REVIEW

Obesity in kidney transplantation

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SUMMARY

The prevalence of obesity among patients with chronic kidney disease continues to increase as a reflection of the trend observed in the general population. Factors affecting the access to the waiting list and the transplantability of this specific population will be analysed. From observational studies, kidney transplantation in obese patients carries an increased risk of surgical complications compared to the nonobese population; therefore, many centres have been reluctant to proceed with transplantation, despite this treatment modality confers a survival advantage over dialysis. As a consequence, obese patients continue to face decreased access to the waiting list, with a lower likelihood of being transplanted and higher waiting times when compared to the nonobese candidates. In this review will be described the current strategies for treatment of obesity in different settings (pretransplant, at transplant and post-transplant). Obesity represents a risk factor for surgical complications but not a contraindication for kidney transplantation; outcomes could be greatly improved with its multidisciplinary and multimodal treatment. The modern technology with minimally invasive techniques, mainly using robotic platform, allows a reduction in the surgical complications rate, with graft and patient survival rates comparable to the nonobese counterpart.

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Introduction

Since 1975, the prevalence of obesity nearly tripled accounting for about 13% of the world's adult population. Obesity is a worldwide epidemic. In 2016, more than 1.9 billion adults aged 18 years and older were overweight and 650 million obese [1]; by 2030, the prevalence is projected to reach 2.16 billion overweight and 1.12 billion obese. In the United States (US), the rates of obesity in 2014 were 35% of men and 40% of women [2]. This condition is a major risk factor of noncommunicable disease including but not limited to cardiovascular disease and diabetes, which in turn affect the progression of chronic kidney disease (CKD) [3–5]. As a result, the prevalence of obesity is increasing also in the end-stage kidney disease (ESRD) population [6].

Obesity is defined by the World Health Organization as an abnormal or excessive fat accumulation and body mass index (BMI), a simple index of weight-for-height, is commonly used for its classification [7]. It is stratified according to the following categories: 30.0 ± 34.9 kg/m^2 (class I obesity), 35.0 ± 39.9 kg/m^2 (class II obesity) and 40+ kg/m^2 (class III obesity). The BMI classification (which will be adopted in this review), despite being an imperfect tool to define obesity, is currently the most widely adopted in the literature [8] and in clinical

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practice [9]. Its main limitation is related to the fact that does not take into account important patient demographics such as age and ethnicity, percentage and composition (subcutaneous versus visceral) of body fat and muscle mass [10–14].

Obesity and CKD

Obesity is closely linked to CKD and is considered an important risk amplifier in presence of diabetes, hypertension and cardiovascular disease, which are commonly associated. The hazard ratio for CKD in obese adolescents is estimated to range between 7 and 20 when other comorbidities are considered [15]. Interestingly, the risk of obesity-associated CKD seems to be lower in metabolically healthy subjects compared to those with metabolic syndrome [16,17]. The pathophysiological mechanism of this association remains ill-defined [16]. Metabolic effects of different adipokines (leptin, resistin and visfatin) and downregulation of adiponectin may contribute to hemodynamic and structural renal lesions via insulin resistance, increased insulin blood level, renin-angiotensin system activation, oxidative stress and microinflammation [17].

Several histopathological studies characterized the obesity-associated nephropathy [18]. Common findings are increased kidney weight hypertrophy of individual nephrons with increase in glomerular size and reduction in glomerular density. Some authors observed an increased number of glomerular capillaries suggesting de novo formation of microvessels [19], theory yet to be confirmed.

Obesity and survival

In the general population, obesity is associated with increased risk of death, particularly as a result of metabolic syndrome and cardiovascular disease [3]. Data from the global burden of disease study showed that the mortality related to high BMI increased by 28.3% (from 41.9 per 100 000 in 1990 to 53.7 per 100 000 in 2015), accounting for 4.0 million deaths; similarly, BMI-related disability-adjusted life years increased by 35.8% (from 1200 per 100 000 in 1990 to 1630 per 100 000 in 2015) [20].

In some studies of healthy adults, a 'J' curve has been observed in the association between BMI and death; that is those with a low BMI also exhibit increased mortality, although not as high as those who are obese [21,22]. In contrast to trends seen in the general population, higher BMI has generally not been associated with an increase in mortality rate in ESRD patients [23–30]. This phenomenon, referred as obesity paradox [31] or reverse epidemiology [32], has interested nephrologists ever since the first report by Fleischmann *et al.* [24]. The Dialysis Outcomes and Practice Patterns Study analysis of 9714 dialysis patients showed higher BMI to be associated with lower mortality rates [33], findings confirmed in a recent and large US registry study [34]. As pointed out by Zoccali *et al.* [35] such reverse epidemiology may simply be a reflection of low body weight being harmful and sign of underlying comorbidity rather than obesity per se being protective. This phenomenon may be related to a selection bias in a highly selected population of high-BMI patients and most authors concur that survival advantage associated with higher BMI in dialysis patients is restricted to those with normal or high muscle mass [36–39]. The mechanisms underlying this observation remain poorly understood, still debated and outside the scope of this review [40–42]. In conclusion a better understanding of the nutritional status (i.e. malnutrition, sarcopenia) may help to confer a survival benefit in ESRD patients [26,41–44]; the current focus of research is shifting towards the study of protein-energy wasting biomarkers (i.e. serum albumin, prealbumin, transferrin values) as the strongest and most consistent mortality risk factors in ESRD [45,46].

Obesity and transplantation

Access to transplant waiting list

According to most clinical guidelines, obesity per se is not considered a barrier to transplantation. The European Association of Urology position is that transplantation provides a better survival and better quality of life in obese ESRD patients and there is not enough evidence to recommend exclusion based on BMI [47]. The British Transplant Society guidelines statement paves the way for caution when it comes to transplantation of obese patients; it is clearly affirmed that '... while obese patients (BMI >30 kg/m^2) present technical difficulties and are at increased risk of peri-operative complications, obesity is not an absolute contraindication to transplantation ... individuals with a BMI of >40 kg/m^2 are less likely to benefit' [48]. The reality is that many centres do not transplant obese patients [49] and still use BMI as a contraindication to transplantation [50].

In the United States many programs consider a BMI of 35 kg/m^2 a relative contraindication to kidney transplantation [51]. It is very likely that programs will become even 'more conservative' after receiving a low-performance Scientific Registry of Transplant Recipients report paradoxically are more likely to remove low-BMI patients, rather than higher BMI patients; suggesting that there is an underlying appreciation for reasonable outcomes in the obese who are otherwise considered good surgical candidates [52].

Access to transplantation

Once listed, obese patients continue to face decreased access to transplantation, with a lower likelihood of transplant and higher waiting times when compared to the nonobese candidates, further compounded by gender-related differences [51,53]. An analysis of United Network for Organ Sharing (UNOS) data on 132353 patients in the transplant waiting list showed that the likelihood of receiving a deceased donor kidney transplant decrease with increasing BMI. In their allocation-adjusted model, the likelihood of receiving a deceased donor kidney transplant was 0.93 for class I (95% CI 0.90–0.97; $P < 0.001$), 0.72 for class II (95% CI 0.68–0.77; $P < 0.001$) and 0.56 for class III obesity (95% CI 0.50–0.62; $P < 0.001$). The likelihood of being bypassed, when a kidney became available for transplant, increased with BMI, 1.05 for class I (95% CI 1.02–1.08; $P < 0.001$), 1.11 for class II (95% CI 1.07–1.14; $P < 0.001$) and 1.22 for class III obesity (95% CI 1.13–1.32; $P < 0.001$). As a result, the median time to transplantation for patient awaiting a deceased donor kidney transplant increased with BMI (39, 42, 51, 59 months for normal weight, class I, II and III obesity, respectively) ($P < 0.001$) [6].

Survival on renal replacement therapy versus transplantation

Despite the above-mentioned potential protective effect of obesity in ESRD patients, transplantation still provides a clear survival advantage over dialysis [54,55]. In an analysis of United States Renal Data System (USRDS) data, Glanton *et al.* looked at the outcomes of 7443 patients with class I, II and III obesity, who were waitlisted for transplantation. The mortality rate for those who underwent deceased donor transplantation (1719 patients with 3.3 deaths per 100 patient-years) was still half the mortality rate (6.6. deaths per 100 patient-years) of those who stayed on dialysis waiting for a kidney. An even lower mortality rate (1.9 deaths per 100 patient-years) was calculated in the cohort of 552 patients who underwent a living donor transplant [56]. Interestingly, the beneficial effect of transplantation was lost in the subgroup analysis of patients with class III obesity [56]. A more recent study by Gill *et al.* (USRDS data) reported a survival benefit of transplantation in all classes of obesity in both deceased and living donor setting. For patients receiving a living donor kidney, the reduction in the risk of death was 66% in all BMI groups; whereas among the deceased donor recipients the reduction in the risk of death was 66% in patients with class I and II obesity and 48% in patients with class III obesity [54]. The analysis of deceased donor recipients receiving an organ formerly defined as expanded criteria (donors older than 60 years and donors older than 50 years with at least two of the following criteria – hypertension, cardiovascular cause of brain death – terminal serum creatinine level >1.5 mg/dl) showed a reduction of risk of death of 57% in recipients with class I and II obesity and of 46% in recipients with class III obesity. The survival benefit of transplantation was not observed in selected subgroups (i.e. African-American with class III obesity) [54]. The important finding of this study which highlights a survival advantage utilizing live donors may encourage its use in the obesity population [54].

Obesity and post-transplant outcomes

Obesity and patient/graft survival

According to some studies, obesity has a negative impact on patient and graft survival [57,58], while others found no association [59–63]. A large registry study of over 50 000 adult transplant recipients reported a U-shaped association between BMI and both patient and graft survival. Recipients with a very high and very low BMI at the time of transplant were most at risk for either death or graft loss [58]. More recently, a systematic review by Lafranca *et al.* assessed the relationship between BMI and graft and patient outcomes postrenal transplantation. In this review, the authors found a higher risk of both patient and graft loss at 1, 2 and 3 years after transplantation in obese compared to nonobese recipients [64]. This is in contrast with the Australian and New Zealand Dialysis and Transplant Registry database analysis ($n = 5684$), in the multivariate analyses obesity was not associated with worse patient and graft outcomes [65]. Single-centre retrospective studies also showed no association between higher BMI and graft loss or all-cause mortality [61–63]. Others have reported a trend towards similar or even improved patient and graft survival among obese transplant recipients compared with their nonobese counterparts [66]. Of interest, in one single-centre retrospective study consisting of 491 nonobese and 345 obese transplant recipients, the prevalence of surgical site infections (SSIs) was higher among obese recipients, but those who were free of SSIs had patient and graft survival comparable with nonobese recipients [67]. In conclusion, the association between obesity and recipient patient and graft survival, previously evaluated with conflicting results, as described later in the paper, could be improved with a multidisciplinary and multimodal approach. Prospective studies are needed to substantiate the good results obtained with the application of minimally invasive techniques [68].

Obesity and DGF risk

Delayed graft function, defined by most studies as need of dialysis during the first week post-transplant, appears to be associated with recipient BMI in most retrospective studies and a recent meta-analysis [69,70]. An analysis of the UNOS database showed a statistically significant and gradual increase in the risk of DGF according to the class of obesity, the odds ratio for DGF in patients with class I, class II and class III obesity, compared with nonobese patients, was 1.34, 1.68 and 2.68, respectively [71]. The exact pathophysiology is multifactorial with both immunologic and nonimmunologic mechanisms; technical challenges of transplanting obese patients, which often translate in longer operative times and longer warm ischaemia time, may have a prominent role [72,73]. In a retrospective, single-centre study, anastomosis time was significantly longer in recipients with a BMI more than 25 than in those with a BMI less than 25; a sub-analysis (DGF group versus no DGF group) showed longer warm ischaemia time in the DGF group (33.08 ± 0.57 vs. 30.4 ± 0.34 min, respectively – $P < 0.0001$) [70]. Notably, in a paired deceased donor kidney analysis, whereby the transplant procedures were performed by the same surgical team, obesity was not a risk factor for DGF [74]. In a retrospective single-centre study the authors adopting a minimally invasive (robotic) approach in the obese population report an incidence of 11.3% in the living donor cohort and 34.2% in the deceased donor cohort [68]. In conclusion, prospective studies looking specifically at DGF and obesity are needed.

Obesity and rejection risk

The association between obesity and biopsy-proven acute rejection (BPAR) is more controversial. Some single-centre studies and two large registry studies have identified an increased risk associated with obesity [60,66,75]. Wu *et al.* [76] believe that this increased risk is consistent with the model of obesity as an inflammatory state. A commonly reported challenge in the obese population is the difficulty to achieve an adequate exposure to maintenance immunosuppression, with frequent overexposure responsible for drug toxicity [77,78] and underexposure responsible for increased rejection risk [79]. However, other authors did not observe an increased risk of BPAR [59,73,79–81]. The use of induction therapy has become routine in many transplant centres, resulting in reduced rates of acute cellular rejection after renal transplantation [82].

Currently, rabbit antithymocyte globulin is used as induction agent among obese recipients in most centres [79] (including the author's centre) but prospective studies evaluating the type of induction therapy and acute rejection rates among obese recipients are needed [83].

Kidney transplantation in the obesity: surgical considerations

As described earlier, data on outcomes post-transplantation in obese patients are from registry and retrospective single-centres studies with conflicting results; it is clear that performing surgical procedures on obese patients is technically more difficult, takes longer and there is enough evidence in the literature to say that there is an increased risk of surgical complications [67,80,84,85]. Considering that some studies show comparable outcomes between obese and nonobese patients in absence of surgical complications, its minimization is of paramount importance [67]. Despite attention to details in planning the operation (i.e. choice of the operating table, bariatric equipment) and meticulous surgical technique the obese kidney transplant population has an increased incidence of wound complications (superficial/deep infections, dehiscence and fluid collections) [67,86–90]. Obese recipients are likely to have up to a fourfold increase in SSIs and near threefold increase in hernias [89]. The incidence of SSIs has been reported to range from 20–30% (class I and II obesity) to 40% (class III obesity) [67].

Surgical innovation has led to the development of minimally invasive approaches in many surgical specialties, which is contributing to improved outcomes. Kidney transplantation was initially not considered feasible with conventional laparoscopic techniques because its higher complexity and necessary precision. With the introduction of robotic technology, with its three dimensional, higher resolution visual system, and wrist-like, multidimensional instrument motions, the application of minimally invasive approach became a reality in kidney transplantation. After the first reports in the early 2000s [91], robotic-assisted kidney transplantation (RAKT) gained slowly but steadily popularity worldwide. RAKT has shown promising results compared to open KT; a matched-pair cohort study (28 patients each arm) found comparable patient and graft survival [92]. Additionally, RAKT has resulted in statistically significant reduction in SSIs in a population of obese recipients and comparable graft and patient survival rates to the nonobese population [68,93,94].

Strategies for weight management of ESRD patients and kidney transplant recipients with obesity

Prevention of obesity seems to be a logical approach and has been applied in schools, workplaces and communities, but so far with little impact [95,96]. Therefore, treatment is indicated and guidelines have been developed in the United States [97–99], in United Kingdom [100] and in Europe [101,102]. The common denominator of the guidelines is a multidisciplinary team approach and the necessity of a multimodal treatment, which includes lifestyle changes, dietary modification, physical activity, medications and in selected cases surgery.

Different strategies for the treatment of obesity in the ESRD population have been reported in the literature [51]; for clarity of description the treatment modalities can be applied in the different settings, namely pretransplant, at transplant and post-transplant. In all cases, a multidisciplinary approach, provided by physicians, nutritionists and physical therapists, is paramount to avoid malnutrition and sarcopenia, which have a profound impact on morbidity and mortality [36–38,54,95].

Pretransplant

As mentioned earlier in this review, many institutions adopt a BMI cut-off for access to transplantation, therefore, propose to the patient to lose weight in the pretransplant setting with medical and/or surgical treatment [103]. Medical weight loss techniques, nutritional and pharmacological could potentially be effective but are resource intensive and have a modest long-term success rate [104]. While medical management has a very limited role in the CKD population [103], surgery has proven to be highly effective for weight reduction [105]. Bariatric surgery which was considered, no longer than a decade ago, high risk among kidney transplant candidates [106], has shown in recent reports acceptable morbidity and mortality rates in CKD [105,107] and ESRD patients [108,109]. The procedures most commonly performed are laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (RYGB); the former is mainly a restrictive procedure with resection of the greater curve of the stomach, the latter is a restrictive/malabsorptive procedure that entails creation of a gastric pouch and formation of a Roux-en-Y gastrojejunostomy. Both procedures achieve a significant excess body weight loss (up to 80% within 24 months); to date there are no prospective randomized studies comparing the two procedures. In a recent analysis on the ESRD population, Choudhury *et al.* [110], using a probabilistic Markov model, conclude that RYGB improves access to renal transplantation and thereby increases long-term survival. However, at present, the preferred approach is LSG [110–114]. LSG offers several advantages over RYGB [116]. It is technically less challenging, faster, and has a lower incidence of surgical complications [117]. Furthermore, LSG does not affect intestinal drug absorption with more predictable immunosuppressive drug levels avoiding under- and overimmunosuppression. Several authors report on the efficacy of pretransplant LSG to increase access to the transplant waitlist and improve post-transplant outcomes [114,115,118]. Prospective controlled trials would be needed to better define the role of LSG before kidney transplantation and its benefit on post-transplant outcome.

At transplant

An innovative treatment modality has been proposed and described from the group of University of Illinois which is a combined RAKT and sleeve gastrectomy [119]. The authors report the first case as a proof of concept for an ongoing prospective randomized control study, which compares the safety and efficacy of combining robotic sleeve gastrectomy and RAKT to RAKT alone in obese (class II and III obesity) kidney transplant recipients. The control group will undergo standard of care diet and exercise evaluations and will be encouraged to lose weight prior to kidney transplantation. Each group will consist in 30 study participants. A sample size of 60 subjects has sufficient power to detect clinically significant differences between the experimental and control groups in BMI and estimated glomerular filtration rate. The expected duration of the entire proposed pilot study is three years and each patient will be followed for 1 year after surgery [120].

Post-transplant

Weight gain following transplantation is extremely common, to the point that, according to several authors, it occurs almost universally [57,121]. As pointed out by Chang *et al*. [121], significant post-transplant weight gain, quantified as >20% in the first year or 10% in the second year, has been associated with decreased patient survival. This finding has been substantiated by a very interesting multicentre study conducted in the Netherlands, and the authors found that post-transplant BMI at 1 year and BMI increment post-transplantation were more strongly associated with death or graft compared to pretransplant BMI [57]. As a consequence, the majority of the patients would benefit more from strategies to prevent weight gain post-transplantation rather than to reduce weight pretransplantation. Prevention of weight gain post-transplant largely follows the same approach described earlier, based on multidisciplinary team and multimodal treatment. Studies are needed to evaluate how newer immunosuppressive agents, strategies of steroid-minimization or steroid-free protocols will impact on post-transplant outcomes in the obese population.

A selected subgroup of patients may benefit from bariatric surgery [122]; although the experience is still limited to a small number of cases, the results seem to be promising [122,123]. A recent single-centre, retrospective study [122] conducted on 34 post-transplant patients who underwent LSG or LRYGB shows significant weight loss and improvement in comorbidities without serious graft rejection or dysfunction. However, as a note of caution, the same authors report an increased risk of surgical complications in transplant patients compared to the general population.

Conclusions

Obesity has reached pandemic proportions over the last decades in the general population and, as a consequence, the number of CKD patients seeking access to transplantation is ever increasing. This current scenario is raising several controversies in the transplant community. Is the BMI an appropriate measure to decide who should get a transplant? If yes, what would be the cut off? There is enough evidence in the literature to state that obesity represents a risk factor for surgical complications but not a contraindication for kidney transplantation. The outcomes could be greatly improved adopting multidisciplinary and multimodal treatment strategies. The modern technology with minimally invasive techniques, mainly using robotic platform, allows a drastic reduction in the surgical complications rate with comparable graft and patient survival rates to the non-obese population.

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Conflicts of interest

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