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EFFICACY OF SURGICAL TECHNIQUES FOR MORBID OBESITY AND THEIR POTENTIALS IN END-STAGE RENAL DISEASE IN PREPARATION FOR KIDNEY TRANSPLANTATION

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Obesity is a modern "epidemic" not only in the general population but also among patients with end-stage renal disease (ESRD) who require kidney transplantation (KTx). The objective of this literature review is to analyze global studies on surgical methods of treating morbid obesity and their potentials in ESRD patients in preparation for KTx.

Keywords: morbid obesity, kidney transplantation, bariatric surgery.

The World Health Organization defines obesity as abnormal or excessive fat accumulation that presents a risk to health. It is classified based on the body mass index (BMI), the ratio of body weight to height: 30.0 to 34.9 kg/m^2 (class I obesity), 35.0 to 39.9 kg/m^2 (class 2 obesity), and ≥40 kg/m^2 (class 3 obesity). Over the past three decades, the number of overweight (BMI ≥25 kg/m^2) and obese (BMI ≥30 kg/m^2) adults worldwide has increased substantially [1]. The BMI classification, although an imperfect tool for defining obesity, is currently the most widely used in clinical practice [2]. BMI's limitation is due to the fact that important demographic data of patients are not considered, such as age and ethnicity, percentage and composition (subcutaneous or visceral) of adipose tissue and muscle mass [3, 4]. Despite these limitations, it is likely that BMI will continue to be used as part of the diagnosis in kidney transplant candidate selection. It is easily calculated from weight and height, can be easily recorded and tracked over time, is well established in clinical practice, and is by far the most widely used anthropometric measure of body weight [5].

In fact, obesity is an independent risk factor for chronic kidney disease (CKD). Arterial hypertension and diabetes mellitus, the two most frequent comorbidities associated with obesity, may be a major cause of kidney failure and pose a major challenge for candidate selection, waiting list management and prediction of pre- and post-transplant outcomes [6, 7]. The relationship between increased body weight and ESRD is complex and paradoxical. Given the evidence of extremely adverse effects of obesity on various pathological processes, it seems paradoxical that obesity is persistently associated with lower mortality in patients with severe CKD and ESRD. At least some of the beneficial effects associated with increased BMI have been shown to be down to the presence of higher muscle mass. However, there is evidence to suggest that increased adipose tissue, especially subcutaneous (nonvisceral) tissue, may also be associated with better patient outcomes. In this regard, dietary protein-energy restriction efforts may lead to increased mortality, which should be considered in the management of potential kidney transplant recipients.

BMI ≥35 is generally considered to be a relative contraindication to KTx because of adverse outcomes, including postoperative complications, higher rates of new-onset diabetes after transplantation (NODAT), delayed graft function and/or receipt of a primary nonfunctioning graft [8]. Obese patients on hemodialysis are excluded from the waiting list despite therapeutic possibility of reducing body weight; there is limited possibility of performing a kidney transplant and living a full life [9].

SHORT-TERM AND LONG-TERM CLINICAL AND SURGICAL OUTCOMES OF KIDNEY TRANSPLANTATION IN OVERWEIGHT PATIENTS

KTx improves survival in obese recipients compared to treatment with long-term hemodialysis. However, overweight in renal transplant recipients is accompanied by increased incidence of delayed function and acute rejection, risk of graft loss, surgical complications and prolonged hospitalization [2, 10].

In a 2014 meta-analysis, **Nicoletto et al.** analyzed the results of studies on obese and nonobese patients who underwent KTx and evaluated the following outcomes – delayed graft function, acute rejection, graft and patient survival at 1 or 5 years after transplantation, and death by cardiovascular disease. Twenty-one studies involv-

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ing 9,296 patients were analyzed. It was concluded that pre-transplant obesity was associated with a relative risk of delayed graft function. However, no association was found between obesity and acute graft rejection [11]. The authors report that possible explanations for this distribution may be related to major changes and advances in immunosuppressive therapy along with improved surgical and clinical management of obese patients and prevention of their complications (e.g., hypertension, cardiovascular disease, diabetes, etc.).

In another meta-analysis, **Lafranca et al.** included 56 studies and 5,526 patients who were divided into those with high BMI (>30 kg/m^2) and low BMI (<30 kg/m^2). The main outcomes analyzed were survival (patient survival, graft survival, mortality), kidney function outcomes (delayed graft function and acute rejection) and metabolic conditions (new-onset post-transplant diabetes and hypertension). Other outcomes were related to infection and surgery (length of surgery, length of hospital stay, wound infection, incisional hernia, wound dilation, and other side effects). This latter group is of particular interest because the study showed more surgical complications in obese patients than in non-obese patients [2]. Renal transplant recipients with a BMI >30 kg/m^2 had worse 3-year graft and patient survival. The deleterious effect of higher BMI on renal function was also manifested in the fact that the incidence of delayed graft function and acute rejection was higher in patients with a higher BMI [12]. The incidence of new onset diabetes and high blood pressure was higher in obese patients. Finally, with regard to surgical outcomes, patients with low BMI show significantly fewer complications; the only exceptions are lymphocele and hematomas – perhaps because these two conditions are not necessarily dependent on BMI, as the authors themselves observed. Nevertheless, despite worse results in patients with high BMI, transplantation remains the most effective approach in patients with CKD, but weight loss before transplantation should be recommended [2].

Naik et al. conducted a retrospective analysis in 2016 to investigate the effect of obesity on allograft survival in first-time kidney transplant recipients [13]. The results showed an independent stepwise association between higher BMI and cumulative incidence of dysfunction and overall graft loss. The authors suggested that despite the evidence suggesting that transplantation has a positive effect in patients with high BMI, surgical and clinical management tactics should be adopted with caution. The 1-year follow-up showed no worsening of outcomes in obese patients compared with overweight and non-obese patients. Another study also showed no difference in rates of new-onset diabetes or allograft loss, although the glomerular filtration rate was lower in overweight and obese patients at 3 and 6 months after transplantation [14].

In obesity, surgical intervention is longer and warm ischemia time increases, which is a risk factor for delayed graft function [15]. Obesity is closely related to high sympathetic nervous system activity, which leads to renal vasoconstriction [16]. Moreover, rapid administration of calcineurin inhibitors after transplantation, possibly at higher doses in overweight or obese patients, can aggravate vasoconstriction and further impair graft perfusion, increasing the risk of delayed function. Another possible explanation is the association between obesity and increased prothrombotic activity and endothelial dysfunction [17]. Body fat mass, in particular central obesity, is associated with higher levels of thrombin formation [18], which is a risk factor for venous thromboembolism [19]. Increased prothrombotic activity and endothelial dysfunction may contribute to the risk of graft microthrombosis, which itself may play an important role in delayed graft function [20].

In the last decade, studies have shown that robot-assisted KTx can be performed in patients with extremely high BMI. **Garcia-Roca et al.** reported that 52.8% of procedures among transplant candidates with a BMI of 45 kg/m^2 were performed using a robotic technique [21]. This procedure is costly, but initial results show less postoperative pain and fewer wound complications, such as surgical site infections and hernia. These results may be particularly beneficial for obese patients with regard to overall costs and rehospitalization.

Thus, a higher BMI creates more problems in terms of perioperative, short-term and long-term outcomes in patients requiring renal transplantation, especially with regard to increased risk of delayed graft function and graft loss. There are probably three reasons for the increased risk: immunosuppression, a subclinical proinflammatory state well known in patients with high BMI, and a higher incidence of associated cardiovascular disease.

CURRENT APPROACHES TO SURGICAL TREATMENT OF MORBID OBESITY, INCLUDING IN CKD PATIENTS

Increased incidence of complications and suboptimal outcomes in obese and morbidly obese kidney transplant recipients has led many transplant centers to reject patients with a BMI of 30 to 40 kg/m^2 [22]. In this situation, weight loss becomes unavoidable to be eligible for KTx. However, regardless of the rules followed by each clinic, weight loss prior to transplantation should be strongly recommended in order to speed up listing and improve surgical and renal outcomes in obese and CKD patients [23]. To achieve this result, there are two main strategies: the conservative one, which mainly involves diet and exercise, and the more aggressive one, which involves surgical intervention. The conservative approach has been preferred for many years because of its lower cost and less traumatic nature. Kidney transplant candidates

were advised to see a nutritionist as soon as possible with regular monitoring of body weight variation. Dietary recommendations were highly individualized and included dietary and exercise plans to achieve specific goals. A possible initial therapy strategy for weight loss consisted of a recommendation to reduce body weight by about 10% of baseline, with a weight loss of 1 to 2 kg per month [24]. Behavioral interventions targeting both diet and physical activity show small but significant benefits in maintaining weight loss. However, a significant number of patients fail to reach their target weight either because of poor compliance or inadequate therapy plans [25].

The first problem to be faced with this conservative approach is the high level of exclusion in the follow-up of obese patients committed to diet and exercise. Another major concern is that, despite an encouraging initial response in terms of weight loss, long-term outcomes are still a matter of debate since weight gain occurs at different rates in different patients.

In this sense, bariatric surgery has proven to be a highly effective method for weight loss compared to therapeutic weight loss methods [26]. It has been found that these surgeries can be performed safely, including in dialysis patients [27]. In an effort to overcome morbid obesity as a barrier to KTx, a two-stage approach is being developed for such kidney transplant candidates. ESRD patients suitable for KTx but having BMI >30 kg/m^2, undergo bariatric surgery first. After persistent weight loss, the patients are reassessed and then placed on the KTx waiting list.

In gastric surgery, many surgical methods of treatment have been developed and implemented, with resection methods occupying a leading spot [28].

Gastric bypass anastomosis was developed in the late 1970s, which was later transformed into Roux-en-Y anastomosis. This procedure was found to produce a weight loss equivalent to the first technique, but with a much lower risk of complications. Sleeve gastrectomy was for a long time only an integral part of biliopancreatic bypass surgery as modified by Hess-Marceau. In the early 2000s, **M. Gagner et al.** (USA) decided to perform biliopancreatic bypass in two stages in severe overweight patients: the first was "Sleeve gastrectomy", and already after weight loss and improvement in patients' condition, they planned to perform the second stage "Intestinal stage" [29]. It turned out that for some patients, the first stage was quite sufficient to achieve the desired weight loss [29]. The surgical intervention is performed using laparoscopic access, which reduces trauma and promotes early postoperative rehabilitation of the patient. Over time, laparoscopic sleeve gastrectomy (LSG) became adapted as a stand-alone procedure for weight loss. Currently, it is the most commonly performed bariatric procedure in the world [30, 31].

Long-term follow-up results have demonstrated its similar efficacy in weight loss, allowing patients to lose 80% of excess body weight within the first year after surgery [32–34], in the resolution of comorbidities, and in mortality and morbidity rates compared to Roux-en-Y gastric bypass (RYGB), recognized as the gold standard of bariatric surgery.

Thus, bariatric surgeries can be divided into three categories:

1. Malabsorptive surgeries. These procedures create an artificial anatomical change that bypasses part of the small intestine with the effect of reducing the amount of nutrients and calories a person absorbs. Biliopancreatic diversion with or without duodenal switch is a typical type of malabsorptive procedure.
2. Restrictive surgeries. The goal of these procedures is to reduce the amount of food consumed by reversible or irreversible, fixed or adjustable resizing of the stomach, leaving less room for food and creating a quick sense of fullness in patients. The main restrictive procedures are placing an adjustable laparoscopic gastric band, performing an LSG, and placing an intragastric balloon [35].
3. Mixed operations. These interventions include both restrictive and malabsorptive techniques (usually gastric size reduction and bypass anastomosis of the small intestine, respectively) [36]. A typical mixed procedure is the RYGB.

Bariatric surgeries can be performed from a traditional surgical approach, using laparoscopy or robotics.

All of the above approaches have advantages and disadvantages. Suffice it to emphasize that a pure malabsorption procedure is associated with important pharmacokinetic consequences, since the integrity of the intestinal tract is important for both nutrients and drug absorption. Simple malabsorptive surgery should hardly be considered in the pre-transplant evaluation of obese patients [37]. However, the results are mixed. Some restrictive procedures, such as laparoscopic gastric banding [38], possibly related to a higher likelihood of gastric band erosion and displacement in immunocompromised patients, have also been reported [39]. Although various bariatric approaches to post-transplant patient management have been reported [40]; two types are the most common: LSG and RYGB. In terms of frequency of performance in Russia, longitudinal gastric resection has taken the leading position among bariatric operations [41].

Thomas et al. published a single-center retrospective analysis on the clinical outcomes of the RYGB technique in 33 CKD patients before KTx with a mean BMI of 43.5 ± 0.7 kg/m^2 [42]. The authors found that 87% of patients using RYGB achieved a BMI <35 kg/m^2, perioperative mortality was 0%, and improved metabolism in diabetes and hypertension. These achievements made it possible to perform kidney transplantation in patients.

However, post-transplant outcomes showed that biopsy-proven acute rejection occurred significantly higher among RYGB vs control patients, and this is consistent with the fact that these patients had a lower trough calcineurin inhibitors. This may be related to the RYGB mechanism: in reducing the absorption capacity of the intestinal tract, RYGB also adversely affects the bioavailability of immunosuppressants [43]. The problem related to pharmacokinetics is not present in the other main type of bariatric surgery for kidney transplant candidates, namely LSG, because it is a restrictive procedure mainly affecting the size of the stomach.

In 2018, **Kim et al.** published a retrospective analysis from a single center comparing pre- and post-transplant outcomes in patients after sleeve resection. Post-LSG kidney recipients were compared with similar-BMI recipients who did not undergo LSG [44]. Among post-LSG patients, mean BMI was 41.5 kg/m^2 at initial encounter, which decreased to 32.3 prior to KTx and persisted further; the rate of 30-day rehospitalization, complications and mortality after LSG was 0%. In addition to weight loss, some other positive effects of bariatric surgery are also evident, especially for high blood pressure. Observations have shown that after kidney transplantation, patients who underwent LSG had lower rates of new-onset diabetes mellitus, delayed graft function and other common complications in obese transplant patients [44]. In addition, the overall postoperative period of these patients did not differ significantly from that of control group patients.

The incidence of serious post-LSG complications ranges from 0% to 6% [45–47]. Early complications include leakage from the resection site, bleeding, symptomatic stenosis, pulmonary embolism, including a particular risk of portomesenteric venous thrombosis and dehydration. Late complications include stricture, weight gain, and malnutrition [45, 47, 48].

Thus, morbidly obese patients represent a multidisciplinary problem and were until recently considered inoperable because of such limitations. Research findings suggest that bariatric surgical procedures appear to be effective in reversing the effects of morbid obesity prior to KTx and that they may improve access to the surgical field. Thus, LSG is recommended as a feasible procedure and the procedure of first choice for transplant candidates with high BMI.

AVAILABILITY AND EFFICACY OF TRANSPLANTATION CARE FOR CKD PATIENTS AFTER SURGICAL TREATMENT OF OBESITY

Meta-analyses have confirmed that bariatric surgery has higher effectiveness than nonsurgical therapy in achieving sustained weight loss in obese patients in the general population, and including potential renal transplant recipients [49, 50]. In 1996, **Marterre et al.** first described an open gastric bypass anastomosis in three morbidly obese kidney transplant recipients 6–8 years following KTx. The authors reported a significant reduction in body weight, hypertension, post-transplant diabetes mellitus and hyperlipidemia [51]. Since then, successful KTx after weight loss surgery has been directly associated with improved survival and quality of life compared with dialysis [52]. Morbid obesity still remains a significant obstacle to KTx because of suboptimal postoperative outcomes. According to the findings of **Segev et al.**, obese patients were less likely to receive a transplant from a deceased donor after being placed on the waiting list, and they stayed on the waiting list longer [53]. **Gill et al.** published a retrospective analysis of 702,456 CKD patients aged 18–70 years (captured in the US Renal Data System between 1995 and 2007), where they found that obesity affects many interrelated aspects of transplant practice, including candidate selection, prediction of pre- and post-transplant outcomes, and waiting list management [54].

Recently, using laparoscopic gastric resection, patients with CKD have been able to achieve significant weight loss and become eligible for transplantation. **Kim Y. et al.** reported significant improvements in type 2 diabetes mellitus, hypertension, delayed graft function and new-onset diabetes after transplantation in patients with laparoscopic gastric resection compared with kidney recipients without it [44]. Improvements in comorbid conditions such as diabetes, hypertension, and renal function have been reported in three studies [32, 55, 56].

Dziodzio et al. published a review of bariatric surgery in CKD patients before transplantation and found only 8 retrospective studies involving 154 patients. These authors documented weight loss in all published series (weight loss range 21–68%) and noted that gastric bypass was the most effective procedure (weight loss rate 64.3 versus 48.9% after laparoscopic gastric resection). The overall mortality rate was 4.2% for patients with gastric bypass and 3.9% for patients with laparoscopic gastric resection [32].

According to **Hoogeveen EK et al.**, ESRD patients with morbid obesity after LSG before kidney transplantation have improved post-transplant outcomes [58].

CONCLUSION

Obesity in the general population has reached pandemic proportions in recent decades, and as a consequence, this is affecting growth in the population of CKD patients requiring KTx who are simultaneously obese. There is enough evidence in the literature to argue that obesity is a risk factor for surgical complications but not a contraindication for KTx. Outcomes can be greatly improved by multidisciplinary and multimodal treatment strategies. Current techniques with minimally invasive techniques, mainly using robotic and laparoscopic tech-

niques, can dramatically reduce the incidence of surgical complications with comparable graft and survival rates for patients with a non-obese population.

Bariatric surgery is a modern method of treating obesity and related conditions, but its use in patients with severe CKD remains limited because of the risk of severe postoperative complications [4]. However, rapid and persistent loss of excess body weight can significantly reduce blood pressure, compensate for blood sugar levels, which will have an impact on the effectiveness of renal replacement therapy procedures, reducing the frequency and severity of diabetes mellitus [59, 60]. This will lead to earlier inclusion of ESRD patients in the waiting list and will increase the post-KTx survival rate due to better kidney transplant function and lower percentage of graft rejection. In this regard, surgical treatment of obesity should be considered as an intermediate stage of preparation for KTx [33]. One of the minimally invasive methods of treatment for morbid obesity in ESRD patients can be LSG, the results of which have demonstrated effectiveness and safety in abdominal surgery, although nutrient deficiency remains a problem in this situation [61]. In general, these surgeries do not appear to have an adverse effect on absorption of immunosuppressive drugs [62].

Thus, studies on the use of laparoscopic gastric reduction in ESRD patients are important and the study of this method will further increase the availability of transplant care for overweight patients who previously had relative contraindications to surgical interventions.

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