog korteksa uz hipoaktivaciju amigdale i striatuma, što se tumači obrascem pojačane kognitivne kontrole uz oslabljenu obradu nagrade (35).

Kod BN i PP, međutim, postoje dokazi o promijenjenoj obradi nagrade unutar limbičkog sustava, osobito u nukleusu akumbensu, temeljnom području uključenom u dopaminske putove nagrade (v. kasnije u tekstu o dopaminu) (51).

Pokazalo se da **hipotalamus,** odgovoran za upravljanje glađu i energetskom ravnotežom, abnormalno funkcionira u osoba s PH. Pacijenti s AN često pokazuju disfunkciju hipotalamusa što dovodi do oslabljenih signala gladi i neuobičajene otpornosti na osjećaj gladi unatoč teškom kaloričnom ograničenju (43). Disfunkcija hipotalamusa ne remeti samo signale gladi

underlie their impulsive eating-related behavior and lack of control over binge-purge cycles (48).

The **limbic system**, which includes structures such as the amygdala and hippocampus, is also associated with ED owing to its role in emotion regulation and reward processing. In ED, abnormalities of the limbic system are thought to contribute to heightened emotional reactions, especially anxiety and fear related to food and weight gain (49). For example, individuals with AN often show an aversive reaction to food, probably driven by amygdala hyperactivity to salient stimuli (food, body), which reinforces their restrictive eating-related behavior as a means of controlling that anxiety (50).

Nevertheless, the findings on the amygdala are not entirely unequivocal and depend on the paradigm examined: while hyperactivation is described during the processing of salient and aversive stimuli, more recent neuroimaging meta-analyses in the context of reward processing in AN find hyperactivation of the prefrontal cortex and the anterior cingulate cortex together with hypoactivation of the amygdala and striatum, which is interpreted as a pattern of enhanced cognitive control with impaired reward processing (35).

However, in BN and BED, there is evidence of altered reward processing within the limbic system, especially in the nucleus accumbens, a key area involved in dopaminergic reward pathways (see later in the text on dopamine) (51).

The **hypothalamus**, responsible for the management of hunger and energy balance, has been shown to function abnormally in individuals with ED. The hypothalamic–pituitary–adrenal axis and the involvement of various neurotransmitters and hormonal systems will be addressed in greater detail later in the text. For example, patients with AN often show hypothalamic dysfunction, leading to impaired hunger signals and an unusual resistance to the sensation of hunger despite severe caloric restriction (43). Hypotha-

nego utječe i na razine kortizola pojačavajući stres i potencijalno učvršćujući restriktivno ponašanje vezano uz hranjenje (52). U osoba s BN abnormalna funkcija hipotalamusa može doprinositi pojačanim signalima gladi, što često dovodi do epizoda prejedanja (53). Ti poremećaji u regulaciji gladi vjerojatno se dodatno pogoršavaju i genetskim predispozicijama i okolišnim stresorima stvarajući povratnu petlju koja održava poremećen obrazac hranjenja.

Navedeni nalazi naglašavaju ponekad oprečne neurobiološke profile AN i BN upućujući na to da, iako oba poremećaja uključuju disregulaciju u sličnim moždanim područjima, različito se očituju ovisno o razinama aktivnosti unutar tih područja (34,35).

Neurotransmiterski sustavi i hormoni

Uloga dopamina

Vjerojatno kod PH postoji disfunkcija barem triju neurotransmiterskih sustava: dopamin, serotonin i noradrenalin, a vjerojatno su uključeni i drugi sustavi npr. GABA sustav (54,55).

Dopamin je neurotransmiter uključen u nagradu i motivaciju. Gen za dopaminski receptor D2 (DRD2) proučavan je u vezi s PH (56). Varijacije u genu DRD2 mogu utjecati na obradu nagrade i ponašanje vezano uz hranjenje, potencijalno doprinoseći razvoju PH. Istraživanja pokazuju da su određeni polimorfizmi gena DRD2 povezani s promijenjenom dopaminskom signalizacijom, što bi moglo utjecati na reakcije pojedinaca na nagrađujuće podražaje poput hrane (41). Iako je disregulacija dopamina uključena i kod AN i BN, njezini se učinci razlikuju: kod AN pojačana dopaminska aktivnost doprinosi restriktivnom hranjenju, te umjesto da ona bude ugodna, može postati izvor tjeskobe, stresa i averzije prema hrani; dok kod BN promijenjena obrada nagrade i poremećena signalizacija sitosti olakšavaju ponašanje prejedanja i čišće-

lamic dysfunction not only disrupts hunger signals but also affects cortisol levels, intensifying stress and potentially reinforcing restrictive eating-related behavior (52). In individuals with BN, abnormal hypothalamic function may contribute to heightened hunger signals, which often lead to binge-eating episodes (53). These disturbances in hunger regulation are probably further aggravated by both genetic predispositions and environmental stressors, creating a feedback loop that maintains disordered eating patterns.

These findings underscore the sometimes opposing neurobiological profiles of AN and BN, suggesting that although both disorders involve dysregulation in similar brain areas, they manifest differently depending on the levels of activity within those areas (34,35).

Neurotransmitter Systems and Hormones

The Role of Dopamine

In ED, there is probably dysfunction of at least three neurotransmitter systems: dopamine, serotonin, and noradrenaline, and other systems are probably also involved, e.g., the GABA system (54,55). Given the broader focus of this paper, only the dopaminergic and serotonergic systems will be presented in what follows (see Table 2). Dopamine is a neurotransmitter involved in reward and motivation. The dopamine receptor D2 gene (DRD2) has been studied in connection with ED (56). Variations in the DRD2 gene may affect reward processing and eating-related behaviors, potentially contributing to the development of ED. Research shows that certain DRD2 gene polymorphisms are associated with altered dopaminergic signalling, which could affect individuals' responses to rewarding stimuli, such as food (41). Although dopamine dysregulation is implicated in both AN and BN, its effects differ: in AN, increased dopaminergic activity contributes to restrictive eating, and rather than being pleasurable, it may become a source of anxiety,

nja (41). Gen za katehol-O-metiltransferazu (COMT), uključen u razgradnju dopamina, također je ispitivan u vezi s PH (57). Polimorfizmi gena COMT mogu utjecati na razine dopamina u prefrontalnom korteksu djelujući na kognitivne funkcije i regulaciju emocija. Te promjene mogu doprinositi karakterističnim ponašanjima koja se uočavaju u osoba s PH. Noviji radovi naglašavaju ulogu mezolimbičkog dopaminskog puta u regulaciji ponašanja hranjenja pri čemu se njegova disregulacija povezuje s razvojem i održavanjem PH (58).

Uloga serotonina

Serotonin je odgovoran za regulaciju emocija i impulzivnost. Geni za serotoninske (5-HT) receptore i prijenosnike utječu na regulaciju emocija i impulzivnost, koji se često uočavaju u osoba s PH, osobito kod BN i AN-PČ tipa (43). Varijacije u tim genima mogu predisponirati pojedince na pojačane emocionalne reakcije ili tjeskobu, što potencijalno potiče restriktivno hranjenje ili cikluse prejedanja i čišćenja kao neprilagođene mehanizme suočavanja (59). Kod BN se povezuje promijenjena regulacija serotonina, gdje hrana bogata ugljikohidratima privremeno povisuje razine serotonina, što bi moglo objasniti epizode prejedanja kao pokušaj poboljšanja raspoloženja (60,61). Recentni pregledi potvrđuju da PH vjerojatno uključuje istodobnu disfunkciju serotoninskog i dopaminskog sustava, koji međusobno djeluju u regulaciji raspoloženja, impulzivnosti i obrade nagrade (62).

Hormonalni čimbenici

Hormonalna disregulacija kod PH postoji kod svih hormonalnih sustava u tijelu (24,63). Os hipotalamus-hipofiza-nadbubrežna žlijezda (HPA os), koja regulira odgovor tijela na stres, jedan je od hormonalnih sustava koji je kod PH često poremećen, što dovodi do pojačanog lučenja kortizola (23) (v. tablicu 2). Povišene razine kortizola

stress, and food aversion; whereas in BN, altered reward processing and impaired satiety signalling facilitate binge-eating and purging behavior (41). The catechol-O-methyltransferase gene (COMT), involved in the breakdown of dopamine, has also been examined in connection with ED (57). COMT gene polymorphisms may affect dopamine levels in the prefrontal cortex, influencing cognitive functions and emotion regulation. These changes may contribute to the characteristic behaviors observed in individuals with ED. Recent studies have emphasized the role of the mesolimbic dopaminergic pathway in the regulation of eating behavior, with its dysregulation being associated with the development and maintenance of ED (58).

The Role of Serotonin

Serotonin is responsible for emotion regulation and impulsivity. Genes for serotonin (5-HT) receptors and transporters affect emotion regulation and impulsivity, which are often observed in individuals with ED, especially in BN and the AN-BP type (43). Variations in these genes may predispose individuals to heightened emotional reactions or anxiety, potentially encouraging restrictive eating or binge-purge cycles as maladaptive coping mechanisms (59). In BN, altered serotonin regulation is implicated, whereby carbohydrate-rich food temporarily raises serotonin levels, which could explain binge episodes as an attempt to improve mood (60,61). Recent reviews confirm that ED probably involve simultaneous dysfunction of the serotonergic and dopaminergic systems, which interact in the regulation of mood, impulsivity, and reward processing (62).

Hormonal Factors

Hormonal dysregulation in ED is present across all hormonal systems in the body (24,63). The hypothalamic–pituitary–adrenal axis (HPA axis), which regulates the body's response to stress, is one of the hormonal systems that is often disturbed in ED, leading to increased secretion of

često se nalaze u osoba s AN i BN i povezane su s pojačanim stresom, tjeskobom i poremećenim obrascima spavanja (24). Kod AN visoke razine kortizola mogu biti i posljedica i čimbenik koji doprinosi poremećaju; kronična pothranjenost i restriktivna ponašanja mogu aktivirati HPA os dovodeći do disregulacije kortizola i dodatno učvršćujući restriktivna ponašanja kao mehanizam suočavanja sa stresom (64). Ta disregulacija odgovora na stres može doprinositi intenzivnoj tjeskobi i opsesivno-kompulzivnim ponašanjima koja se često uočavaju kod AN (65). Noviji radovi naglašavaju da se AN smatra stanjem funkcionalnog hiperkortizolizma, uz povišen CRH i relativnu rezistenciju na supresiju deksametazonom, što upućuje na oštećenu osjetljivost glukokortikoidne povratne sprege; HPA disfunkcija kod AN povezuje se i s deficitom estrogena te demineralizacijom kostiju (65).

Kod BN povišene razine kortizola često su povezane sa stresom ciklusa prejedanja i čišćenja. Psihološki distres nakon epizoda prejedanja može pokrenuti lučenje kortizola, što zauzvrat može potaknuti želju za čišćenjem kao neprilagođenim mehanizmom suočavanja. Taj odgovor na stres potaknut kortizolom može stvoriti povratnu petlju u kojoj povišene razine kortizola učvršćuju nagon za poremećenim ponašanjem vezanim uz hranjenje radi upravljanja negativnim emocijama (24).

Hormonalna disregulacija kod poremećaja hranjenja postoji kod svih hormonalnih sustava, a ovdje posebno ističemo spolne (reproduktivne) hormone, osobito kod AN (18,21,66,67). Razine estrogena i progesterona često se značajno smanjuju zbog pothranjenosti kod djevojaka, što dovodi do amenoreje i drugih reproduktivnih problema (68). Te hormonalne promjene mogu imati dalekosežne učinke na ponovnu pojavu puberteta, gustoću kostiju, kardiovaskularno zdravlje i emocionalnu dobrobit, budući da estrogen ima zaštitnu ulogu. Obnavljanjem TM dolazi do pojave menstruacije u djevojaka, s boljim zdravstvenim ishodima i

cortisol (23) (see Table 2). Thus, elevated cortisol levels are often found in individuals with AN and BN and are associated with increased stress, anxiety, and disturbed sleep patterns (24). In AN, high cortisol levels may be both a consequence and a contributing factor of the disorder; chronic undernutrition and restrictive behaviors may activate the HPA axis, leading to cortisol dysregulation and further reinforcing restrictive behaviors as a mechanism for coping with stress (64). This dysregulation of the stress response may contribute to the intense anxiety and obsessive-compulsive behaviors often observed in AN (65). Recent work emphasizes that AN is regarded as a state of functional hypercortisolism, with elevated CRH and relative resistance to dexamethasone suppression, suggesting impaired glucocorticoid feedback sensitivity; HPA dysfunction in AN is also associated with estrogen deficiency and bone demineralization (65).

In BN, elevated cortisol levels are often associated with the stress of the binge-purge cycle. Psychological distress after binge episodes may trigger cortisol secretion, which in turn may encourage the urge to purge as a maladaptive coping mechanism. This cortisol-driven stress response may create a feedback loop, in which elevated cortisol levels reinforce the drive toward disordered eating-related behavior to manage negative emotions (24).

Hormonal dysregulation in eating disorders is present across all hormonal systems, and here we particularly highlight the sex (reproductive) hormones, especially in AN (18,21,66,67). Estrogen and progesterone levels are often significantly reduced owing to undernutrition in girls, leading to amenorrhea (absence of menstruation) and other reproductive problems (68). These hormonal changes may have far-reaching effects on the resumption of puberty, bone density, cardiovascular health, and emotional well-being, since estrogen has a protective role. With restoration of BW, menstruation reappears in girls, with better health outcomes and a reduced risk of long-term complications (69,70).

smanjenim rizikom od dugoročnih komplikacija (69,70).

Ostali hormonalni sustavi

Dva glavna hormona uključena u regulaciju apetita i energije su leptin i grelin, koje se često naziva „hormonom sitosti" odnosno „hormonom gladi" (28) (v. tablicu 2). Abnormalne razine tih hormona često se uočavaju u osoba s PH i mogu doprinositi održavanju restriktivnog ponašanja ili ponašanja prejedanja.

Leptin je hormon koji proizvode masne stanice, a koji mozgu signalizira sitost i pomaže u regulaciji energetske ravnoteže potiskivanjem gladi. U osoba s AN razine leptina obično su niske zbog smanjene tjelesne masti, što bi inače signaliziralo mozgu da poveća glad kao odgovor na niske energetske zalihe (71). Međutim, kod AN taj se mehanizam često nadjačava, vjerojatno zbog psiholoških čimbenika, neurobioloških promjena ili dodatnih hormonalnih utjecaja koji potiskuju znakove gladi omogućujući pojedincima da nastave s restrikcijom unatoč teškim energetskim manjcima. Niske razine leptina povezane su s disfunkcijom hipotalamusa koja može dodatno mijenjati regulaciju apetita, raspoloženje i ponašanje otežavajući oporavak od restriktivnog hranjenja (28). Kako se razine leptina postupno normaliziraju s obnavljanjem tjelesne mase tijekom liječenja AN, signali gladi mogu se ponovno pojaviti što podupire ideju da hormonalni oporavak može biti najvažniji aspekt liječenja PH (43). Recentna meta-analiza razina leptina, prilagođena indeksu TM, potvrđuje sustavne razlike u koncentracijama leptina među različitim PH, naglašavajući njegovu ulogu kao mogućeg biološkog biljega (72).

Grelin se proizvodi u želucu i odgovoran je za poticanje gladi. U osoba s BN razine grelina često su povišene, što može poticati povećan unos hrane i doprinositi epizodama prejedanja (53). Ta hormonalna neravnoteža može dovesti do ciklusa intenzivne gladi praćene pre-

Other Hormonal Systems

Two main hormones involved in the regulation of appetite and energy are leptin and ghrelin, often referred to as the "satiety hormone" and the "hunger hormone" respectively (28) (see Table 2). Abnormal levels of these hormones are often observed in individuals with ED and may contribute to the maintenance of restrictive or binge-eating behavior.

Leptin is a hormone produced by fat cells that signals satiety to the brain and helps regulate energy balance by suppressing hunger. In individuals with AN, leptin levels are usually low owing to reduced body fat, which would normally signal the brain to increase hunger in response to low energy stores (71). However, in AN, this mechanism is often overridden, probably owing to psychological factors, neurobiological changes, or additional hormonal influences that suppress hunger cues, allowing individuals to continue restricting despite severe energy deficits. Low leptin levels are associated with hypothalamic dysfunction, which may further alter appetite regulation, mood, and behavior, impeding recovery from restrictive eating (28). As leptin levels gradually normalize with the restoration of body weight during AN treatment, hunger signals may reappear, which supports the idea that hormonal recovery may be a key aspect of treating ED (43). A recent meta-analysis of leptin levels, adjusted for body-mass index, confirms systematic differences in leptin concentrations among different ED, highlighting its role as a possible biological marker (72).

Ghrelin is produced in the stomach and is responsible for stimulating hunger. In individuals with BN, ghrelin levels are often elevated, which may encourage increased food intake and contribute to binge-eating episodes (53). This hormonal imbalance may lead to a cycle of intense hunger followed by binge eating, as the body's regulatory mechanisms fail to provide adequate satiety signals after eating. Elevated

jedanjem, jer regulacijski mehanizmi tijela ne uspijevaju pružiti odgovarajuće signale sitosti nakon jela. Povišene razine grelina u pacijenata s BN također su povezane s osjećajem krivnje i gubitkom kontrole, budući da pretjerani signali gladi nadjačavaju sposobnost pojedinca na umjereni unos hrane (24). Nasuprot tome, kod AN razine grelina također mogu biti povišene zbog kaloričnog ograničenja, no uobičajeni odgovor gladi je oslabljen što može odražavati i psihološki otpor i neurobiološke prilagodbe koje potiskuju apetit (28). Novija istraživanja usmjerena su na ravnotežu grelina i njegova endogenog antagonista (LEAP2) pri čemu poremećena postprandijalna regulacija grelina može doprinositi održavanju abnormalnih obrazaca hranjenja kod PH (73).

ZAKLJUČCI

Kod PH su biološki čimbenici vjerojatno u interakciji s drugim psihološkim i socijalnim čimbenicima.

Kod PH postoje razlike između AN i BN u genetskim čimbenicima što pokazuju studije blizanaca, obiteljske studije te GWAS studija. Genetske predispozicije vjerojatno utječu na regulaciju raspoloženja, apetit i odgovor na stres.

Neurobiološki čimbenici koji se dovode u vezu s PH su prefrontalni korteks, limbički sustav, hipotalamus, od neurotransmitera dopamin i serotonin, visoki kortizol, disfunkcija spolnih hormona, te promjene leptina i grelina.

Neurobiološke abnormalnosti u obradi nagrade, kontroli impulsa i regulaciji gladi oblikuju različite obrasce ponašanja kod PH. Hormonalna neravnoteža dodatno doprinosi poremećenom hranjenju utječući na apetit, regulaciju stresa i reproduktivno zdravlje.

U početnim fazama liječenja poremećaja hranjenja važne su nutricionističke i pedijatrijske terapije, uz psihosocijalne terapije za dijete i roditelje.

ghrelin levels in patients with BN are also associated with feelings of guilt and loss of control, since excessive hunger signals override the individual's ability to moderate food intake (24). In contrast, in AN, ghrelin levels may also be elevated owing to caloric restriction, but the usual hunger response is impaired, which may reflect both psychological resistance and neurobiological adaptations that suppress appetite (28). Recent research has focused on the balance between ghrelin and its endogenous antagonist (LEAP2), whereby impaired postprandial regulation of ghrelin may contribute to the maintenance of abnormal eating patterns in ED (73).

CONCLUSIONS

In ED, biological factors probably interact with other psychological and social factors.

In ED, there are differences in the diagnostic and laboratory findings of AN compared with BN, owing to the presence of undernutrition and a possibly more dangerous metabolic and electrolyte imbalance and more serious cardiac consequences. Differences between AN and BN also exist in genetic factors, as demonstrated by twin, family, and GWAS studies. Genetic predispositions probably affect mood regulation, appetite, and the stress response.

The most frequent neurobiological factors associated with ED are the prefrontal cortex, limbic system, hypothalamus, neurotransmitters dopamine and serotonin, elevated cortisol, dysfunction of sex hormones, and changes in leptin and ghrelin.

Neurobiological abnormalities in reward processing, impulse control, and hunger regulation appear to shape different behavioral patterns in ED. Hormonal imbalance further contributes to disordered eating, affecting appetite, stress regulation, and reproductive health.

In the initial phases of treating eating disorders, nutritional and pediatric therapies are

Relativno rano, već nakon prvog mjeseca liječenja, može se primijeniti dodatno i psihofarmakološko liječenje koje ima poveznicu s prije navedenim genetskim i neurobiološkim čimbenicima.

Kod AN se olanzapin navodi kao lijek s najvišom preporukom koji dominantno djeluje na dopaminsku disfunkciju.

Kod BN se fluoksetin pokazao kao lijek s najvišom preporukom, koji djeluje primarno na serotoninsku disfunkciju, a mogu se primijeniti i drugi slični lijekovi, kao i drugi ostali lijekovi (npr. topiramat).

Treba nastojati mjeriti koncentracije lijekova u krvi, što se ne primjenjuje dovoljno u dječjoj psihijatriji kao ni u psihijatriji.

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SUKOB INTERESA

Autori izjavljuju da ne postoji sukob interesa povezan s ovim rukopisom.

important, together with psychosocial therapies for the child and parents.

Relatively early, already after the first month of treatment, psychopharmacological treatment may additionally be applied, which is linked to the previously mentioned genetic and neurobiological factors.

In AN, olanzapine is cited as the medication with the highest recommendation (LoE: A; GoR: 2: strong evidence that the intervention is effective; limited recommendation for using the intervention), as a potent medication that predominantly acts on dopaminergic dysfunction, and there is also knowledge of recommendations for other psychopharmaceuticals from the antipsychotic group (e.g., haloperidol, aripiprazole), as well as other medications.

In BN, fluoxetine has proven to be the medication with the highest recommendation (LoE: A; GoR: 1: strong evidence that the intervention is effective; strong recommendation for using the intervention), which primarily acts on serotonergic dysfunction, and other similar medications may also be applied, as well as other medications (e.g., topiramate likewise has the highest recommendation: LoE: A; GoR: 1: strong evidence that the intervention is effective; strong recommendation for using the intervention).

New directions in the use of medications should, in the near future, aim to measure drug concentrations in the blood, which is not sufficiently applied in child psychiatry or psychiatry in general.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this manuscript.

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. izd., tekst revizija (DSM-5-TR). Washington, DC: American Psychiatric Association, 2022.
2. World Health Organization. International classification of diseases for mortality and morbidity statistics, 11th revision (ICD-11). Geneva: World Health Organization, 2022. Preuzeto 1. lipnja 2026. https://icd.who.int/.
3. Begovac I, Pleština S, Žaja O, Santrić L. Poremećaji hranjenja. U: Begovac I (ur.). Dječja i adolescentna psihijatrija. Zagreb: Sveučilište u Zagrebu, Medicinski fakultet, 2021, 807-836. Preuzeto 26. veljače 2025. https://urn.nsk.hr/urn:nbn:hr:105:694914.
4. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders. Biol Psychiatry 2007;61(3):348-58.
5. Galmiche M, Déchelotte P, Lambert G, Tavolacci MP. Prevalence of eating disorders over the 2000-2018 period: a systematic literature review. Am J Clin Nutr 2019;109(5):1402-13.
6. Swanson SA, Crow SJ, Le Grange D, Swendsen J, Merikangas KR. Prevalence and correlates of eating disorders in adolescents: results from the national comorbidity survey replication adolescent supplement. Arch Gen Psychiatry 2011;68(7): 714-23.
7. Smink FR, van Hoeken D, Hoek HW. Epidemiology of eating disorders: incidence, prevalence and mortality rates. Curr Psychiatry Rep 2012;14(4):406-14.
8. Vidović V, Jureša V, Begovac I, Mahnik M, Tocilj G. Perceived family cohesion, adaptability and communication in eating disorders. Eur Eat Disord Rev 2005;13:19-28.
9. Batista M, Žigić Antić L, Žaja O, Jakovina T, Begovac I. Predictors of eating disorder risk in anorexia nervosa adolescents. Acta Clin Croat 2018;57:399-410.
10. Jakovina T, Crnković Batista M, Ražić Pavičić A, Žurić Jakovina I, Begovac I. Emotional dysregulation and attachment dimensions in female patients with bulimia nervosa. Psychiatr Danub 2018;30:72-8.
11. Mohorić T, Pokrajac-Bulian A, Anić P, Kukić M, Mohović P. Emotion regulation, perfectionism, and eating disorder symptoms in adolescents: the mediating role of cognitive eating patterns. Curr Psychol 2022; 42: 28505-16.
12. Grubišin J, Medved V. Farmakoterapija poremećaja hranjenja. Soc Psihijat 2002;30(1):128-36.
13. Himmerich H, Keeler JL, Tchanturia K, Treasure J. Treatment escalation for people with anorexia nervosa: setting, therapies and nutritional interventions. Curr Opin Psychiatry 2024;37(6):404-16. doi: 10.1097/YCO.0000000000000964.
14. Marzola E, Nasser JA, Hashim SA, Shih PB, Kaye WH. Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. BMC Psychiatry 2013;13:290. doi: 10.1186/1471-244X-13-290.
15. Steinglass JE, Albano AM, Simpson HB, Wang Y, Zou J, Attia E i sur. Confronting fear using exposure and response prevention for anorexia nervosa: a randomized controlled pilot study. Int J Eat Disord 2014;47(2):174-80. doi: 10.1002/eat.22214.
16. Thorey S, Blanchet C, Guessoum SB, Moro MR, Ludot M, Carretier E. Efficacy and tolerance of second-generation antipsychotics in anorexia nervosa: a systematic scoping review. PLoS One 2023; 18(3): e0278189. doi: 10.1371/journal.pone.0278189.
17. Keel PK, Forney KJ. Psychosocial risk factors for eating disorders. Int J Eat Disord 2013;46(5): 433-9.
18. Westmoreland P, Krantz MJ, Mehler PS. Medical complications of anorexia nervosa and bulimia. Am J Med 2016;129(1):30-7.
19. Gibson D, Workman C, Mehler PS. Medical complications of anorexia nervosa and bulimia nervosa. Psychiatr Clin North Am 2019;42(2):263-74. doi: 10.1016/j.psc.2019.01.009. PMID 31046928.
20. Lock J, Le Grange D. Anorexia nervosa, bulimia nervosa, and binge eating disorder. U: Martin A, Bloch MH, Volkmar FR, ur. Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook. 5. izd. Philadelphia: Wolters Kluwer; 2018, 548-62.
21. Mehler PS, Brown C. Anorexia nervosa - medical complications. J Eat Disord 2015;3:11. doi: 10.1186/s40337-015-0040-8.
22. Mehler PS, Walsh K. Electrolyte and acid-base abnormalities associated with purging behaviors. Int J Eat Disord 2016;49(3):311-8. doi: 10.1002/eat.22503.
23. Treasure J, Claudino AM, Zucker N. Eating disorders. Lancet 2010;375(9714): 583-93. doi: 10.1016/S0140-6736(09)61748-7.
24. Misra M, Klibanski A. Endocrine consequences of anorexia nervosa. Lancet Diabetes Endocrinol 2014;2(7): 581-92. doi: 10.1016/S2213-8587(13)70180-3.
25. Støving RK. Mechanisms in Endocrinology: Anorexia nervosa and endocrinology: a clinical update. Eur J Endocrinol 2019;180(1):R9-R27. doi: 10.1530/EJE-18-0596.
26. Nitsch A, Dlugosz H, Gibson D, Mehler PS. Medical complications of bulimia nervosa. Cleve Clin J Med 2021;88(6):333-43. doi: 10.3949/ccjm.88a.20168.
27. Mehler PS, Rylander M. Bulimia nervosa medical complications. J Eat Disord 2015;3:12.
28. Germain N, Galusca B, Grouselle D, Frere D, Billard S, Epelbaum J i sur. Ghrelin and obestatin circadian levels differentiate bingeing-purging from restrictive anorexia nervosa. J Clin Endocrinol Metab 2010;95(6):3057-62. doi: 10.1210/jc.2009-2196.
29. Hebebrand J, Holm JC, Woodward E, Baker JL, Blaak E, Durrer Schutz D i sur. A proposal of the European Association for the Study of Obesity to improve the ICD-11 diagnostic criteria for obesity based on the three dimensions etiology, degree of adiposity and health risk. Obes Facts 2017;10(4):284-307. doi: 10.1159/000479208.
30. Hudson JI, Lalonde JK, Coit CE, Tsuang MT, McElroy SL, Crow SJ i sur. Longitudinal study of the diagnosis of components of the metabolic syndrome in individuals with binge-eating disorder. Am J Clin Nutr 2010;91(6):1568-73. doi: 10.3945/ajcn.2010.29203.

31. Mitchell JE. Medical comorbidity and medical complications associated with binge-eating disorder. Int J Eat Disord 2016;49(3):319-23. doi: 10.1002/eat.22452.
32. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA i sur. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 2019;51(8):1207-14.
33. Bulik CM, Coleman JRI, Hardaway JA, Breithaupt L, Watson HJ, Bryant CD, Breen G. Genetics and neurobiology of eating disorders. Nat Neurosci 2022;25(5):543-54. doi: 10.1038/s41593-022-01071-z.
34. Frank GKW, Shott ME, DeGuzman MC. The neurobiology of eating disorders. Child Adolesc Psychiatr Clin N Am 2019;28(4): 629-40. doi: 10.1016/j.chc.2019.05.007.
35. Bronleigh M, Baumann O, Stapleton P. Neural correlates associated with processing food stimuli in anorexia nervosa and bulimia nervosa: an activation likelihood estimation meta-analysis of fMRI studies. Eat Weight Disord 2022;27(7):2309-20. doi: 10.1007/s40519-022-01390-x.
36. Thornton LM, Mazzeo SE, Bulik CM. The heritability of eating disorders: methods and current findings. Curr Top Behav Neurosci 2011;6:141-56.
37. Hübel C, Abdulkadir M, Herle M, Loos RJF, Breen G, Bulik CM, Micali N. One size does not fit all. Genomics differentiates among anorexia nervosa, bulimia nervosa, and binge-eating disorder. Int J Eat Disord 2021;54(5):785-93. doi: 10.1002/eat.23481.
38. Steiger H, Booij L. Eating disorders, heredity and environmental activation: getting epigenetic concepts into practice. J Clin Med 2020;9(5):1332. doi: 10.3390/jcm9051332. PMID 32466291.
39. Bulik CM, Blake L, Austin J. Genetics of eating disorders: what the clinician needs to know. Psychiatr Clin North Am 2019;42(1):59-73. doi: 10.1016/j.psc.2018.10.007.
40. Bulik CM, Sullivan PF, Tozzi F, Furberg H, Lichtenstein P, Pedersen NL. Prevalence, heritability, and prospective risk factors for anorexia nervosa. Arch Gen Psychiatry 2006;63(3):305-12.
41. Steiger H, Bruce KR. Phenotypes, endophenotypes, and genotypes in bulimia spectrum eating disorders. Can J Psychiatry 2007;52(4):220-31.
42. Yilmaz Z, Hardaway JA, Bulik CM. Genetics and epigenetics of eating disorders. Adv Genomics Genet 2015;5:131-50. doi: 10.2147/AGG.S55776.
43. Kaye WH, Fudge JL, Paulus M. New insights into symptoms and neurocircuit function of anorexia nervosa. Nat Rev Neurosci 2009;10(8):573-84.
44. Klengel T, Binder EB. Epigenetics of stress-related psychiatric disorders and gene × environment interactions. Neuron 2015;86(6):1343-57. doi: 10.1016/j.neuron.2015.05.036.
45. Steinglass JE, Walsh BT. Neurobiological model of the persistence of anorexia nervosa. J Eat Disord 2016;4:19. doi: 10.1186/s40337-016-0106-2.
46. Tchanturia K, Davies H, Roberts M, Harrison A, Nakazato M, Schmidt U i sur. Poor cognitive flexibility in eating disorders: examining the evidence using the Wisconsin Card Sorting Task. PLoS One 2012;7(1):e28331. doi: 10.1371/journal.pone.0028331.
47. Zastrow A, Kaiser S, Stippich C, Walther S, Herzog W, Tchanturia K i sur. Neural correlates of impaired cognitive-behavioral flexibility in anorexia nervosa. Am J Psychiatry 2009;166(5):608-16.
48. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. Trends Neurosci 2013;36(2):110-20. doi: 10.1016/j.tins.2013.01.003.
49. Bello NT, Hajnal A. Dopamine and binge eating behaviors. Pharmacol Biochem Behav 2010; 97(1):25-33. doi: 10.1016/j.pbb.2010.04.016.
50. Hebebrand J, Müller TD, Holtkamp K, Herpertz-Dahlmann B. The role of leptin in anorexia nervosa: clinical implications. Mol Psychiatry 2007;12(1):23-35. doi: 10.1038/sj.mp.4001909.
51. Mantzoros C, Flier JS, Lesem MD, Brewerton TD, Jimerson DC. Cerebrospinal fluid leptin in anorexia nervosa: correlation with nutritional status and potential role in resistance to weight gain. J Clin Endocrinol Metab 1997;82(6):1845-51. doi: 10.1210/jcem.82.6.4006.
52. Monteleone P, Serritella C, Martiadis V, Maj M. Deranged secretion of ghrelin and obestatin in the cephalic phase of vagal stimulation in women with anorexia nervosa. Biol Psychiatry 2008; 64(11): 1005-8.
53. Marsh R, Steinglass JE, Gerber AJ, O'Leary KG, Walsh BT, Peterson BS. Deficient activity in the neural systems that mediate self-regulatory control in bulimia nervosa. Arch Gen Psychiatry 2009; 61(1): 1-63. doi: 10.1001/archgenpsychiatry.2008.504.
54. Díaz-Marsá M, Alberdi-Páramo I, Niell-Galmés L. Nutritional supplements in eating disorders. Actas Esp Psiquiatr 2017; 45(Suppl): 26-36.
55. Soliman A, Alaaraj N, Hamed N, Alyafei F, Ahmed S, Shaat M i sur. Nutritional interventions during adolescence and their possible effects. Acta Biomed 2022;93(1):e2022087. doi: 10.23750/abm.v93i1.12789.
56. Bergen AW, Yeager M, Welch RA, Haque K, Ganjei JK, Mazzanti C i sur. Association of multiple DRD2 polymorphisms with anorexia nervosa. Neuropsychopharmacology 2005;30(9):1703-10. doi: 10.1038/sj.npp.1300719. PMID 15920508.
57. Favaro A, Clementi M, Manara R, Bosello R, Forzan M, Bruson A i sur. Catechol-O-methyltransferase genotype modifies executive functioning and prefrontal functional connectivity in women with anorexia nervosa. J Psychiatry Neurosci 2013;38(4):241-8. doi: 10.1503/jpn.120068. PMID 23046831.
58. Tharwani ZH, Shaeen SK, Zahid K i sur. Exploring the link between dopamine dysregulation and eating disorders: a narrative review. J Neuroendocrinol 2025; 37(10): e70070. doi: 10.1111/jne.70070.

59. Gauthier C, Hassler C, Mattar L, Launay JM, Callebert J, Steiger H i sur. Symptoms of depression and anxiety in anorexia nervosa: links with plasma tryptophan and serotonin metabolism. Psychoneuroendocrinology 2014;39:170-8. doi: 10.1016/j.psyneuen.2013.09.009.
60. Kaye WH, Gwirtsman HE, Brewerton TD, George DT, Wurtman RJ. Bingeing behavior and plasma amino acids: a possible involvement of brain serotonin in bulimia nervosa. Psychiatry Res 1988;23(1):31-43. doi: 10.1016/0165-1781(88)90032-7.
61. Steiger H. Eating disorders and the serotonin connection: state, trait and developmental effects. J Psychiatry Neurosci 2004;29(1):20-9. PMID 14719047.
62. Murray SB, Kaye WH. Brain neurotransmitters and eating disorders. U: Robinson P, Wade T, Herpertz-Dahlmann B, Fernandez-Aranda F, Treasure J, Wonderlich S, ur. Eating Disorders. Cham: Springer; 2024. doi: 10.1007/978-3-031-46096-8_46.
63. Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol 2017;13(3):174-86. doi: 10.1038/nrendo.2016.175. PMID 27811940.
64. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP; American College of Sports Medicine. American College of Sports Medicine position stand. The female athlete triad. Med Sci Sports Exerc 2007;39(10): 1867-82. doi: 10.1249/mss.0b013e318149f111.
65. Duclos M, Corcuff JB, Roger P, Tabarin A. The dexamethasone-suppressed corticotrophin-releasing hormone stimulation test in anorexia nervosa. Clin Endocrinol (Oxf) 1999; 51(6): 725-31. doi: 10.1046/j.1365-2265.1999.00872.x.
66. Warren MP. Endocrine manifestations of eating disorders. J Clin Endocrinol Metab 2011;96(2): 333-43. doi: 10.1210/jc.2009-2304.
67. Miller KK. Endocrine dysregulation in anorexia nervosa update. J Clin Endocrinol Metab 2011; 96(10):2939-49. doi: 10.1210/jc.2011-1222.
68. Klump KL. Puberty as a critical risk period for eating disorders: a review of human and animal studies. Horm Behav 2013;64(2):399-410. doi: 10.1016/j.yhbeh.2013.02.019.
69. Baker JH, Thornton LM, Lichtenstein P, Bulik CM. Pubertal development predicts eating behaviors in adolescence. Int J Eat Disord 2012;45(7):819-26. doi: 10.1002/eat.22022.
70. Striegel-Moore RH, Bulik CM. Risk factors for eating disorders. Am Psychol 2007;62(3): 181-98.
71. Misra M, Miller KK, Kuo K, Griffin K, Stewart V, Hunter E i sur. Secretory dynamics of leptin in adolescent girls with anorexia nervosa and healthy adolescents. Am J Physiol Endocrinol Metab 2005;289(2):E373-81. doi: 10.1152/ajpendo.00041.2005.
72. Cassioli E, Lucherini Angeletti L, Rossi E, Selvi G, Riccardi E, Siviglia S i sur. Leptin levels in acute and recovered eating disorders: an arm-based network meta-analysis. Eur Eat Disord Rev 2025; 33(3):525-37. doi: 10.1002/erv.3163.
73. Tezenas du Montcel C, Duriez P, Cao J, Lebrun N, Ramoz N, Viltart O i sur. The role of dysregulated ghrelin/LEAP-2 balance in anorexia nervosa. iScience 2023;26(10):107996. doi: 10.1016/j.isci.2023.107996.
74. Himmerich H, Lewis YD, Conti C, Mutwalli H, Karwautz A, Sjögren JM i sur.; WFSBP Task Force on Eating Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders. World J Biol Psychiatry 2023;24(8):643-706. doi: 10.1080/15622975.2023.2179663.
75. Jelcic N, Likic R, Tripkovic M. Spotlight commentary: the role of therapeutic drug monitoring in optimizing treatment with antipsychotic medicines. Br J Clin Pharmacol 2024;90(12):3084-6. doi: 10.1111/bcp.16323.