







Obesity in work-up of kidney transplant candidates – review of clinical practice guidelines

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Abstract

Background: Incidence of morbid obesity is rising worldwide. Current clinical practice guidelines for the pre-transplant evaluation of end-stage kidney disease (ESKD) patients lack clear recommendations on morbid obesity. **Material and methods:** The aim of this review was to summarize the current guidelines on the role and treatment of obesity in kidney transplant recipients. Eight current national and international clinical practice guidelines were identified in a comprehensive literature search. **Results:** All guidelines underline early detection of obesity and obesity-related comorbidities in ESKD patients. Only two guidelines explored the role of weight-loss surgery, however due to the lack of sufficient evidence no formal recommendation of surgical procedure was given. **Conclusions:** Diagnosis and treatment of obesity remains underappreciated in the current guidelines, most of which do not include pharmacological and surgical interventions. High-quality evidence is warranted to assess the role of weight-loss including surgery in ESKD patients and to update the recommendations in future guidelines.

Keywords: obesity · end-stage kidney disease · bariatric surgery

Citation

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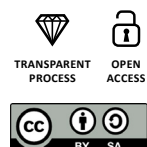
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Introduction

The number of obese and morbidly obese end-stage kidney disease (ESKD) patients is rising. Due to the obesity epidemic, nearly 60% of all kidney transplant recipients are overweight or obese, with male predominance [1]. Kidney transplantation (KT) is the most effective method of ESKD treatment but it is still a debatable whether obese patients are suitable candidates for KT [2-6]. Clinical practice guidelines (CPGs) review current research and formulate recommendations based on available evidence and expert opinion. Clear guidance regarding obesity assessment and treatment options would be an essential part for the selection process of candidates for KT. The aim of this review is to assess the availability, quality, and consistency of recommendations for obesity evaluation and treatment before KT included in current national and international CPGs for kidney transplant candidates.

Material and methods

A systematic review was performed according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [7]. The search strategy included literature published until January 2020, using the following search query: ("kidney transplantation" OR ("kidney" AND "transplantation" OR "kidney transplantation" OR ("kidney" AND "transplant") OR "kidney transplant") AND ("Assessment") AND ("guideline" OR "guidelines"). Two researchers independently searched and assessed the guidelines. We included only CPGs for the selection of candidates for deceased donor kidney transplantation. CPG for living donor kidney transplantation were excluded after screening due to identification of recommendation for obesity only in kidney donors [8-9]. The study protocol was presented in PRISMA flowchart (Figure 1). The following data were extracted: society, year of publication, inclusion of obesity into recommendation, recommendations for obesity treatment and grade of evidence.

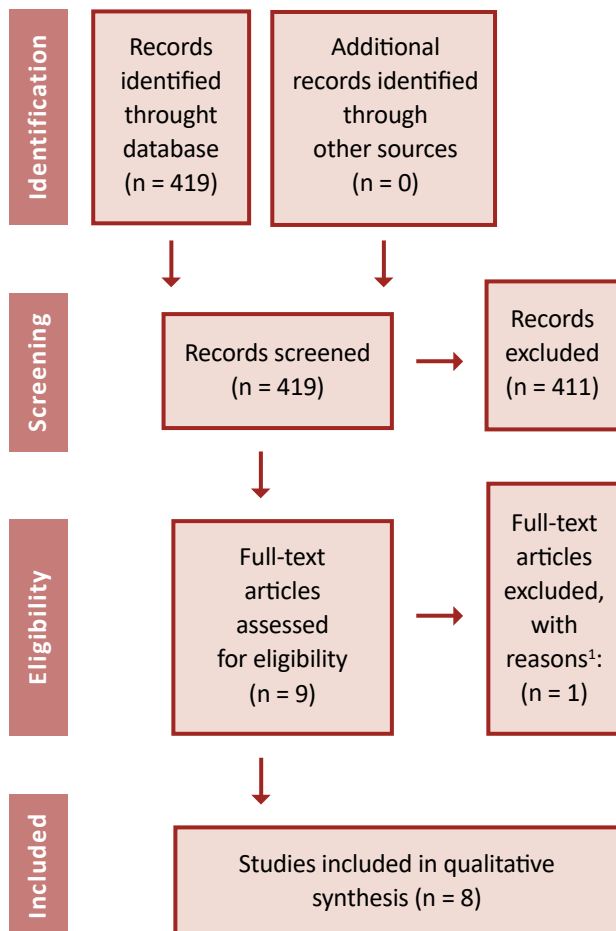


Figure 1. PRISMA flowchart.¹ Clinical Practice Guideline excluded due to lack of recommendation for inclusion to kidney transplantation [7].

Results

The literature search revealed 419 articles. A total of 411 were excluded during screening of titles and abstracts. The remaining 8 CPGs were searched for obesity evaluation recommendations. Key facts about the included studies are summarized in Table 1.

Recommendations for obesity evaluation before kidney transplantation

Three CPGs recommended that obesity should be routinely assessed at each pre-transplant consultation [10-12]. The included measurements should be as follows: patients height, weight, calculation of BMI. Additionally, waist circumference should be assessed when weight and physical appearance suggest obesity, but calculated BMI is $< 35 \text{ kg/m}^2$ [10]. The definition of obesity in adults includes waist circumference $\geq 102 \text{ cm}$ in men and $\geq 88 \text{ cm}$ in women [11]. Two guidelines recommended weight reduction before transplantation if BMI exceeds 30 kg/m^2 [12-13]. One study set the upper limit of BMI to 40 kg/m^2 [14]. Another CGP states that in patients with BMI $> 36 \text{ kg/m}^2$ the transplantation is associated with an unacceptably high risk of death and needs careful consideration [12]. All CPGs state that obesity of the kidney recipient by itself is not a contraindication for KT, however if co-existing with other comorbidities (e.g. advanced cardiovascular diseases, peripheral vascular

Table 1. Obesity in current clinical practice guidelines

Guidelines	Region	Obesity in candidates for transplantation	Recommendation in obesity
AST (2001)	USA	Obesity without comorbidities* is not a contraindication for KT (Level of evidence not provided).	Weight reduction (role of limited exercise in dialyzed patients) (Level of evidence not provided).
Canadian Society of Transplantation (2005)	Canada	Obesity without comorbidities is not a contraindication for KT (Grade C). In patients with BMI > 36 kg/m ² KT is contraindicated.	<ul style="list-style-type: none"> • Weight reduction to BMI < 30 kg/m² • Surgical intervention for obesity may be considered in extreme cases (Grade B)
Bunnapradist & Danovich (2007)	USA	In patients with BMI > 40 kg/m ² KT contraindicated.	Weight reduction (the benefit is unclear, method not specified) (Level of evidence not provided).
Lisbon Conference Report (2007)	Europe	In morbidly obese KT is contraindicated (BMI not applicable) (Level of evidence not provided).	No recommendation
KDIGO (2009)	International	In patients with BMI > 30 kg/m ² KT is contraindicated.	<ul style="list-style-type: none"> • Early diagnosis of obesity (Level of evidence not provided). • Obese individuals should be offered a weight-reduction programme (Level of evidence not provided). • Diet and other behavior modifications are safe in KT recipients (Level of evidence not provided). • Bariatric surgery may be performed safely in selected KT recipients (Level of evidence not provided).
KHA-CARI (2013)	Australia	No recommendation	<ul style="list-style-type: none"> • Obesity should be assessed at each visit (Grade C). • Diet and behavioral modification are likely to be safe. Diet that is individually planned with a moderate energy restriction of about 30% of energy expenditure, with monthly follow up with a dietician (Level of evidence not provided). • There is insufficient evidence to make recommendations or suggestions with respect to bariatric surgery (Level of evidence not provided).
European Renal Best Practice Guideline (2015)	Europe	BMI > 30 kg/m ² is a contraindication for KT (Level of evidence not provided).	Obese patients should reduce weight before KT (Level of evidence not provided).

* advanced cardiovascular, peripheral vascular, liver or pulmonary disease, HIV, active hepatitis, active pulmonary or systemic tuberculosis

diseases, liver or pulmonary disease, active hepatitis) it increases the risk of perioperative complications and may impair graft and patient survival [12, 15].

Recommendations for diet and behavioral therapy

These therapies were considered safe in ESKD population but they were related only to a short-term weight reduction [10]. Only one study clearly stated that overweight kidney transplant recipients should have an individually-planned diet with a moderate energy restriction of about 30% of energy expenditure, with dietician follow-up [11]. It recommended also to create a caloric deficit of 500-1000 kcal/day along with increased physical activity [11].

Recommendations for pharmacological obesity therapies

The analyzed CPGs briefly discussed the role and the risk of novel pharmacological weight reduction therapies [10-11]. There were no trials examining the safety of those interventions in this specific population. Two medications (orlistat and sibutramine) were mentioned in recommendations [10-11]. Orlistat is related to decreased absorption of fat-soluble vitamins and may also interfere with the absorption of immunosuppressive medications and may be associated with higher risk in ESKD patients [10]. Sibutramine may increase blood pressure and heart rate and is not advised in patients with cardiovascular risk [10].

Recommendations for bariatric surgery

Little was mentioned about bariatric surgery in the current CPGs. Two of eight CPGs recommend weight-loss surgery before kidney transplantation [10-11]. However, the quality of existing evidence was insufficient to form recommendations about qualification, procedure type or procedure timing (i.e. before or after the KT).

pared to the nonobese candidates [16-17]. Additionally, obesity is associated with inferior short-term results of transplantation [3, 5].

Current CPGs are consistent regarding a strong need of early obesity assessment before enrollment to transplant waiting list. Most guidelines use BMI to assess obesity for waiting listing purposes [10, 13, 18]. BMI < 30kg/m² prior transplantation is recommended but in some studies BMI below 35kg/m² is considered a selection criterion [19-20]. The limitations of BMI as a metric of body fat must be appreciated. Anthropometric measures (waist circumference and waist-to-hip ratio (WHR)) are considered as an alternative to BMI in body composition assessment. These measures were shown to have a direct association with increased cardiovascular mortality in dialyzed ESKD patients as well as post-transplant mortality more precisely than BMI [21-22]. The existing guidelines are based on available original studies at the time of their publication. All current clinical practice guidelines were published before 2015. The role of diet and pharmacological treatment was poorly discussed but the level of evidence is sufficient to consider them safe for kidney transplant candidates [10-11]. The surgical treatment of obesity was not included in most CPGs due to limited evidence on safety and outcomes of bariatric procedures at the time of their publication. Only two CPGs mentioned possible implementation of bariatric surgery in that indication [11-12]. Since then several large studies were published giving new insights into the management of obese ESKD patients [23-25]. The results of these studies are presented below. It is likely that these data will be included in new editions of CPGs.

Based on the current knowledge, the use of pharmacological interventions for the treatment of obesity is limited in ESKD patients. First, orlistat use in patients with chronic disease is contraindicated because of its association with acute kidney injury and chronic kidney disease due to increased absorption of oxalate and the risk of nephrocalcinosis, inflammation and kidney fibrosis as a result [26-28]. Moreover, post-transplant drug interaction, particularly with cyclosporin, results in reducing their bioavailability and limits its use [29]. Secondly, sibutramine was withdrawn from the obesity treatment due to unacceptable increased cardiovascular risk [30]. A newer drug lorcaserin, is associated with potential kidney benefit, but limited to the lower risk of new-onset of albuminuria. Its use in ESKD patients is contraindicated due to worsening of chronic kidney disease stage [31-32]. Bupropion, likewise, should not be used in ESKD patients [32-33].

The role of physical activity was discussed in only one guideline [11]. Research has shown that pre-

Discussion

The prevalence of obesity among patients with ESKD continues to increase. Obesity was shown to be an independent risk factor not only of the ESKD development but also to accelerate the progression of that disease [5]. Kidney transplantation is considered as gold standard in ESKD treatment. Obesity is now limiting the access to KT by delaying the enrollment to transplant list and prolonging the waiting time com-

-transplant aerobic exercise, long-term progressive resistance exercise, resistance training, and home-based exercise are tolerable in patients with ESKD [34-35]. Interestingly, the aerobic exercise is not related to weight reduction but has an positive impact on dialyzed patients' quality of life [36]. After transplantation, aerobic exercise, resistance training and individualized progressive exercise programs are effective in weight-loss programs [34].

Feasibility and safety of bariatric surgery is currently investigated and discussed. A recent study has shown an increasing number of patients with ESKD undergoing bariatric surgery as a bridge to KT [23]. Nevertheless, no consensus was reached regarding the management options for obese KT candidates. It was previously believed that bariatric surgery use in ESKD patients may be limited because of higher mortality risk. However the safety and significance of weight loss surgery in ESKD patients increased over the years [25, 37-39]. Two bariatric procedures were preferred [23, 40]. LSG (laparoscopic sleeve gastrectomy) and LRYGB (laparoscopic roux-en-y gastric bypass) appear to cause effective weight-loss before KT and improve surgical access during transplantation [41-42]. Uncertainties exist regarding optimal timing of bariatric surgery [38]. It has not been proven yet if the bariatric procedure should be performed before or after engraftment. Both approaches are related to low risk of graft failure and low mortality in long-term analysis when compared to the mortality rate of obese patients without ESKD [43]. Complication rates of LSG were similar between patients with and without ESKD [23, 44]. It should be noticed that LSG performed before transplantation is associated with significant changes of pharmacokinetics of tacrolimus and mycophenolate mofetil (increased maximal concentration and decreased clearance) in that group of patients [45]. Whereas malabsorptive procedures are related to hypoxaluria and increased risk of nephrolithiasis [46].

Interestingly, an obesity paradox was described in dialyzed patients [47-48]. It is associated with better survival of obese patients who were transplanted than all patients who stay on transplant waiting list. However these results may be confounded by worse outcome of malnourished ESKD patients [47, 49-50]. Moreover, obesity reduces the likelihood of being enrolled to the waiting list, but not the transplantation once enrolled, especially among women [17].

Recent large metaanalyses support higher risk of KT of obese patients and better survival in lower BMI patients [51-53]. It was proven that kidney recipients have an inferior survival when their BMI is > 40 kg/m²

[19, 54]. Recent metaanalysis (of 209,000 patients) revealed lower mortality, delayed graft function (DGF), acute rejection, infectious complication rate and better 1-, 2- and 3-year survival in kidney recipients with BMI < 30 kg/m² [52]. In another metaanalysis (17 studies, 138081 patients) obesity was demonstrated not to be related with higher mortality risk but was associated with higher risk of graft loss and DGF [53]. A metaanalysis of 9296 patients confirmed higher risk of DGF but not acute rejection and death risk [55]. The results of those analyses support the necessity of obesity treatment in ESKD patients. Several studies investigated the benefits and risk of bariatric surgery in that group of patients [24, 56-58]. Laparoscopic SG has replaced Roux-en-Y gastric bypass (RYGB) as the most common bariatric surgical procedure in patients with ESKD [23]. SG in ESKD patients is not related to higher risk of leaks, reoperations, or mortality in 1 year follow-up [59]. Our center morbidly obese ESKD patients have similar weight loss results after bariatric procedure than non-ESKD [42, 44]. Nine of twenty of them underwent kidney transplantation without any perioperative complications and with good kidney function in follow-up. Patients who underwent KT after SG have good 1-year and long term transplantation results in small group analysis [58]. Morbidly obese patients after LSG experienced lower rates of DGF and readmission related to graft insufficiency in 1 year follow-up [58]. The mortality rate of obese individuals with ESKD after SG is lower (1.8/100 patient-years compared to 7.3 in the control group) [60]. Moreover, in stage 3 CKD significant improvement of kidney function was observed [60]. The emerging evidence from those studies supports the low risk and safety of bariatric surgery in ESKD patient.

Conclusion

In conclusion, the obesity epidemic has major implications on kidney transplant candidates' evaluation. In existing CPGs there is a consensus regarding the need of obesity assessment in transplant candidates. However, most of the evaluated CPGs are inconclusive concerning the role of pharmacological and surgical interventions for the treatment of obesity. New large-scale studies seem to be the missing link that suggests clear recommendations for obese patients' management. It seems necessary to update the guidelines with results of recent studies on the new measures in the assessment of obesity and its treatment, with special attention to surgical treatment.

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