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Snežana Polovina<sup>1,2</sup>, Dragan Micić<sup>3,4</sup>, Dušan Micić<sup>3</sup>, Mirjana Šumarac Dumanović<sup>1,3</sup>, Aleksandra Kendereški<sup>1,3</sup>, Micić J<sup>3,5</sup>, Danica Stamenković Pejkić<sup>1,3</sup>, Goran Cvijović<sup>1,3</sup>, Zorić S<sup>1</sup>, Jeremić D<sup>1</sup>, Miloš Bjelović<sup>3,6</sup>

## NEHIRURŠKE KOMPLIKACIJE HIRURŠKOG LEČENJA GOJAZNOSTI

**Sažetak:** Hirurško lečenje gojaznosti je najefikasniji vid lečenja sa najvećim uticajem na smanjenje telesne mase, na poboljšanje metaboličkih poremećaja i komorbiditeta i sa najvećom održivošću postignutih efekata. Vrsta operacije određuje stepen efikasnosti, ali i moguće neželjene pojave nakon hirurškog lečenja. Pojedine procedure dovode do značajno smanjene apsorpcije i makro i mikronutrijenata, što sve zajedno može da dovede do deficita pojedinih neophodnih hranljivih materija. Deficit gvožđa posle hirurškog lečenja gojaznosti pojavljuje se kod 20–50% operisanih i može biti posledica nepodnošenja mesa ili manjka želudačne kiseline usled odstranjenja pilorusa ili premošćenja duodenuma. Deficit vitamina B12 se razvija nakon 6 meseci od operacije ako su bili samo na oralnoj suplementaciji ovog vitamina. Barijatrijske procedure mogu da dovedu do smanjenja mineralne koštane gustine. Prva tri meseca posle RYGB (Roux-en-Y gastric bypass) ubrzava se koštani metabolizam, a nivo koštanih markera se povećava i do 200% tokom narednih godinu dana. Zbog poremećene apsorpcije D vitamina može da dođe do smanjene apsorpcije kalcijuma i povećanja nivoa paratireoidnog hormona. Nivo testosterona kod muškaraca se značajno povećava nakon barijatrijske hirurgije, ali je zapažena veća stopa infertiliteta posle RYGB zbog pojave oligoastenozoospermije i teratospermije usled mineralno-vitaminskog deficita. Prvih godinu dana posle gastričnog bajpasa je osetljiv period za trudnoću zbog najvećeg smanjenja telesne mase i mogućeg nutritivnog

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<sup>1</sup> Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Klinički centar Srbije, e-mail: snezanapolovina@gmail.com

<sup>2</sup> Farmaceutski fakultet Novi Sad, Univerzitet Privredna akademija

<sup>3</sup> Medicinski fakultet Univerziteta u Beogradu

<sup>4</sup> Klinika za urgentnu hirurgiju, Urgentni centar, Klinički centar Srbije

<sup>5</sup> Klinika za ginekologiju i akušerstvo, Klinički centar Srbije

<sup>6</sup> Klinika za digestivnu hirurgiju, Klinički centar Srbije

i mineralno-vitaminskog deficita, što bi moglo da se odrazi na indeks fetalnog rasta. Pojava alkoholizma unutar pet godina od RYGB dvostruko je češća u odnosu na pacijente posle restriktivnih barijatrijskih operacija, kao i značajno veća učestalost pokušaja suicida među operisanim pacijentima.

**Gljučne reči:** anemija i RYGB, kost i barijatrijska hirurgija, reprodukcija i barijatrijska hirurgija, alkoholizam i barijatrijska hirurgija

Hirurško lečenje gojaznosti je najefikasniji vid lečenja sa najvećim uticajem na smanjenje telesne mase, poboljšanje metaboličkih poremećaja, redukciju komorbidity i sa najvećom održivošću postignutih rezultata. Vrsta operacije određuje stepen efikasnosti, ali i moguće neželjene pojave nakon hirurškog lečenja. Pojedine procedure dovode do značajno smanjene apsorpcije i makro i mikronutrijenata, što sve zajedno može da dovede do deficita pojedinih neophodnih hranljivih materija, a u krajnjem slučaju i do stanja teške pothranjenosti (1).

**Laparoscopic Sleeve gastrectomy (LSG)** Američko društvo za barijatrijsku i metaboličku hirurgiju predlaže kao prvi korak u hirurškom lečenju visokorizičnih, ekstremno gojaznih pacijenata jer se ovom operacijom postiže sličan efekat na smanjenje telesne mase kao sa malapsorptivnim operacijama, a učestalost komplikacija je manja (2). Iako je LSG restriktivna procedura, zbog odstranjivanja fundusa želuca značajno je smanjena produkcija oreksigenog hormona grelina, što utiče na smanjenje osećaja gladi i doprinosi gubitku telesne mase. Odstranjivanje većeg dela pilorusa prilikom ove operacije, zbog gubitka hlorovodonične kiseline poreklom iz parijetalnih ćelija pilorusa, uzrokuje smanjenje apsorpcije vitamina B12, ali i gvožđa i kalcijuma (3).

**Bilopancreatic diversion (BPD)** i njena kasnija modifikacija, **bilopancreatic diversion with duodenal switch (BPD/DS)**, su kombinovane, restriktivno-malapsorptivne procedure koje karakteriše značajno smanjen energetski unos uz deficit proteina, vitamina i minerala (4).

Iako je gojaznost uzrokovana povećanim unosom energije u odnosu na potrebe, kod gojaznih se konstatuju mnogobrojni nedostaci mikronutrijenata, a najčešće deficit vitamina D, vitamina B grupe, folata, gvožđa i kalcijuma. Prekomeran unos visokokalorijske hrane manje nutritivne vrednosti uzrokuje povećanu potrošnju neenzimatskih antioksidanata kod gojaznih osoba i povećan oksidativni stres (5).

### **Anemija posle barijatrijskih operacija**

Neodgovarajuća hranljiva vrednost namirnica kod gojaznih osoba je jedan od razloga nedostatka gvožđa, folata i vitamina B12 pre operacije. Drugi razlog je sistemska inflamacija u gojaznosti koja smanjuje apsorpciju gvožđa i povećava nivo hepcidina,

ključnog regulatora za ulazak gvožđa u cirkulaciju (6). Snižen nivo feritina se zapaža 6 meseci posle RYGB. Nizak nivo feritina, uz normalnu koncentraciju serumskog gvožđa, ukazuje na smanjene rezerve gvožđa u organizmu. Niži nivo gvožđa posle hirurškog lečenja gojaznosti pojavljuje se kod 20–50% operisanih i može biti posledica nepodnošenja mesa ili manjka želudačne kiseline usled odstranjenja pilorusa ili premošćenja duodenuma. Anemija se viđa 6 meseci do 3 godine nakon operacije i češća je kod žena.

Nedovoljna količina vitamina B12, ako već nije postojala preoperativno, kod velikog broja se razvija nakon 6 meseci od operacije. Preko 30% pacijenata nema dovoljno B12 vitamina godinu dana nakon RYGB, a preko 60% nakon 2 godine od operacije ako su bili samo na oralnoj nadoknadi (7). Nedostatak folata se ređe javlja jer se folati resorbuju duž čitavog ileuma i do njihovog deficita može da dođe uglavnom zbog smanjene količine unete hrane. Pacijenti koji nemaju dobar odgovor nakon oralne nadoknade gvožđa treba da se leče parenteralnim preparatima. Kod takvih pacijenata neophodna je provera zapremine eritrocita i odgovora retikulocita. U slučaju perzistiranja anemije i citopenije nakon nadoknade oligoelemenata, neophodno je da se uradi biopsija kostne srži (8, 9).

### ***Gubitak koštane mase posle barijatrijske hirurgije***

Barijatrijske procedure mogu da dovedu do smanjenja mineralne koštane gustine (MKG). Nekoliko različitih mehanizama može da utiče na gubitak koštane mase, počevši od rasterećenja skeleta zbog manje telesne mase i manjeg savladavanja otpora pri kretanju, do promene u koncentraciji hormona koji utiču na koštani metabolizam. Apsorptivna površina je smanjena u mešovitim (RYGB i BPD/DS) procedurama, što podrazumeva i smanjenu apsorpciju minerala i liposolubilnih vitamina.

Kod gojaznih osoba koštani metabolizam je često oštećen zbog manje bioraspoloživosti D vitamina. Niži nivo D vitamina kod gojaznih nastaje zbog nakupljanja D vitamina u depoima masnog tkiva, manje izloženosti suncu, zbog nealkoholnog statohepatitisa i sistemske inflamacije niskog stepena. Osteoblasti i adipociti potiču iz iste mezenhimalne ćelije. Veći sadržaj adipocita u kostnoj srži kod gojaznih osoba dovodi se u vezu sa manjom mineralnom koštanom gustinom. Visceralna gojaznost ima negativan uticaj na MKG, a potkožno masno tkivo deluje zaštitno na gustinu kostiju. Gojazne žene imaju veći nivo leptina, PTH, fibroblastnog faktora rasta (FGF-23) i manji nivo 1,25 dihidroksi vitamina D u odnosu na normalno uhranjene žene (10). Nakon postavljanja podesive želudačne trake (LAGB – *Laparoscopic Adjustable Gastric Banding*) ne menja se nivo D vitamina ni PTH, a smanjuje se nivo leptina i estrogena. Merenjem C-telopeptida (CTX) uočava se povećana razgradnja kostiju šest meseci nakon intervencije koja se održava naredne dve godine (11). Broj studija koje su istraživale koštani metabolizam nakon LSG je nedovoljan da bi mogao da

se proceni uticaj ove procedure na MKG (12). Prva tri meseca posle RYGB ubrzava se koštani metabolizam, a nivo koštanih markera se povećava i do 200% tokom narednih godinu i po dana. Jedna studija je pokazala da osteokalcin i koštana alkalna fosfataza (BSAP – *Bone Specific Alkaline Phosphatase*) ostaju povećane čak 10 godina posle RYGB u odnosu na kontrolnu grupu (13). Nakon barijatrijske operacije koja je praćena malapsorpcijom liposolubilnih vitamina, prethodna insuficijencija može da pređe u deficit D vitamina što smanjuje resorpciju kalcijuma i dovodi do povećanja nivoa paratireoidnog hormona (PTH) (14). Neprepoznat i nelečen sekundarni hiperparatireoidizam povećava rizik za nastanak osteopenije i osteoporoze a hipokalcemija usled deficita vitamina D pogoršava defekt mineralizacije i ubrzava nastanak osteomalacije (15).

Studije su pokazale da se postoperativni nivo D vitamina ne menja ni nakon preporučene nadoknade od 5000IU D vitamina dnevno, mada nema dovoljno podataka o komplijansi pacijenata za uzimanje nadoknade (16). Posle najmutilantnije barijatrijske operacije, BPD/DS, više od polovine pacijenata ima deficit D vitamina i sekundarni hiperparatireoidizam. Većina pacijenata podvrgnutih BPD/DS ima oštećenu mineralizaciju kostiju, što se ogleda u smanjenju mineralne gustine lumbalnih pršljenova 4–10 godina nakon ove operacije. Kod većine pacijenata je nakon četiri godine i postizanja stabilizacije telesne mase primećeno povećanje izgradnje kostiju. Pretpostavlja se da je početno smanjenje MKG posledica rasterećenja skeleta smanjenjem telesne mase, a da se taj efekat gubi nakon prilagođavanja na novonastalu telesnu masu. Biopsijom kostiju četiri godine nakon BPD/DS dobijen je podatak o smanjenju debljine kortikalnog sloja kosti, dok je trabekularna kost ostala nepromenjene arhitektonike (13). Na kvalitet kostiju posle barijatrijske hirurgije utiče i promena crevnih hormona. Naime, nivo PYY negativno utiče na aktivnost osteoblasta. Poznato je da nivo GLP-1 i grelina takođe utiče na koštani metabolizam, ali za sada nema podataka da li promena nivoa ovih hormona doprinosi smanjenju MKG i većem riziku od preloma kostiju. Niži nivo insulina i amilina posle hirurškog lečenja gojaznosti povećava osteoklastnu, a smanjuje osteoblastnu aktivnost (17). Smanjenje mišićne mase, osim rasterećenja skeletal, može da doprinese većoj sklonosti ka padovima (18).

Većina preporuka za nadoknadu D vitamina posle barijatrijskih operacija preporučuje dozu od 800IU, koja se pokazala kao nedovoljna posle RYGB. Studija urađena na 45 ispitanika pokazala je značajno veći porast nivoa D vitamina i normalizaciju nivoa PTH kod pacijenata koji su uzimali 2000IU i 2000mg kalcijuma u odnosu na grupu koja je supstituisana dozom od 800IU. Dalje povećanje doze D vitamina povećava kalcijuriju i potrebna su dalja ispitivanja koja podrazumevaju merenje kalcijuma u 24h urinu radi preciznijeg određivanja doze za nadoknadu, a bez povećanja rizika od nastanka kamena u bubrežima i mokraćnim putevima (19). Savetuje se unošenje kalcijuma u formi kalcijum-citrata jer, za razliku od kalcijum-karbonata, obezbeđuje kiselu sredinu koja je idealna za apsorpciju kalcijuma. Važno je da se

preparat kalcijuma uzima odvojeno od preparata gvožđa (7). S obzirom na to da se tokom jednog unosa apsorbuje do 600mg kalcijuma, preporučuje se da se dnevni unos 1500–2000mg kalcijuma podeli u više dnevnih doza. Pacijentima se savetuju redovne kontrole 25OH vitamina D, kontrola 24-časovne kalciureze na 6 meseci, posle dve godine jednom godišnje. Pre operacije i posle dve godine od operacije trebalo bi uraditi osteodenzitometriju (3).

Adolescenti, kao populacija koja nije postigla potpunu koštanu zrelost i maksimalnu koštanu masu, i postmenopauzalne žene su dve posebno osetljive kategorije kod kojih mora pažljivo da se već preoperativno proceni rizik od smanjenja MKG posle operacije (13).

### ***Reproduktivni poremećaji posle barijatrijske hirurgije***

Poznata je povezanost između insulinske rezistencije, metaboličkog sindroma i dijabetesa tipa 2 i stečenog muškog hipogonadizma. Promene u hormonskom statusu podrazumevaju snižen nivo testosterona i sex hormone binding globulina (SHBG), povišen nivo estrogena, insulina i leptina. Povećanje telesne mase za svakih 9kg povećava rizik za infertilitet muškaraca za 10% (20, 21). Nakon značajnog smanjenja telesne mase posle barijatrijske operacije povećava se nivo slobodnog testostosterone i dolazi do pada nivoa estrogena, FSH i SHBG. Bolji hormonski odgovor postignut je kod mlađih muškaraca. Pretpostavlja se da lečenje gojaznosti barijatrijskom hirurgijom remodeluje epigenetske promene nastale usled DNA metilacije kod gojaznih muškaraca (22). Osim povoljnih efekata barijatrijske hirurgije na nivo androgena i poboljšanja kvaliteta seksualne funkcije, nakon malapsorptivnih operacija, usled deficita nutritienata može da se pogorša kvalitet sperme. Naime, zapažena je veća stopa infertiliteta posle RYGB zbog pojave oligoastenozoospermije i teratospermije. Ovu činjenicu treba uzeti u obzir kod donošenja odluke o vrsti barijatrijske operacije kod mlađih muškaraca koji planiraju potomstvo (23).

Efekti gojaznosti se manifestuju u skoro svakom aspektu reproduktivnog života žene, bilo kao metaboličke ili reproduktivne komplikacije ili kao tehnički problemi, kao što su teškoće u izvođenju ultrasonografskih pregleda ili operativnih zahvata (24). Gojaznost uzrokuje infertilitet preko različitih mehanizama koji obuhvataju: oštećenje razvoja folikula, promenu kvaliteta i broja oocita, oplodnju i implantaciju (25). Povećana koncentracija leptina, FSH i insulin olakšava steroidogenezu što povećava uticaj LH na ćelije granulose, inhibišući dalje mitoze i diferencijaciju granulosa ćelija u preovulatornim folikulima. Posledica ove aktivnosti je prestanak daljeg rasta folikula, prevremena luteinizacija, oligo ili anovulacija i poremećaj menstrualnog ciklusa (26). Rizik od anovulatornog infertiliteta raste sa povećanjem indeksa telesne mase, kao i rizik od gestacijskog dijabetesa, hipertenzije, preeklampsije, poremećaja rasta fetusa,

fetalnih malformacija i distocije. Incidenca spontanih pobačaja je tri puta veća kod gojaznih žena u odnosu na normalno uhranjene (27, 28).

Smanjenje telesne mase nakon hirurškog lečenja gojaznosti je do sada najefikasniji metod lečenja PCOS koji dovodi do normalizacije menstrualnog ciklusa, povlačenja simptoma hiperandrogenizma, uspostavljanja ovulacije i povećanja fertilne sposobnosti (29). Posle barijatrijske operacije, trudnice su izložene manjem riziku od makrozomije i komplikacija vezanih za trudnoću, ali su sklonije anemiji i rađanju novorođenčadi male porođajne težine u odnosu na gestacijsku dob (30). Poseban oprez zbog mogućeg nutritivnog i mineralno-vitaminskog deficita potreban je kod trudnica nakon RYGB. Prvih godinu dana posle gastričnog bajpasa je osetljiv period zbog najvećeg smanjenja telesne mase i mogućeg nutritivnog i mineralno-vitaminskog deficita, što bi moglo da se odrazi na indeks fetalnog rasta u slučaju koncepcije u tom periodu. Važno da pacijentkinje koje planiraju trudnoću uzimaju predviđenu nadoknadu minerala i vitamina. Moguć je deficit liposolubilnih vitamina A i D, vitamina B12, tiamina, folata, gvožđa i kalcijuma. Nedostatak tiamina tokom intrauterinog rasta može da uzrokuje Wernicke-ovu encefalopatiju.

Nakon biliopankreatične diverzije značajno se povećava fertilitnost ali skoro 30% novorođenčadi ima malu težinu na rođenju. Oko četvrtine trudnoća začetih nakon BPD se završi pobačajem, ali se procenat makrozomija značajno smanjuje. Preporuka je da se trudnoća nakon BPD odloži do stabilizacije telesne mase (31).

### ***Psihički problemi i unakrsna zavisnost nakon barijatrijske hirurgije***

Mogući psihički problem nakon perioda naglog smanjenja telesne mase posle barijatrijske operacije je pojava unakrsne zavisnosti. Posle barijatrijskih operacija, kad je onemogućen prekomerni unos hrane, primećena je veća učestalost unosa alkohola, zavisnost od kockanja, nekontrolisana kupovina, gladovanje ili binge eating, preterano vežbanje i povećana seksualna aktivnost (32). Depresija je čak pet puta češća u populaciji ekstremno gojaznih u odnosu na normalno uhranjene osobe. Razlog za značajno veću učestalost depresije u ovoj populaciji može da bude stigmatizacija od strane društva i postojanje pridruženih bolesti koje značajno remete kvalitet života. Deaktivacijom inflamatornih puteva i normalizacijom hipotalamo-hipofizno-adrenalne osovine značajno se smanjuje skor depresije i anksioznosti posle barijatrijske hirurgije. S druge strane, povećanje telesne mase, do kojeg dolazi obično posle dve godine od operacije, ponovo pogoršava depresiju (33). Pojava alkoholizma unutar pet godina od RYGB je dvostruko češća u odnosu na pacijente posle LAGB (34). Metaanaliza objavljena od strane brazilskih istraživača pokazala je da se incidenca alkoholizma posle barijatrijskih operacija kreće od 2 do 6.5%. Kod pacijenata koji konzumiraju alkohol posle RYGB primećene su češće epizode hipoglikemije usled supresije glukoneogeneze. Ovi pacijenti su podložni intoksikaciji alkoholom zbog većeg procenta

apsorpcije alkohola nakon anatomske modifikacije kod ove operacije. Većina studija je pokazala da su muškarci podložniji pojavi alkoholizma nakon RYGB u odnosu na žene (35). Studija sprovedena u Švedskoj od 2001. do 2010. prikazala je veću učestalost prekomerne primene alkohola i psihotropnih supstanci kod gojaznih žena koje se pripremaju za barijatrijsku hirurgiju u odnosu na normalno uhranjene žene. Posle operacije rizik od pogoršanja depresije nastavio je da se povećava kod oba pola. Pokušaji suicida su bili značajno učestaliji posle RYGB u odnosu na pacijente koji nisu gojazni (36). Zabeležena je i nagla promena ponašanja praćena oftalmoplegijom i upornim povraćanjem kod pacijenta kome je dva meseca pre hospitalizacije urađen RYGB, nakon čega je smanjio telesnu masu 18kg. Ustanovljeno je da pacijent ima Wernicke-ovu encefalopatiju usled deficita tiamina koji je nastupio posle operacije, a nije adekvatno supstituisan. Nakon parenteralne primene 500mg tiamina svakih 8 sati tokom tri dana, svi simptomi su se povukli (37).

Prilikom donošenja odluke o hirurškom lečenju gojaznosti neophodna je saglasnost multidisciplinarnog konzilijuma kako bi se procenila podobnost pacijenta za tu vrstu terapije. Spremnost pacijenta da posle barijatrijske operacije nastavi sa redovnim kontrolama i daljim lečenjem u referentnom centru za lečenje gojaznosti preduslov je da se nastanak hroničnih komplikacija hirurškog lečenja gojaznosti svede na najmanju moguću meru.

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Snežana Polovina<sup>1,2</sup>, Dragan Micić<sup>3,4</sup>, Dušan Micić<sup>3</sup>,  
Mirjana Šumarac Dumanović<sup>1,3</sup>, Aleksandra Kendereški<sup>1,3</sup>, Micić J<sup>3,5</sup>,  
Danica Stamenković Pejčković<sup>1,3</sup>, Goran Cvijović<sup>1,3</sup>, Zorić S<sup>1</sup>,  
Jeremić D<sup>1</sup>, Miloš Bjelović<sup>3,6</sup>

## **NON-SURGICAL COMPLICATIONS FOLLOWING BARIATRIC SURGERY**

**Abstract:** Bariatric surgery is the most efficient treatment for obesity and comorbidities. This treatment modality is the most potent for weight reduction with long-term weight maintenance and positive metabolic effects. The effect on weight loss and possible side effect depends of type of surgery. Micro and macronutrient deficiencies can occur after malabsorptive procedures. Iron deficiency occurs in almost half of patients following RYGB (Roux-en-Y gastric bypass). The main causes of iron deficiency are insufficient meat ingestion and lack of hydrochloric acid after removal of pylorus. B12 deficiency occurred 6 months after RYGB in patients with oral supplementation of B12. Bone turnover increased three months after RYGB, and the levels of bone turnover markers increased 200% in next 12-18 months. Impaired vitamin D absorption leads to decreased calcium absorption and secondary hyperparathyroidism with lower bone mineral density. After the bariatric surgery, testosterone level becomes higher and all sexual quality indicators improving. Malabsorptive procedures with nutritive deficiency can cause oligo-asthenozoospermia and male infertility. Due to the same reason pregnancy is not recommended in the first year bariatric surgery. Possible side effect of pregnancy within 12 months after surgery is fetal growth retardation. There is twice higher incidence for developing alcohol or other addiction after bariatric surgery then in

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<sup>1</sup> Clinic for endocrinology, diabetes and metabolic diseases, , Clinical Center of Serbia, e-mail: snezanapolovina@gmail.com

<sup>2</sup> Faculty of Pharmacy Novi Sad, University Privredna akademija

<sup>3</sup> Medical faculty, University in Belgrade

<sup>4</sup> Clinic for Emergency Surgery, Emergency Center, Clinical Center of Serbia

<sup>5</sup> Clinic for Gynecology and Obstetrics, Clinical Center of Serbia

<sup>6</sup> Clinic for Digestive Surgery, Clinical Center of Serbia



non operated obese patients. The frequency of depressive episodes and suicide attempt is higher after bariatric surgery.

**Key words:** anaemia and bariatric surgery, bone and bariatric surgery, fertility and bariatric surgery, addiction and bariatric surgery

Surgical treatment of obesity is the most effective form of treatment with the greatest impact on weight loss, improvement of metabolic disorders, reduction of comorbidity and the highest sustainability of the achieved results. The type of surgery determines the degree of efficacy and possible side effects after surgical treatment. Certain procedures lead to significantly reduced absorption of both macro and micro-nutrients, which together can lead to the deficiency of certain nutrients needed, and ultimately to the state of severe malnutrition (1).

**Laparoscopic Sleeve gastrectomy (LSG).** The American Society for Bariatric and Metabolic Surgery proposes LSG as a first step in the surgical treatment of high-risk, extremely obese patients, because this operation achieves a similar effect on weight loss as with malabsorptive surgery, and the incidence of complications is lower (2). Although the LSG is a restrictive procedure, due to the removal of the stomach fundus, the production of orexigenic hormones is significantly reduced, which affects the reduction of hunger and contributes to weight loss. Removing the greater part of the pylorus during this operation, due to the loss of hydrochloric acid originating from the parietal pylori cells, causes a decrease in the absorption of vitamin B12, but also iron and calcium (3).

**Bilopancreatic diversion (BPD)** and its subsequent modification, **bilopancreatic diversion with a duodenal switch (BPD / DS)**, are combined, restrictive-malabsorptive procedures characterized by a significantly reduced energy intake with a deficit of proteins, vitamins and minerals (4).

Although obesity is caused by increased energy intake compared to needs, in obese people numerous deficiencies of micronutrients are found, and most often vitamin D deficiency, vitamin B group, folate, iron and calcium. Excessive intake of high calorie foods with less nutritional value causes increased consumption of non-enzymatic antioxidants in obese people and increased oxidative stress (5).

### *Anaemia following bariatric surgery*

Inadequate nutritional content of foods in obese people is one of the reasons for the lack of iron, folate and vitamin B12 even before surgery. Another reason is low grade systemic inflammation in obesity that reduces iron absorption and increases the level of hepcidin, a key regulator for the entry of iron into the circulation (6). Lowered ferritin levels are observed for 6 months after RYGB. Low levels of ferritin with normal serum iron levels indicate reduced iron reserves in the body. Lower levels of

iron after surgical treatment of obesity appear in 20-50% of the operative and may be due to lack of the meat in diet or gastric acid deficiency due to the removal of the pylorus or the duodenum overlap. Anemia is seen for 6 months to 3 years after surgery and is more common in women.

Insufficient amount of vitamin B12, if it had not already existed too far, in large numbers develops after 6 months of surgery. Over 30% of patients do not have enough B12 vitamins a year after RYGB, and over 60% after 2 years of surgery if they were only on oral substitution (7). The lack of folate occurs less often because folate is absorbed along the entire ileum and can lead to their deficiency mainly due to a reduced amount of food intake. Patients who do not have a good response to oral iron replacement should be treated with parenteral preparations. In such patients it is necessary to check the volume of erythrocytes and the response of the reticulocytes. In the case of persistent anemia and cytopenia after the replacement of the oligoelements, it is necessary to do a biopsy of the bone marrow (8, 9).

### ***Bone loss after bariatric surgery***

Bariatric procedures can lead to decrease in bone mineral density (BMD). Several different mechanisms can affect the loss of bone mass, starting from relieving skeletons due to lower body weight and less resistance to movement, to changes in the hormone concentration that affect bone metabolism. The absorptive surface is reduced in mixed (RYGB and BPD/ DS) procedures, which also means reduced absorption of minerals and liposoluble vitamins.

In obese individuals bone metabolism is often damaged due to the lower bioavailability of D vitamin. Lower level of vitamin D in obesity occurs due to the accumulation of D vitamins in fat tissue depots, less exposure to the sun, due to non-alcoholic statohepatitis and low-grade systemic inflammation. Osteoblasts and adipocytes originate from the same mesenchymal cell. Higher content of adipocytes in the bone marrow in obese people is associated with lower mineral bone density. Visceral obesity has a negative impact on BMD, and the subcutaneous fat tissue acts protective on the bone density.

Obese women have a higher level of leptin, PTH, a fibroblast growth factor (FGF-23) and a lower level of 1,25 dihydroxy of vitamin D in relation to normally weight women (10). After adjusting the adjustable gastric band (LAGB-Laparoscopic Adjustable Gastric Banding), the level of vitamin D or PTH is not changed, and the level of leptin and estrogen decreases. By measuring C-telopeptide (CTX), increased bone degradation is observed six months after intervention, which does not change for the next two years (11). The number of studies that investigated bone metabolism after the LSG was insufficient to assess the impact of this procedure on BMD (12).

The first three months after RYGB accelerates bone metabolism, and the level of bone markers increases up to 200% over the next year and a half. One study showed that osteocalcin and bone-specific alkaline phosphatase (BSAP) remained elevated 10 years after RYGB compared to the control group (13). After bariatric surgery followed by malabsorption of liposoluble vitamins, the previous insufficiency may translate into vitamin D deficiency, which reduces calcium resorption and leads to an increase in parathyroid hormone levels (PTH) (14). Unrecognized and untreated secondary hyperparathyroidism increases the risk of osteopenia and osteoporosis, and hypocalcaemia due to vitamin D deficiency aggravates the defect of mineralization and accelerates the occurrence of osteomalacia (15).

Studies have shown that the postoperative level of vitamin D does not change even after the recommended reimbursement of 5000 IU of vitamin D daily, although there is insufficient data regarding the compliance for supplementation intake (16). After the most potent bariatric surgery BPD/DS, more than half of patients have a vitamin D deficiency and secondary hyperparathyroidism. Most patients undergoing BPD/DS have damaged bone mineralization, which is reflected in the decrease in the mineral density of the lumbar spines 4-10 years after this operation. In most patients, after four years and achieving weight stabilization, an increase in bone build-up was observed. It is assumed that the initial reduction in BMD is due to the relaxation of the skeleton by decreasing the body weight, and that the effect is lost after adjusting to the new body mass. Bone biopsy four years after BPD / DS obtained data on the reduction in the bone cortical thickness while the trabecular bone remained unchanged (13).

Bone quality after bariatric surgery is affected by the change in intestinal hormones. Namely, the level of PYY negatively affects the activity of osteoblasts. It is known that the level of GLP-1 and grees also affects bone metabolism, but for now there is no evidence that the change in levels of these hormones contributes to a decrease in MKG and a higher risk of bone fracture. A lower level of insulin and amylin after surgical treatment of obesity increases the osteoclastic, and reduces osteoblastic activity (17). Decrease in muscle mass, apart from scattering of the skeleton, can contribute to a greater tendency to fall (18).

Most guidelines for the replacement of D vitamins after bariatric surgery recommend a dose of 800IU which proved to be insufficient after RYGB. A study of 45 subjects showed a significantly higher rise in vitamin D levels and normalization of PTH levels in patients who took 2000 IU and 2000 mg of calcium compared to a group that was substituted with a dose of 800 IU. A further increase in the dose of vitamin D increases serum calcium and requires further studies involving the measurement of calcium in 24h urine for more accurate determination of the compensation dose, without increasing the risk of stone formation in the kidneys and urinary tract (19). Calcium-citrate is advised, because, unlike calcium carbonate, it provides an acidic

environment that is ideal for calcium absorption. It is important that the calcium preparation is taken separately from the iron preparation (7). Given that up to 600 mg of calcium is absorbed during one intake, it is recommended that the daily intake of 1500-2000 mg calcium is divided into several daily doses. Patients are advised to regularly monitor 25OH vitamin D, control 24-hour calciuria every 6 months, and after two years, once per year. Before surgery and two years after surgery, osteodensitometry should be performed (3).

Adolescents, as a population that did not achieve maximal bone mass as well as postmenopausal women, are particularly sensitive categories in which the risk of a reduction in BMD after surgery must be carefully evaluated preoperatively and followed postoperatively (13).

### ***Reproductive disorders after bariatric surgery***

The relationship between insulin resistance, metabolic syndrome, type 2 diabetes and acquired male hypogonadism is known. Changes in the hormone status include reduced levels of testosterone and sex hormone binding globulin (SHBG), elevated levels of estrogen, insulin, and leptin. Increasing weight for every 9kg increases the risk of men's infertility by 10% (20, 21). After a significant reduction in body weight after bariatric surgery, the level of free testosterone increases and the level of estrogen, FSH and SHBG decrease. A better hormone response is achieved in younger men. It is assumed that the treatment of obesity by bariatric surgery removes epigenetic changes due to DNA methylation in obese men (22). Apart from the beneficial effects of bariatric surgery on the level of androgen and improvements in the quality of sexual life, after malabsorptive surgery, due to nutrient deficiency, the quality of sperm can be impaired. Namely, a higher infertility rate has been observed after RYGB due to the onset of oligo-asthenozoospermia and teratospermia. This fact should be taken into account when deciding on the type of bariatric surgery for younger men (23).

Obesity affects almost every aspect of the reproductive life of women and causes either metabolic or reproductive complications, or as technical problems such as difficulties in performing ultrasonographic examinations or surgery (24). Obesity causes infertility through various mechanisms that include: damage to follicular development, changes in the quality and number of oocytes, fertilization and implantation (25). Increased leptin, FSH and insulin relieves steroidogenesis, which increases the effect of LH on granulosa cells, inhibiting further mitosis and differentiation in preovulatory follicles. The consequence of this activity is the discontinuation of further follicular growth, premature luteinization, oligo or anovulation, and menstrual cycle disorders (26). The risk of anovulatory infertility increases with an increase in the body mass index as well as the risk of gestational diabetes, hypertension, preeclampsia, fetal

growth retardation, fetal malformations, and dystocia. The incidence of spontaneous abortion is three times higher in obese women compared to normal ones (27, 28).

Weight loss after the surgical treatment of obesity is so far the most efficient method for the treatment of PCOS which causes normalization of the menstrual cycle, regression of the symptoms of hyperandrogenism, restores of ovulation and increase reproductive ability (29). After bariatric surgery, pregnant women are at lower risk of macrosomia and complications of pregnancy but they are more prone to anemia and newborn are at higher risk low birth weight in relation to gestational age (30). Particular caution due to possible nutritional and mineral-vitamin deficiency in pregnant women is needed after RYGB. The first year after gastric bypass surgery is a sensitive period for the possible nutritional and mineral-vitamin deficiency that could affect the fetal growth in the case of conception in this period.

It is important that patients planning pregnancy taking the minerals and vitamins in preconception period. It is possible to deficit of fat-soluble vitamins A and D as well as vitamin B 12, thiamine, folate, iron, and calcium. Thiamine deficiency during intrauterine growth can cause Wernicke's encephalopathy.

After biliopancreatic diversion, fertility increases significantly, but nearly 30% of newborns have low birth weight. About a quarter of pregnancies started after BPD end with abortion but the percentage of macrosomia significantly decreases. It is recommended to postpone pregnancy after BPD until body weight stabilization (31).

### ***Psychological problems and cross-addiction after bariatric surgery***

A possible mental problem after a period of rapid weight loss after bariatric surgery is the occurrence of cross-dependence or cross-addiction. After bariatric surgery, when excessive food intake is prevented, a higher alcohol intake rate, gambling addiction, uncontrolled shopping, starvation or binge eating, excessive exercise and increased sexual activity are observed (32). Depression is much then five times frequent in the population with extreme obesity compared to normally weight persons. The reason for significantly higher incidence of depression in this population can be stigmatization by society and the existence of associated illnesses that significantly impair quality of life. Deactivation of inflammatory pathways and normalization of the hypothalamic-pituitary-adrenal axis significantly reduces the rate of depression and anxiety after bariatric surgery. On the other hand, the increase in body weight that usually occurs after two years of surgery again aggravates depression (33). The occurrence of alcoholism within five years of RYGB is twice more frequent compared to patients after LAGB (34). Metaanalysis published by Brazilian researchers has shown that the incidence of alcoholism after bariatric surgery ranges from 2 to 6.5%. In patients who consume alcohol after RYGB, more frequent episodes of hypoglycaemia due to gluconeogenesis suppression have been observed. These patients are

susceptible to alcohol intoxication due to a higher percentage of alcohol absorption after anatomical modification in this operation. Most studies have shown that men are more susceptible to alcoholism after RYGB than women (35). A study conducted in Sweden from 2001 to 2010 showed a higher incidence of excessive use of alcohol and psychotropic substances in obese women preparing for bariatric surgery compared to normal-weight women. After surgery, the risk of worsening depression continued to increase with both sexes. Suicide attempts were significantly more common after RYGB than in non-obese patients (36). A sudden change in behavior followed by ophthalmoplegia and persistent vomiting was noted in the patient who was treated with RYGB after which he reduced body weight of 18 kg. It was found that the patient had Wernicke's encephalopathy due to the deficiency of thiamine that occurred after surgery, and was not adequately substituted. After parenteral administration of 500 mg of thiamine every 8 hours for three days, all symptoms were withdrawn (37).

When making a decision on surgical treatment of obesity, the consent of a multidisciplinary consilium is required to assess the patient's suitability for this type of therapy. The readiness of a patient to continue with regular controls after further bariatric surgery and further treatment at the reference center for the treatment of obesity is necessary for successful weight loss and prevention of chronic side effects.

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