GENERAL REVIEW

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Metabolic surgery and obesity related comorbidities

Metabolička hirurgija i komorbiditeti gojaznosti

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Introduction

Extreme obesity is associated with a lot of comorbidities like cardiovascular and cerebrovascular diseases, type 2 diabetes, gallstones, gastroesophageal reflux disease, malignancies, obstructive sleep apnea syndrome (OSAS), fatty liver disease, infertility, osteoarthritis, etc. These comorbidities significantly reduce quality of life and longevity. Extreme obesity shortens life expec-tancy by 8.9 years compared to the average life expectancy of 75 years. Middle aged with body mass index (BMI) 32 kg/m^2, compared to people with a BMI 24 kg/m^2 have 3 years less life expectancy [1].

Peripheral type of obesity is associated with peripheral venous stasis or thrombosis and degenerative diseases of the joints. Central or visceral obesity is accompanied by metabolic disorders and diseases arising from increased intra-abdominal pressure. Visceral obesity is often accompanied by insulin resistance with consequent disturbance of glucose control and type 2 diabetes, hepatic steatosis, non alcoholic fatty liver disease (NAFLD), hypertension, OSAS and polycystic ovary syndrome (PCOS) in women. The insulin resistance and chronic low-grade inflammation are the underlying mechanisms of most of comorbidities or perhaps, it is more proper to call them the complications of obesity [2–4].

Very early surgery attempt in order to control clinically severe obesity started in 1954. In 1991 the National Institutes of Health (NIH) Consensus Statement on Gastrointestinal Surgery for Severe Obesity officially designates surgery as a treatment of choice for patients with severe obesity. The introduction of laparoscopy in bariatric surgery increased the popularity of bariatric surgery among patients with morbid obesity. The desired effect of this therapeutic approach was excessive weight loss and significant reduction of comorbidities, primary the metabolic ones. This is the reason for increasing use of the term metabolic surgery instead of bariatric surgery, but the both terms are still in use equally [5, 6].

Diabetes remission after bariatric surgery

The risk of developing type 2 diabetes (T2DM) is exactly proportional to the increase of BMI and differs by gender. Specifically, women with BMI > 35kg/m^2 have a risk of diabetes 93.2%. That means that 9 out of 10 women with such BMI are likely to suffer from diabetes. In male population, the risk of diabetes in this BMI category is 42.1% [7]. A close connection between the risk of diabetes development and ethnicity is proven, regardless of BMI, so that the International Diabetes Federation (IDF) and World Health Organization (WHO) recommended specific reference values for the stages of obesity to different ethnic groups. The complexity of the epidemic of obesity and diabetes arises from many factors involved in both metabolic disorders, ranging from genetic factors, age of the mother, the microbiota in the intestine and epigenetic factors that affect fetus and newborn in the first few weeks of life. Insulin resistance is associated with impaired lipid oxidation in mitochondria, accumulation of lipid metabolites and inactivation of the insulin signal. Moderate weight loss in obese patients reduces the risk of diabetes by about 50%, with a favorable effect on the lipid status [8, 9]. Results of recently published Look AHEAD

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study [10] demonstrated significant improvement in glucose control in the group of obese patients with T2DM with lifestyle changes that included diet therapy and physical activity. During the study, body weight decreased by 8.6 % after one year in comparison with initial weight and reduction in body weight was sustainable for the next 4 years. Alternative treatment for obese patients with T2DM and poor glucose control with oral medications and with sufficient insulin secretion is electrical gastric stimulation. The gastric pacemaker is implanted laparoscopically into the abdominal cavity. Excessive weight loss (EWL) with this procedure is between 1.3% up to 40% during two years, with consequent significant improvement in glucose control measured by fasting glucose and glycosilated haemoglobin (HbA1c) [11]. In the mid-nineties, in the last century, Pories et al. [12] suggested a theory that type 2 diabetes is surgical disease, based on their surgical experience. The reason for this brave theory was the excellent results in diabetes management that were achieved after bariatric procedures [12].

Complete remission of T2DM after bariatric surgery was described in 78.1% of patients and improvement of diabetes in 86.6% patients and this percentages depend of type of surgery [13]. Data from National Database for the American Society for Metabolic and Bariatric Surgery (ASMBS) demonstrated that 12-month diabetes remission rates for BPD-DS (bilio-pancreatic diversion with duodenal switch) was 74%, for Roux-en-Y gastric bypass (RYGB) 62%, for sleeve gastrectomy (SG) 52% and 28% for adjustable gastric banding (AGB). Long-term diabetes remission rates after bariatric surgery have been reported in many observational studies like Swedish Obese Subjects Study (SOS study) [14]. The SOS study showed improvement in 30% of glucose control, lipids, blood pressure and decrease in mortality rate after bariatric surgery in comparison with 8.6 % in patients who introduced life style changes. Also, in 70% of patients, diabetes remission persisted for the next 3 years after bariatric surgery, and in about one third of patients for the next 10 years. STAMPEDE study [15], which compared 3 years of intensive medical treatment of type 2 diabetes obese patients who underwent bariatric surgery with patients on intensive medical therapy alone, demonstrated similar results. The patients with surgical treatment experienced better quality of life, more body weight loss and need less glucose lowering medications than non-surgical group. The sugested explanations for the observed changes may be: low-calorie diet (400–800 kcal/day in the first month after bariatric surgery) improves insulin sensitivity and β cell function; changes in gastrointestinal hormones secretion - glucagon-like-peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), peptide-YY (P-YY), oxyntomodulin (OXM) and ghrelin; β-cell function improvement; improvement in insulin sensitivity changes in enterohepatic recirculation of bile acids and gut microbiota changes [16–18]. Diabetes remission score (DRS) can be used in order to predict the postoperative diabetes remission and select a type of surgical procedure. This score includes the age of the patient, BMI, duration of diabetes, micro or macrovascular complications, insulin use and C peptide level. Lower DRS indicates better chance for diabetes remission [19]. Very early application of bariatric surgery in the course of T2DM was recently suggested on the basis of the facts that the best diabetes remission rates were accomplished among the patients with recent onset of T2DM and among the patients with initial macro- and microvascular complications. Contrary to these, it was shown that end-stage chronic vascular complications could be worsened after bariatric surgery [20]. Accumulated experience gave evidence for the role of metabolic/bariatric surgery in the treatment of diabetes in obese patients. Consensus guideline that define the position of metabolic surgery in algorhythm for treatment of T2DM was developed during the 2nd Diabetes Sugery Summit in 2015, where 48 international clinicians and diabetes organizations concluded that metabolic surgery should be recommended for T2DM patients with BMI > 40 kg/m^2 as well as for those with BMI 35–39.9 kg/m^2 in whom previous therapy with changes of their lifestyle and medical treatment failed. In comparison with the European guidelines for bariatric surgery the only difference refers for the category of BMI 30.0–34.9 kg/m^2 (for Asians 2.5 kg/m^2 less) which now becames the indication for metabolic surgery if previous medical treatment of diabetes failed [21].

Non-alcoholic fatty liver disease and obesity

Non-alcoholic fatty liver disease is a progressive liver disease that starts with steatosis, continues with fibrosis and ultimately ends in cirrhosis. Underlying mechanism in NAFLD is insulin resistance and strong correlation was found between intrahepatic triglyceride deposition and BMI, waist circumference, alanine aminotransferase (ALT) and aspartate minotransferase (AST) levels, insulin level and blood pressure. NAFLD is a hepatic component of metabolic syndrome and is in close association with visceral obesity and T2DM. Dietary habits with high energetic meals with low ingestion of dietary fibers and sedentary lifestyle dramatically increase incidence of NAFLD. It was sugested that in the future NAFLD will be the main indication for liver transplantation [22]. In obese persons with decreased physical activity, low level of irisin could be a connection between insulin resistance and fatty liver. Irisin works as a signal transmitter between muscles and fat tissue by activation of mitochondria and expression of uncopling protein 1 (UCP-1) [23].

Bariatric surgery has beneficial effects on insulin resistance, lipid profile, inflammation and adipokines involved in the pathophysiology of NAFLD, and has positive effect on histological and biochemical parameters of NAFLD. A significant drop in blood transaminase levels was demonstrated by meta-analysis of studies for different methods of bariatric surgery (RYGB, SG and AGB). Improvement in insulin resistance and liver lipid content after RYGB occurred before a significant body weight loss, probably due to weight reduction independent mechanisms [24, 25].

It was described that patients with non alcoholic steato hepatitis (NASH), who under-went bariatric surgery, have a greater risk of death compared with patients without NASH during a follow-up of 10.2 years after bariatric surgery. There are 32 genes which may help to identify patients with NASH with potential shorter survival time after bariatric surgery [26, 27].

Obstructive "sleep apnea" syndrome and bariatric procedures

In obese people high intraabdominal pressure causes hypoventilation, interruptions of breathing during the sleep OSAS, pseudotumor of brain (idiopathic intracranial hypertension), gastroesophageal reflux disease (GERD) and urinary incontinence. The shortening of sleep (on average less than 7 hours a day), reduced energy expenditure, the use of drugs for the treatment of mental illnesses, autoimmune and chronic inflammatory diseases contribute to increase in body weight [28, 29]. Possible mechanisms for interaction between the "sleep apnea" and obesity are increased sympathetic activity due to interrupted sleep, reduced consumption of glucose in the brain, and increased levels of cortisol and growth hormone. These mechanisms impair neuroendocrine control of appetite which results in a further increase in body weight. OSAS increases 4 to 6-fold risk of death early in the morning [30]. Criteria for OSAS are apnea-hypopnea index (AHI) ≥ 15 during one hour or ≥ 5 and ≤ 14 during one hour with information of sleepiness during the day, mood changes, ischemic heart disease, hypertension or previously stroke. Weight reduction significantly decreases number of apnea episodes [31, 32].

Previous studies demonstrated that weight reduction after bariatric surgery significantly improves OSAS in approximately 75% of patients. Moderate to severe OSAS persists in 25% patients after RYGB. Predictive factor for the persistent OSAS were EWL after surgery less than 60%, preoperative AHI ≥ 30/hr, hypertension and patients with ≥ 50 years of age [33].

The systemic analyses of 22 related articles demonstrated that the combined restrictive-malabsorptive procedures like R-en-Y gastric bypass and biliopancreatic diversion with duo-denal switch are more efficient in all aspects of OSAS than pure restrictive procedures like sleeve gastrectomy or adjustable gastric banding. OSAS improvement was associated with decrease of the neck circumference after bariatric surgery. Also, after bariatric surgery the quality of sleep was better and rapid eye movement (REM) phase was longer [34].

Hypertension after bariatric surgery

High blood pressure in obesity may results from direct compression of fat tissue on kidney, increased pressure in kidney blood vessels and increased intrathoracic pressure [35]. Obese women with idiopathic intracranial hypertension, which is common finding in the extreme obesity, have increased intrathoracic pressure [28]. High intrathoracic pressure compromises blood flow, decreases the amount of blood from left ventricle to aorta and activates renin-angiotensin-aldosterone system which leads to blood vessels constriction and water retention in the body. Increased pressure in the renal veins can lead to glomerulopathy with following proteinuria [35].

Inflammatory cytokines from adipocytes, even in reference range have an impact on endo-thelial function. Obesity affects the morphology and function of the heart muscle which is associated with coronary heart disease and sudden cardiac death. The accumulation of body fat between muscle fibers and degeneration of myocytes (adipositas cordis) through lipotoxicity leads to cardiomyopathy. Heart failure in obesity is a result of the left ventricle hypertrophy, diastolic dysfunction, increased blood volume and increased ejection fraction [36]. Blood pressure is normalized in 60% of patients after RYGB. There is a difference in hypertension remission rate between the RYGB, SG and AGB. After RYGB, 63.6% of patients have hypertension remission, and after AGB, remission occurred in 34.8% of patients. The lowest remission rate of 14.3% was in the group of patients after sleeve gastrectomy [36]. One year after biliopancreatic diversion almost half of the patients experienced remission of hypertension and further 10% also become normotensive in the next 3 years. Some authors demonstrated that antihypertensive drugs were discontinued within the first year of bariatric operations in 58% of patients after RYGB and in 54% of patients after gastric banding. In the meantime, antihypertensive drugs were stopped only in 13% of patients after life style changes. In another investigation favourable effect of biliopancreatic diversion (BPD) on blood pressure was proven. After BPD, blood pressure was normalized and antihypertensive drugs were discontinued in 85% of patients, at least two years after operation [36–39]. Possible epigenetic mechanism for hypertension remission after bariatric/metabolic surgery, independent of age and sex is hypometylation of CpG sites six months after RYGB. CpG sites (cg00875989, cg09134341) were metylated in obese patients before the surgical treatment and were associated with hypertension [40].

Female reproductive function after bariatric surgery

Obesity has impact on almost every aspect of female reproductive system. The most common endocrine disorder in obese women is polycystic ovary syndrome (PCOS). PCOS is associated with metabolic diseases like diabetes, hypertension, hyperlipidemia and metabolic syndrome. Almost 60% women with PCOS are obese [41]. The exact pathogenetic mechanism for obesity in PCOS is still unclear. Some investigations described the differences in neuro-peptide Y and ghrelin levels between the obese women with PCOS in comparison with the obese women without PCOS [42].

On the other hand, it is known that visceral obesity is associated with low levels of sex hormone-binding globulin (SHBG) and elevated free estrogen levels. The lower level of SHBG results in elevated total testosterone level. Elevated free estrogen level through hypothalamo-pituitary-gonadal axis leads to suppression of gonadotropin relasing hormone (GnRH) secretion. Menstrual irregularity, anovulatory menstrual cycles and polycystic ovary syndrome may appear as a result of potentiation of negative feedback with GnRH suppression. Risk for anovulation increases with higher BMI [43].

Weight reduction following bariatric surgery is the most efficient method for PCOS management with improvement in a few endocrine aspects. In a retrospective study that analyses the effect of bariatric surgery on PCOS symptoms, it was for demonstrated that 82% of patients have improved

menstrual irregularity, hirsutism was improved in one third of patients and 77.8% of patients with diabetes achieved complete diabetes remission. Pregnancy occurred in all pregnancy desiring patients within 3 years after bariatric surgery. In meta-analysis it was confirmed that PCOS prevalence decreased from 45.6% to 6.8% ,12 months after bariatric surgery [44, 45]. Abnormal eating habits due to high level of allopregnenolone is one of the common disturbances in PCOS. Six months after RYGB, total testosterone, SHBG and progesterone decreased while estrogen levels increased. Also, restoration of preovulatory peak of follicle-stimulating hormone (FSH) and (LH) occured, FSH/LH relation became normal, fertile capability increased and overeating dis-appear due to decreased allopregnenolone synthesis [46].

Positive effect of bariatric surgery is a lower risk of macrosomia while negative effects are higher risk for maternal anemia and low birth-weight of newborns [47]. Bariatric surgery should be considered in preconception period in women with BMI $\geq$ 35 kg/m^2 with comorbidities or in women with BMI $\geq$ 40 kg/m^2 in order to prevent delivery maternal and fetal complications among these high risk pregnancies [48]. AGB is a minimaly invasive method with the lowest rate of complications, with relatively good effect on weight reduction and excessive vomiting in pregnancy. Retrospective studies confirmed a lack of differences between pregnancy outcomes in pregnancies that occurred within a first year after AGB application and those that happened more than 12 months after AGB application [49–50]. Bariatric surgery decreased risk for hypertensive disorders in pregnancy from 15% to 3%. Pharmacoeconomic studies based on meta-analyses, carried out by seven insurance companies, indicated that bariatric surgery could reduce neonatal costs associated with hypertension, preeclampsia and eclampsia [51, 52]. Pregnancy is not recommended at least one year after bariatric surgery due to possible nutritional deficiency in a period of the greatest weight loss. However, study of 489 women who became pregnant after bariatric surgery demonstrated lack of difference in pregnancy outcome, maternal complications and newborn outcomes between the women who concieved within one year after bariatric surgery and those who became pregnant more than one year after surgery [53].

Obesity related malignancies after bariatric surgery

World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) published the studies that indicated the relation between fat mass accumulation and esophageal adenocarcinoma, carcinoma of pancreas, large bowel, breast, kidney, gallbladder, and en-dometrial carcinoma. Several studies indicate a link between obesity and prostate cancer, ovarian cancer and non-Hodgkin lymphoma [54]. It was shown that the increase in BMI of 5 kg/m^2 increases relative risk (RR) to 1.5 ($p < 0.001$) for esophageal cancer in both sexes as well as endometrial and gallbladder carcinoma in female; increases RR to 1.3 for thyroid cancer in male and kidney cancer in female and increases RR to 1.2 for large bowel cancer in male. RR for melanoma and rectal carcinoma in male is higher than 1.2, as well as for postmenopausal breast cancer, thyroid and pancreatic cancer in females. In both sexes obesity was associated with higher risk for lymphoma and leukemia [55].

There are multiple links between obesity and malignancy with different mediators like growth factors, hormones, cytokines, and inflammation factors. Factors which are released during inflammation as tumor necrosis factor (TNF) alpha and interleukin (IL)-6 impair cell membrane facilitating low-density lipoprotein (LDL) deposition in blood vessels wall and accelerating the atherosclerosis. Proinflammatory cytokines become dominant in comparison to anti-inflammatory cytokines in obese subjects. This phenomenon is responsible for incapability for recognition and elimination of malignant cells and also, allows the unimpeded development of neoplasms of bowel, pancreas, breast, liver, endometrium and prostate [56, 57].

Weight reduction after bariatric surgery lowers symptoms of GERD and the risk for esophageal carcinoma. Bariatric surgery is highly recommendable treatment for GERD in obese patients. Improvement of symptoms depends on a type of bariatric procedures. RYGB is the most potent bariatric procedure in relation to symptoms of GERD. However, there is not enough literature data on the course of Barrett's disease after bariatric surgery [58]. Some of bariatric procedures like SG have undesirable effects on esophagogastric motility due to increased intragastric pressure. Esophageal dysmotility and symptoms of gastroesophageal reflux were frequent after SG [59]. In order to prevent worsening of GERD after SG, some authors recommended gastropexy to the preaortic fascia as a possible antireflux technique in combination with SG [60].

Recently, it has been suggested that bariatric/metabolic surgery reduces cancer risk from 40% to 50%. An analysis in large tertiary bariatric surgery center that retrospectively included 2943 patients with no history of cancer at the time of RYGB, indicated that 48 months after performed surgery patients that developed organ cancer achieved less weight loss, so that authors concluded that greater weight loss after metabolic surgery may be associated with lower organ cancer risk [61]. Systematic review and meta-analysis of four studies revealed that bariatric surgery was associated with significantly lower colorectal cancer incidence (RR = 0.73) when compared with obese non-operated individuals. Authors concluded that bariatric surgery was associated with a 27% of lower colorectal carcinoma risk [62]. Risk for malignincies after bariatric procedures decreased more in female than in male population [56]. Among the key results from the Swedish Obese Subjects (SOS) trial, a prospective controlled intervention study of bariatric surgery, a decreased incidence of cancer was found (women: adjusted hazard ratio 0.58, $p = 0.008$; men: n.s.) [63].

Conclusion

After few decades of experience in surgical treatment of obesity, bariatric or metabolic surgery becomes powerful approach to management of excessive body weight as well as different obesity related comorbidities which significantly

reduce quality of life and longevity among obese patients. High potential impact and cost effectiveness of some bariatric operations on metabolic comorbidities classify surgical treatment of obesity at the very high position and confirm that the term metabolic is more appropriate than bariatric surgery. Further investigations and meta-analyses are necessary for defining long-term effects and possible side effects of bariatric/metabolic surgery.

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