Transplantation in the obese: separating myth from reality

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Abstract
The prevalence of obesity among patients requiring renal replacement therapy continues to increase inexorably. While observational data have suggested that obesity may be associated with better outcomes among patients on dialysis, many centres have been reluctant to transplant obese patients because of concerns over adverse outcomes in the short and long term. In this review, we evaluate data about the safety of weight loss on dialysis and critically review the impact of pre-transplant body mass index and sarcopenia on post-transplant outcomes. We also highlight comparative data on outcomes of obese patients on dialysis versus those undergoing kidney transplantation. We conclude that while obesity can increase the risk of complications such as wound infections or delayed graft function, selected obese patients can achieve good outcomes after transplantation with the risk being broadly comparable to other recipient co-morbidities such as diabetes mellitus.

Keywords: transplantation; obesity; sarcopenia; kidney; outcomes

Introduction
A 50-year-old patient on haemodialysis with hypertensive nephropathy asks to see her nephrologist. She is distraught at having being suspended from the transplant list—her body mass index (BMI) is 35 kg/m² and a transplant surgeon has suspended her from the transplant list due to central obesity. She is told that she needs to reach a BMI of 30 kg/m², which is equivalent to 15 kg weight loss. Since starting her diet 3 months ago, she feels tired, weak, nauseated and is unable to sleep—and she still has not reached her target BMI. Her friend, whose pre-transplant BMI was 43 kg/m², had a successful transplant at the same centre by a different surgeon 9 years ago without any technical complications and has excellent graft function with an estimated glomerular filtration rate of 60 mL/min/1.73 m². She asks about the equity of such a position—why is she being denied a transplant and why is she being made to lose weight when she feels so unwell while dieting? This scenario will be familiar to many nephrologists and highlights the central ethical and clinical issues when transplanting the obese patient—is weight loss safe on dialysis, how does pre-operative BMI impact on post-operative complications, graft and patient survival after transplantation and does transplantation still confer a survival benefit in the obese when compared with dialysis?

Most clinical guidelines state that obesity per se should not be a barrier to transplantation. The British Transplant Society guidelines [1] state that while ‘obese patients (BMI > 30 kg/m²) present technical difficulties and are at increased risk of peri-operative complications, obesity is not an absolute contraindication to transplantation where individuals with a BMI of >40 kg/m² are less likely to benefit’. The European Association of Urology position is that ‘transplantation provides a better survival and better quality of life in overweight dialysis patients and there is not enough evidence to recommend exclusion based on body mass index’ [2]. Yet despite such guidance, it is clear that many centres do not transplant obese patients [3] or advocate using elevated BMI as a contraindication to transplantation [4].

Obesity and weight loss on dialysis
The so-called ‘obesity paradox’ has long been recognized in dialysis with a higher BMI being associated with an improved survival [5–8]. The DOPPS (Dialysis Outcomes and Practice Patterns Study) analysis of 9714 dialysis patients showed higher BMI to be associated with lower mortality rates [9]. Of course, as Zoccali et al. [10] have previously pointed out, such reverse epidemiology may simply be a reflection of low body weight being harmful and being a sign of underlying co-morbidity rather than obesity per se being protective. This phenomenon may be due to the association between sarcopenia (reduced muscle mass) and low BMI. This was illustrated in a study of a 5-year cohort of 121 762 dialysis patients [11] which used serum creatinine as a surrogate marker of muscle mass. Patients who lost both weight and muscle mass had worse outcomes than those losing weight without change in muscle mass. A key problem with BMI is that it is not able to distinguish sarcopenia from adiposity. Indeed, many patients will have a phenotype of sarcopenic obesity—i.e. low muscle mass associated with increased adiposity. Sarcopenia predicts poor outcomes on dialysis [12] and therefore strategies to promote weight loss among those with sarcopenic obesity may simply...
exacerbate muscle wasting. This was highlighted in an observational analysis of 14,632 waitlisted dialysis patients which found that weight loss of >5 kg was associated with a death hazard ratio of 1.51 (1.3–1.75) when compared with those with minimal weight loss [13]. A further large analysis from the United States Renal Data System (USRDS) database demonstrated that weight loss after transplant listing had no positive impact on post-transplant mortality or graft loss irrespective of BMI at the time of listing [14]. Similar associations between low pre-transplant albumin concentrations and adverse post-transplant outcomes [15] again highlight the risk of exacerbating sarcopenia by promoting weight loss. Of course, such observational data do not ascribe causality and it is not clear whether ‘intentional’ weight loss is harmful in the dialysis population. Indeed, multidisciplinary weight reduction programmes can successfully promote reduction in the CKD population [3]—however, the number of patients on dialysis in such studies has generally been small and the long-term safety of such interventions is difficult to evaluate. Similarly, surgical interventions to reduce weight have been shown to be successful in small case-series [16]. However, there are significant risks associated with bariatric surgery in those with CKD. In a study of 27,376 patients undergoing bariatric surgery in the USA, each CKD stage was shown to correlate with a higher complication rate even after adjustment for diabetes and hypertension, with a complication rate of 9.9% in CKD 5 being just over double the complication rate in CKD 1 [17]. An analysis of 188 patients from the USRDS registry data which included patients undergoing weight-reduction surgery both prior to listing and after transplantation demonstrated a 30-day mortality of 3.5% with a further 3.5% dying at 90 days in the post-transplant group [18].

Taken together, the observational data suggest that both a lower BMI and weight loss associated with sarcopenia predicts poor outcomes on dialysis. Furthermore, clinicians need to be cognizant of the fact that few patients are likely to achieve significant weight loss on dialysis with data from Florida suggesting that only 5% of patients achieve the requisite weight loss required for listing [19]. Thus, given the low likelihood of achieving significant weight loss on dialysis, demanding patients to achieve weight loss prior to listing de facto excludes most from access to transplantation.

Impact of obesity on post-transplant outcomes

While much of the data concerning outcomes post-transplantation in obese patients are from single centres with conflicting results, it is clear that wound infections appear to occur more frequently with higher BMI [20, 21]. Delayed graft function (DGF) also appears to be associated with recipient BMI. In a single-centre retrospective study, Weissenbacher et al. conducted a multivariate regression analysis to show that recipient BMI was an independent predictor of DGF, occurring in over 50% of those with a BMI of >30 kg/m². However, it is worth noting that 5-year graft survival was still nearly 70% in the DGF group [22]. The impact of obesity on DGF appears to be a consistently observed phenomenon [23, 24] that appears to occur independent of confounders such as time on dialysis or race. It is not clear whether the mechanism relates to immunological or surgical factors or difficulties in ensuring adequate area under the curve concentrations of calcineurin inhibitors in the obese.

There is also larger registry data analysing the impact of recipient BMI on long-term graft and patient outcomes. Meier-Kriesche et al. [25] used USRDS data for 51,927 primary adult kidney transplants to demonstrate a U-shaped relationship between BMI and graft loss, death with functioning graft and chronic allograft failure—however, they did not adjust for obesity-related co-morbidities. In a more recent transplant registry analysis of 56,841 patients from Australia and New Zealand, recipient obesity was associated with an increased risk of DGF and acute rejection, but a multivariate analysis failed to show any relationship between obesity and patient and graft survival [26]. Streja et al. [27] analysed 10,090 kidney transplant recipients for up to 6 years post-transplantation. Once again, low pre-transplant BMI (<22 kg/m²) showed a trend towards higher post-transplant mortality, whereas obesity (BMI ≥30 kg/m²) was not associated with mortality, albeit it showed a trend towards higher graft loss. Furthermore, pre-transplant sarcopenia (as reflected by low time-averaged serum creatinine) was associated with significantly lower patient and graft survival. In a larger registry analysis of 27,377 patients from the United Network for Organ Sharing (UNOS), morbid obesity was independently associated with an increased risk of DGF, acute rejection, prolonged hospitalization and reduced overall graft survival [28]. However, multivariate analysis revealed the hazard ratio for graft failure among the morbidly obese to be broadly similar to other recipient co-morbidities such as race, diabetes mellitus, cardiovascular disease, cold ischaemia time and human leucocyte antigen mismatching [28].

In a 20-year follow-up of 1,810 patients transplanted from three centres in the Netherlands, post-transplant BMI at 1 year and BMI increment post-transplantation were much more strongly associated with death or graft failure than pre-transplant BMI [29]. Thus, for many patients, it may be more productive to utilize strategies to prevent weight gain post-transplantation rather than trying to reduce weight pre-transplantation. Furthermore, while there are also conflicting data on whether pre-transplantation BMI is a risk factor for new onset diabetes after transplantation [30, 31], it is worth noting that no large series has yet been published to evaluate the impact of the era steroid-free immunosuppression on post-transplant outcomes in the obese.

Finally, much of the above data are confounded by the fact that BMI may not be a reliable marker of obesity as it is not able to differentiate visceral adiposity from muscle mass and non-visceral fat mass. The waist circumference or waist-to-hip ratio may be better markers of visceral adiposity than BMI and unlike BMI, predict cardiovascular mortality both in the general population [32] and in the dialysis population [33]. These findings were borne out in a prospective transplant cohort of 993 patients, which showed that after correcting for co-morbidity, higher waist
circumference was associated with increased all-cause mortality post-transplantation while a higher pre-transplant BMI was associated with lower mortality [34].

Thus, taking together both registry data and large single-centre experience, it is clear that while obesity (as well as low BMI and sarcopenia) may adversely impact on long-term graft survival, its effect appears to be similar in magnitude to other recipient co-morbidities such as diabetes mellitus which do not preclude successful transplantation.

Transplantation or dialysis for the obese?

The key question perhaps is not whether the obese are more likely to run into complications after transplantation but whether they still have a survival advantage from transplantation. In an analysis of USRDS data, Glanton et al. [35] looked at the outcomes of 7443 patients who had a BMI of >30 kg/m², who were waitlisted for transplantation. The mortality rate for those who underwent 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. Five hundred and fifty-two patients underwent a living donor transplant and the mortality rate was even lower at 1.9 deaths per 100 patient-years. The beneficial effect of transplantation was lost, when BMI was >40 kg/m². While there may be a degree of selection bias, these data suggest that obesity _per se_, in the absence of other co-morbidity, should never be the sole reason for not listing a patient for a transplant—especially in those who have a potential live donor. Despite this apparent benefit of transplantation, obesity appears to adversely affect access to transplantation. In a cohort analysis of 132,353 patients already listed for a transplant on the UNOS database, not only did the likelihood of receiving a transplant decrease with increasing BMI, but the risk of being bypassed when a kidney became available for transplant also increased with BMI [36]. The implication being that there may be systematic clinical or financial bias against those with higher BMIs even if they are deemed as being suitable for transplantation.

The impact of donor obesity

Donor obesity can also impact on both recipient and donor outcomes. While some large single-centre reports suggest that obesity can adversely affect donor kidney function [37, 38] and blood pressure others have found no such effect [39, 40]. Although donor BMI appears to correlate with DGF, there does not appear to be any impact of long-term graft survival [22, 41]. In a large analysis of the Scientific Registry of Transplant Recipients, whilst BMI incrementally associated with an increased risk of DGF, this did not affect long-term graft outcomes unless the donor BMI was >40 kg/m².

Conclusion

There is strong evidence demonstrating that weight-gain and obesity post-transplantation are associated with poorer outcomes, and clearly, it is imperative that such patients have adequate lifestyle and dietary support in achieving a ‘healthy’ weight. With regard to potential recipients who are obese, we believe that clinicians need to be honest with patients and tell them that (i) it is not clear whether weight loss on dialysis is safe and (ii) there is no evidence to demonstrate that intentional weight loss pre-transplantation improves post-transplant outcomes. Furthermore, those patients being counselled to lose weight clearly need multidisciplinary support to ensure that weight loss is achieved in a safe manner avoiding loss of muscle mass. It is essential that all patients being counselled to lose weight have specialist support to avoid sarcopenia. With careful screening to exclude co-morbidities, the current evidence demonstrates that kidney transplantation can be successful even in those with a BMI of up to 40 kg/m². The reluctance among some centres to transplant obese patients is analogous to discussions among the nephrology community 30 years ago about the efficacy of transplanting diabetics. We believe that it is the responsibility of all clinicians to make individual treatment decisions on a holistic evaluation of the patient taking into account all other co-morbidities rather than plucking arbitrary (and impossible) targets out of the air.

Conflict of interest statement. None declared.

References

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