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The obesity in kidney transplantation candidates – methods of treatment

Otyłość w przewlekłej chorobie nerek a transplantacja nerki – metody leczenia

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S u m m a r y

The epidemic of morbid obesity is becoming more likely in patients with chronic kidney disease, worsening the control of comorbid conditions and total cardiovascular risk. Furthermore, it delays or makes the kidney transplantation impossible and sometimes even bypasses obese candidate when the organ becomes available. Most surgical centers consider transplantation if BMI does not exceed 35 kg/m^2. The patients with BMI > 35 kg/m^2 are at great risk of perioperative and postoperative complications and are usually disqualified. Although overweight and obese, dialysed patients have lower general mortality compared to normal weight (reverse epidemiology paradox), kidney transplantation is still a treatment of choice for them. The conservative methods of weight loss fail in many cases. Pharmacological treatment is contraindicated in CKD. The alternative for these patients is bariatric surgery – with acceptable risk of complications and higher rates of successful and permanent weight loss. After the bariatric procedure the malabsorption of immunosupresive drugs occurs and the doses regimen should be individual and well controlled.

S t r e s z c z e n i e

Epidemia patologicznej otyłości coraz częściej dotyczy pacjentów z przewlekłą chorobą nerek, utrudniając leczenie chorób towarzyszących, zwiększając ryzyko sercowo-naczyniowe i opóźniając lub uniemożliwiając kwalifikację do przeszczepienia nerki. W większości ośrodków chirurgii transplantacyjnej warunkiem przeszczepienia nerki jest BMI pacjenta nie przekraczające 35 kg/m^2. Chorzy z BMI > 35 kg/m^2 są obarczeni znacznie większym ryzykiem powikłań okołooperacyjnych i pooperacyjnych, co często staje sie powodem ich dyskwalifikacji z zabiegu. Pacjenci z nadwagą i otyli poddawani hemodializie charakteryzują się niższą ogólną śmiertelnością (odwrócona epidemiologia), jednak przeszczepienie nerki powinno być u nich również postepowaniem z wyboru. Zachowawcze metody obniżania masy ciała w wielu przypadkach okazują się nieskuteczne. Leczenie farmakologiczne jest przeciwwskazane w przewlekłej chorobie nerek. Alternatywą jest leczenie bariatryczne – z akceptowalnym ryzykiem powikłań i gwarancją utrzymania efektu. Zabiegi bariatryczne powodują zaburzenia wchłaniania leków immunosupresyjnych, co wymaga indywidualizacji leczenia i systematycznej kontroli.

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INTRODUCTION

The overweight and obesity are chronic metabolic disorders resulting from an excessive food caloric intake in relation to energy demands and lack of physical activity, which causes a positive caloric balance. As a consequence of overnutrition the extra calories are accumulated as body fat to the extent that it may have serious adverse effects on someones health. The most common and practical way of assessment the nutritional status is calculating the body mass index (BMI), also called the Quetelet's Index. It is measured by dividing a weight in kilograms by height in square meters. If BMI exceeds 30 kg/m^2, a person is considered obese. The standard World Health Organization (WHO) definition from 1997 distinguished four levels of obesity. The first one is called moderate, second – severe, third – pathological, which is a life threating condition requiring medical intervention and may be an indication for bariatric surgery and the last one fourth level named superobesity. The levels of obesity and indicating BMI values are shown in table 1.

Table 1. The levels of obesity and indicating BMI values.

Level	BMI (kg/m^2)	Obesity
1	30-34.9	moderate
2	35-39.9	severe
3	> 40	pathological
4	> 50	superobesity

The importance of pathology is also fat distribution around the body. A special type is visceral obesity, which was differentiated by WHO due to connection with certain illnesses. In this type of obesity intra-abdominal adipose tissue is stored between internal organs in the peritoneal space. Because of constant hormonal and metabolic activity it highly correlates with developing cardiovascular diseases, increased risk of diabetes and malignancy. It is usually called central obesity due to significant abdominal protrusion in opposite to weight accumulation around the hips. The prevalence is higher in males. It is recognized using waist-hip ratio (WHR) (tab. 2).

Table 2. The WHR values of viscelar obesity.

Gender	Viscelar obesity
Female	WHR ≥ 0.8 or > 80 cm in waist circumference
Male	WHR ≥ 1 or > 94 cm in waist circumference

EPIDEMIOLOGY

An optimal body weight is multifactorial equation. It depends on age, gender, genetic susceptibility, comorbidities, sedentary lifestyle and dietary habits. The last two factors have the crucial meaning in obesity epidemic that affects western civilization. Obesity is the leading preventable cause of death worldwide causing 300 000 deaths each year, which can be up to twelve times higher than in communication accidents and ten times than in age-related population. In 1997 WHO recognized obesity as the global epidemic. Nowadays it affects 20% of world population and is considered a disease of affluence. During the last 20 years it's prevalence increased by 50%. Including, it relates to over 1.1 million people. According to WHO data in 2015 there will be about 700 million people with BMI over 30 kg/m^2. In Poland the occurrence of pathological obesity is also still increasing and reached 18%. It is more common in females (2.2%) than in males (0.6%). In the USA it affects 5% of adults. The women in the age between 20 and 30 who achieved BMI > 45 kg/m^2 have the reduction of life- span of 8 year and men of 13 years than in general population (1, 2).

THE ROLE OF OBESITY IN CKD DEVELOPMENT

The obesity is an independent risk factor of CKD development, which in overweight patients is 40% and in obese 85% higher than in healthy controls. The initial kidney injury is caused by hyperfiltration, with time leading to proteinuria and glomerulosclerosis. The obesity involves blood pressure rise in response to compensation the decrease of renal plasma flow, increases the tubular sodium reabsorption, activates renin-angiotensin-aldosteron (RAA) system and stimulates renal sympathetic nerves. The metabolic and hormonal activity of visceral adipose tissue is considered to have an important role in pathogenesis of renal function disorder. Leptin increases tubular sodium reabsorption and influencing on tumor growth factor-β (TGF-β) and collagen type IV synthesis stimulates endothelial hyperplasia in the glomeruli. The adipose tissue secretes also proinflammatory cytokines and interleukins both aggravating fibrosis and proliferation. The glomerular disorder secondary to obesity has been termed in the literature as obesity related glomerulopathy (ORG). Its histological features are similar to that seen in focal segmental glomerular sclerosis (FSGS) with marked glomerular enlargement but lower podocytes foot-process seizure. Obesity associated conditions such as diabetes, hypertension, chronic heart failure, dyslipidemia significantly increase the risk of CKD occurrence. The more components of metabolic syndrome are present, the higher risk of CKD development is obtained (3).

THE BODY MASS AND RENAL REPLACEMENT THERAPY

Among the patients on renal replacement therapy, especially on haemodialysis the most common nutritional disorder is a protein-caloric malnutrition. MIA syndrome (malnutrition-inflammation-atherosclerosis) – a specific form of malnutrition in haemodialysed patients is associated with significantly increased mortality due to cardiovascular complications. The present recommendations for hemodialysed patients suggest increase in caloric intake up to 30-35 kcal/kg/day and protein up to 1.4 g/kg/day. Even if the recommendations are implemented the anthropometric features deteriorate within long term treatment. On the other hand reverse epidemiology paradox is documented on haemodialysis, which shows that patients with BMI > 27.5 kg/m^2 live twice as long as patients with normal BMI values. The reason of this phenomenon is seen in the coexistence of malnutrition and chronic inflammatory state.

THE OBESE CANDIDAT FOR A KIDNEY TRANSPLANT

Considering an increasing trend in prevalence of obesity in the industrialized countries, CKD as a common complication of obesity, diabetes as one of the leading causes of CKD and broad administration of steroid therapy in autoimmune diseases involving kidneys the number of obese patients started renal replacement therapy is markedly higher. This situation and reverse epidemiology paradox rise a question – do we need to treat obese patients that undergo renal replacement therapy? Is kidney transplantation an option for an obese dialysed patient? Most studies indicate that although overweight and obese dialysed patients have lower general mortality compared to normal weight, kidney transplantation is still a treatment

of choice for them. It significantly improves survival rate, the comfort of life and is economically justified. Unfortunately obese patients have higher complication risk and worse long term outcome after kidney transplantation than non-obese transplanted. Most surgical centers consider transplantation if BMI does not exceed 35 kg/m^2. The patients with BMI > 35 kg/m^2 are at great risk of perioperative and postoperative complications and are usually disqualified. Moderately obese patients have prolonged waiting time and are sometimes bypassed if the organ becomes available. Latest studies show that the likelihood of receiving a graft decreases within increasing degree of obesity. Obese graft recipients have increased surgical and medical complication rate, worse long time outcome and higher risk of graft loss. Surgery in obese patients involves high complication rate during the first 30 days post-operation mainly because of technical difficulties during the surgery, prolonged time of the procedure, high risk of wound complication, infections, urological disorders. The delayed graft function (DGF) is more frequent among obese allograft recipients probably because of perioperative difficulties and prolonged cold ischemia time (CIT). Additionally the risk of other medical complications (pulmonary, cardiac, gastrointestinal), the mean length of hospitalization and risk of admission to intensive care units is increased among obese comparing to non-obese renal recipients. The prevalence of post-transplant diabetes and further weight gain is also higher in obese patients. For that reasons is worth to lose the weight before the operation (3-5).

The latest recommendations indicate initial non-pharmacological, conservative management of obesity. It should involve clues used for general population, beginning with setting an achievable aim, for example loss of 5-10% body mass during 3-6 months. The obtaining of negative net caloric balance is crucial – mostly by decrease in total caloric uptake with simultaneous increase in energy expenditure. It involves lifestyle and behavioral modifications and increase in physical activity (30-60 minutes of varied intensity exercises every day most days of the week). The pharmacological intervention should be considered after failure of conservative treatment. The drug options including orlistat, sibutramine and rimonabant used widely in obesity treatment have many limitations in CKD patients. Orilstat may lead to increase in oxalate urine concentration leading to oxalate nephropathy. Additionally it interacts with cyclosporin a decreasing its plasma concentration. Sibutramine causes blood pressure elevation, tachycardia, hypokalemia and QT interval increase. It is contraindicated in diabetic patients. One of the main contraindications for rimonabant is kidney disease (6-9).

Case 1

66-year old patient with diabetic kidney disease in 5th stage, hemodialysed for 5 months, suffered from diabetic neuropathy, Charcot's osteoarthropathy, hypertension, stable ischemic heart disease and obesity (weight 132 kg, BMI 42 kg/m^2), with daily insulin demand > 70 IU. The reduction of body mass eligible him for kidney transplantation was 30 kg. The aim was to obtain the BMI of 32 kg/m^2. The physical exercises were rather impossible due to Charcot's foot. Following present clues the purpose was to lose 10% of total body mass during 6 months. Total caloric expenditure should achieve 24 000 kcal/year, 18 500 kcal/month, 2600 kcal/week and 400 kcal/day. The aim should be reached in less than 13 months. After 5 months the patients weight was 132 kg despite the education and constant motivation.

Due to many comorbid conditions associated with obesity conservative treatment in many cases is ineffective and pharmacological intervention contraindicated. The alternative option is bariatric surgery. The classic indications for bariatric surgery are: BMI ≥ 40 kg/m^2 or BMI 35-40 kg/m^2 with comorbidities that may improve after the procedure (diabetes, hypertension, chronic heart failure). The BMI value qualificating for bariatric surgery may be actual or past, but well documented in patients health history (patients who lost some weight on conservative management but not achieved BMI needful for kidney transplantation). The one necessary condition that must be met prior to the bariatric procedures is failure of conservative treatment or inability of maintaining weight loss despite the proper management. The patients must also accept necessary follow-up visits and dietary postoperative guidelines (3).

TYPES OF BARIATRIC PROCEDURES

The procedures are grouped into the three categories: predominantly restrictive, predominantly malabsorptive and mixed. The first group of procedures act to reduce food intake by limiting gastric volume. They are technically uncomplicated, short to perform and have less adverse effects like malabsorbtion and secondary malnutrition than other types of operations. Unfortunately the weight loss is temporary especially among patients consuming sweets and sweet drinks.

The restrictive procedures include laparoscopic adjustable gastric binding (LAGB) and laparoscopic sleeve gastrectomy (LSG). LAGB is second to Roux-en-Y Gastric Binding (RYGB) most popular bariatric procedure performed in the world. The stomach restriction is created using silicon band, which is adjustable by adding or removing saline through the port placed under the skin. Its main advantage is simple technique, low mortality rate, maintaining natural continuity of gastrointestinal tract and no anastomosis. The complications include gastro-esophageal reflux disease, vomiting, band displacement and enlargement of the pregastric pouch (10).

LSG is a procedure in which a large portion of the stomach is surgicaly resected leaving 15-20% of its original size. The remaining part forms a sleeve like pouch (100-150 ml) and intact pylorus. Originally LSG was the first step in two-steps bariatric procedure performend on morbidly obese patients that had contraindications to mixed or classic malabsorptive procedures.

The second group of procedures is effective through creating a physiological condition of malabsorption. It consist of following operations: biliopancreatic diversion – BPD and biliopancreatic diversion with duodenal switch – BPD-DS). They are often complicated by malnutrition therefore oral supplementation of vitamins and microelements is required. They are technically more challenging, take longer to complete and they have more adverse effects. The have positive metabolic effect (improved control of diabetes) by aversive effect to carbohydrate rich meals.

Roux-an-Y Gastric Binding is the most common mixed bariatric procedure. In described operation a small (15-20 ml) stomach pouch is created with a stapler device and connected to the distal small intestine (nutritional part). The remaining stomach part, the duodenum and upper part of the small intestine (60-100 cm) is then reattached in a Y-shaped configuration (enzymatic part) and connected to nutritional part 100 cm from the pouch allowing effective digestion and absorption. The advantages of this method are: significant and long-term weight loss even among patients consuming high energy snacks and drinks, elimination of esophageal reflux and metabolic effect of malabsorptive procedures. The complication include malnutrition (low risk), ulcerations in jejunal anastomosis, restricted access to distal part of the stomach (diagnostic) and risk of dumping syndrome. Often RYGB is performed after LSG.

The effectiveness of the procedure is measured by percentage of excess weight loss (%EWL) in long-term observation. The successful treatment obtain > 50% EWL in long-term follow up. The mean EWL for RYGB is > 60%, for LAGB > 46% and for LSG ~ 60%. The weight loss after RYGB is usually permanent (EWL 62-69%). The long-term weight loss after LAGB is ineffective (< 50%) with high rate of reoperation and complications (11-13).

The bariatric treatment improves the course of many comorbidities. The metabolic effect of malabsorptive procedures perform a better control of hypertension and diabetes (improves glycemic control and decreases daily insulin and medicines requirement). Additionally weight reduction after bariatric treatment improves all elements of metabolic syndrome, obturative sleep apnea, reflux disease, hepatic steatosis, gout and infertility. Also weight reduction decreases the risk of deep vein thrombosis and cerebral infarct. After the malabsorptive operation low caloric diet is advised with 1-1.5 g/kg/day of protein intake and supplementation of calcium (1500-2400 mg), vitamin B group (mainly vit. B_{12} ~ 1000 mg), vitamin D_3 (400-800 IU) and iron (27-100 mg) (3).

The complication rate after the bariatric treatment reaches 20% in general population. The mortality rate 30 days after the procedure is one of the lowest in surgery and achieve 0.2-0.5%. The main cause of death is pulmonary embolism. A lot of centers does not reveal fatal outcomes, but others have mortality rate expanding from 2-4%. The perioperative mortality rate in CKD patients is higher and reaches 3.5%. Therefore the statistics seem to depend mainly on the center experience. In CKD patients bariatric treatment prior to transplantation has better outcome mainly due to increased infection rate in immunocompromised patients. The EWL in this group is permanent and expanding from 31 to 61% (7, 11-13).

Case 2

24-year old patient with ESRD in the course of systemic lupus erythematosus (SLE), with antifospholipid syndrome, iatrogenic Cushing syndrome, hypertension and obesity with BMI 41.5 kg/m^2 (initial), hemodialysed for 12 months, with unsuccessful weight loss despite proper conservative treatment. Patient was qualified for bariatric treatment – LSG was performed. During the perioperative period there were no complications. The long-term effect was satisfactory with weight loss of 47 kg (> 90%EWL). The patient developed burning sensation in the epigastric region. After endoscopic examination reflux disease was diagnosed. Despite the conservative treatment the following endoscopic examinations revealed progression of the disease (in the last examination the lesions affected most of the esophagus). After surgical consultation the patient was qualified for RYGB to eliminate esophageal reflux. One of disadvantages of this procedure is malabsorption of immunosupressive drugs.

IMMUNOSUPPRESSION AFTER BARIATRIC PROCEDURES

Tacrolimus (Tac) is a highly lipophilic substance. The majority of its absorption after oral administration occurs in proximal duodenum. This is also the primary site of intestinal metabolism of the drug by the cytochrome CYP3A4/5. Additionally its metabolite concentration is highest in duodenum and proximal part of jejunum. It is excreted via gastrointestinal tract. Sirolimus (Sir) pharmacokinetics and absorption site is very similar to tacrolimus. Mycophenolate mofetil (MMF) is a pro-drug primarily absorbed in the stomach and metabolized to its active form mycophenolic acid (MPA) by plasma esterases. MPA is then metabolized to its inactive form – mycophenolic acid glucuronide (MPAG) in the liver, kidneys and gastrointestinal tract. MMF has unique pharmacokinetics – it demonstrates two peaks in plasma concentration (the second peak is thought to be a result of enterohepatic recirculation of MPAG back to MPA). The malabsorption of the immunosuppressive drugs occurs most frequently after RYGB due to increase in gastric pH and decrease in drug absorption area. Recent studies indicate that maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax) and area under maximum plasma concentration versus time curve (AUC) has significant differences comparing to general population (no bariatric treatment). Significant inter-patient variability in these parameters was observed for each drug. Higher doses of Tac and Sir are required to reach similar exposure. Requirement for MMF is inter-patient variable. Cyclosporin

a requires 33% dose increase. Currently there are no reliable data regarding MMF pharmacokintetic differences after RYGB. It is likely to assume that malabsorption of MMF will occur, and individual dose regimen should be set for patients after LSG and RYGB. The drug monitoring should also be obligatory.

CONCLUSIONS

The procedures causing decrease in body mass in obese patients with CKD allow to qualify them to kidney transplantation, reduce the waiting time, improve the general outcome and allograft survival. The failure of conservative treatment should indicate that bariatric procedure should may be considered. The total risk of bariatric treatment in CKD patients in some centers is similar to that in general population. After the operation procedure individual dose regimen must be established because of malabsorption of immunosupresive drugs (3, 14).

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