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Obesity as a barrier to kidney transplantation: time to eliminate the body weight bias?

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ABSTRACT
There is clear evidence that survival rates following transplantation far exceed those for remaining on dialysis, regardless of body size measured by body mass index (BMI). Studies over the past 15 years also suggest little to no difference in long-term outcomes, including graft survival and mortality, irrespective of BMI, in contrast to earlier evidence. However, weight bias still exists, as access to kidney transplantation remains inequitable in centres using arbitrary BMI limits. Clinicians faced with the decision regarding listing based on body size are not helped by conflicting recommendations in national and international guidelines. Therefore, in clinical practice, obesity, and recommendations for weight loss, remain a controversial issue when assessing suitability for kidney transplantation.

Obesity management interventions in end-stage kidney disease (ESKD), whether for weight loss for transplantation listing or for slowing kidney disease progression, are under-explored in trial settings. Bariatric surgery is the most successful treatment for obesity, but carries increased risk in the ESKD population, and the desired outcome of kidney transplant listing is not guaranteed. Centers that limit transplants to those meeting arbitrary levels of body mass, rather than adopting an individualised assessment approach, may be unfairly depriving many ESKD patients of the survival and quality of life benefits derived from kidney transplantation. However, robotic kidney transplantation surgery holds promise for reducing perioperative risks related to obesity, and may therefore represent an opportunity to remove listing criteria based on size.

Keywords: Transplant; obesity, chronic kidney disease; weight loss; dialysis

Introduction

The use of BMI as an assessment criterion for kidney transplantation is out of step with current practice, which favors a personalized medicine approach. BMI, originally derived as a measure predictive of population level mortality risk, is now widely used as a surrogate for obesity; issues with the appropriateness of this will not be considered here [1]. This paper explores this evidence regarding obesity as a risk factor for post-transplant outcomes, graft survival and mortality.

Clinical Practice Guidelines for transplant assessment generally recommend an individualised approach to determining suitability based on body weight, shape and size; however, they are plagued by moderate-to-low certainty evidence, which leads to inconsistencies in practice, often resulting in recommendations for weight loss prior to kidney transplant waitlisting.

The UK Renal Association (UK-RA) [2] and the Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) [3] both recommend that obesity by itself (defined as a BMI $\geq$30kg/m^2) should not preclude listing for transplantation (UK-RA and CARI, GRADE 2B and 1B, respectively), and that assessment should be individualised and cardiovascular risk factors be considered (2B and 1C). Both also suggest that the positive outcomes of transplantation may be diminished in those with a BMI > 40kg/m^2 (2B and 1C).

The European Renal Best Practice guideline group (ERBP) state that the association between BMI and patient survival is uncertain, and refrained from making a guideline statement on kidney transplant listing based on obesity itself [4]. Instead, they took the approach of recommending weight loss for potential candidates with a BMI >30 kg/m^2 (ungraded), cautioning against pharmacological therapy and bariatric surgery due to the increased risks associated with these treatments.

Obesity and kidney transplant outcomes

Recent systematic reviews on kidney transplant outcomes demonstrate an increased risk of delayed graft function with obesity [5-8]; however, the data on mortality and graft survival are less clear [5-12]. The inconsistent conclusions appear to be related to methodological differences of inclusion criteria, date range and statistical analyses. In 2014, Nicoletto et

al reported that obesity did not impact upon death or graft loss in studies published since 2003 [6]. However, in studies published prior to 2003, obesity (BMI >30kg/m^2) was associated with more death and graft loss than was seen in those having a normal BMI range [6]. Meta analyses conducted by Lafranca et al (2016) and Sood et al (2015) report an increased unadjusted risk ratio (RR) and fully adjusted hazard ratio (HR) respectively, for mortality, with BMI >30kg/m^2 [5, 7]. However, neither study split the analysis into "modern" and "older" transplantation eras, which may explain the difference in mortality risk between these studies and that conducted by Nicoletto et al.

The combined risk ratio reported by Lafranca et al suggested an association of obesity with an increased mortality risk (RR 1.52; 95% CI 1.14-2.03) [7]. In the same study, the meta analysis of studies using fully adjusted regression analysis (rather than an absolute risk ratio) demonstrated no association between obesity and mortality after kidney transplantation (HR 1.10; 95% CI 0/89-1.15). This finding concurred with that of Hill et al, who used a similar methodology (HR 1.24; 95%CI 0.9-1.7) [8]. All of these reviews have suggested that it is factors associated with obesity, rather than obesity per se, that explains the differences between studies that have adjusted for potential confounders and those which have not.

Similarly, conflicting results are reported for BMI and graft survival. Meta-analyses indicate a small reduction in the unadjusted risk of graft failure in lower compared to higher BMI recipients (RR 0.97; 95% CI 0.96-0.99) [7] and a small increased risk of graft loss with higher BMI (adjusted HR 1.06; 95% CI 1.01-1.12) [8]; yet in the seven studies using generalized linear modeling there was no difference in graft survival between low and high BMI (HR 1.00; 95% CI 0.96-1.04) [7]. Studies based on US transplant recipient databases all demonstrate an increased risk of, or shorter time to, graft failure with increasing BMI [9-11]. In those with a BMI > 50 kg/m^2, the risk of 30-day perioperative mortality, length of hospital stay, delay in graft function and 1, 3 and 5 year mortality were all significantly greater than in any other BMI group [13].

Conversely, using data extracted from the UK Renal Registry and the National Health Service Blood and Transplant (NHSBT) database for the UK transplant recipient population, fully adjusted hazard ratios for graft survival and patient survival did not differ across BMI bands in transplanted patients, up to BMI >40kg/m^2 [12]. It may be relevant that this study included participants transplanted from 2004 onwards. Furthermore, the authors suggest that the differences in their findings

when compared to other registry studies may be attributed to robust cardiovascular assessment of all potential transplant recipients in the UK.

Regardless of these contrasting (and, when present, relatively minor) findings for graft and patient survival after transplantation, there is clear evidence indicating that outcomes after transplantation are superior to those on dialysis, at any level of BMI [12, 14]. There was a significant survival benefit, in fully adjusted analyses, across all BMI categories for all types of transplant, compared to remaining on the waitlist, in both the UK [12] and US registry-based studies [14]. Survival at 1 and 5 years improved across BMI categories up to BMI >40kg/m^2, compared with remaining on dialysis, and there was no level of BMI at which this survival benefit was not evident [12]. One caveat appeared in the sub-group of black patients with BMI ≥40 kg/m^2, with no survival advantage with transplantation over dialysis; however, this analysis is likely to be underpowered given the small sample size of this group [14].

Weight bias in transplantation and transplant listing

In patients with high BMI, listing for transplantation remains biased against this group despite clear evidence of a survival advantage over remaining on dialysis. In the US, the proportion of wait-listed patients receiving a transplant peaks at 69% when BMI is <18.5kg/m^2, then decreases steadily as BMI increases, down to a low of 45% when BMI is ≥ 40 kg/m^2 [15]. Up to 30% of exclusions from transplant listing can be attributed to obesity [16]. Data from the French Renal and Epidemiology Information Network (REIN) indicate that, after adjustment for potential confounding variables, the likelihood of transplantation falls as BMI increases above 30 kg/m^2. Patients with a BMI of >31kg/m^2 are more likely to remain on dialysis than receive a kidney transplant (HR <1) [17]. Beyond this, patients with a BMI ≥40 kg/m^2 were half as likely to undergo transplantation than those with a BMI between 21-31 kg/m^2 [17]. Furthermore, in those with a BMI ≥ 30kg/m^2 each 1kg/m^2 decrease in BMI is associated with a 9-11% increase in the likelihood of transplantation.

Weight bias in kidney transplantation waitlisting likely exists due to the short-term complications such as higher rates of wound complications, longer hospital stay and delayed graft function. These factors have a direct impact on transplant centre costs and measures of quality and excellence; avoiding transplantation in high BMI patients may be practiced in an attempt to improve these measures [18]. Weight bias is also based on outcome data from "older" eras of transplantation, that likely differ from outcomes in during the "modern" era (the last 15 years)

of kidney transplantation. There appears to be consistency in the findings of studies using data from the early 2000s onwards, demonstrating no difference in patient or graft survival with obesity, compared to the normal BMI category as the reference standard [6, 12]. This equivalence of outcomes is largely supported by the systematic review of findings using multivariate analyses adjusted for likely confounding variables [7, 8].

Weight management options – from lifestyle to bariatric surgery

As BMI remains as a gatekeeper for transplant listing, weight loss interventions, including bariatric surgery, must be undertaken to improve the likelihood for kidney transplant listing for individuals. This is the case even though well-conducted, prospective studies of intentional weight loss on short and long term post transplant outcomes are lacking. Successful transplantation listing after bariatric surgery has been reported in several studies; many of these are small case series, with 55-100% of those undergoing bariatric surgery being listed for, or receiving a kidney transplant during follow up [19-24].

More modest weight loss has been recorded with lifestyle approaches including dietary intervention with or without exercise. Weight management approaches in the CKD population are most frequently assessed prior to dialysis and appear to promote weight loss in a range of 2-10%, sustained for up to 24 months [25-26]. In this weight loss range, several studies have demonstrated improved metabolic health [25-26]. However, this field is limited by small RCTs with high risk of bias, with limited focus on transplant listing as outcomes.

Although bariatric surgery may be able to help patients become listed for or receive kidney transplants, the risks involved from such surgery for people with kidney disease exceed those of the general population. Complications increase as kidney function declines, with almost a 10% increased absolute risk of complication post bariatric surgery in those with stage 5 CKD [27]. Risk of mortality post bariatric surgery is 11 times higher in those with ESKD compared to those without CKD, with the absolute rate increasing from 12 to 157 deaths per 1000 person years [28]. These risks, as well as potential benefits should be explained to, and understood by, individuals as part of decision-making process.

Use of specialised centres for bariatric surgery in ESKD may reduce operative complications and length of stay. Improvements occurred in the last 25 patients compared to the first 25 in a series of 100 patients with CKD undergoing bariatric surgery in a single centre, identifying a

learning curve for surgery in this specific patient population [29]. Risk minimisation protocols may also help to identify and reduce risk. The London Renal Obesity Network developed a joint surgical and nephrology protocol for patients with CKD undergoing bariatric surgery. They outline the steps to be taken for assessment, preparation and post operative monitoring, to improve clarity around management of renal specific issues including, but not limited to, robust cardiovascular risk assessment and fluid management [30].

Many individuals and some guideline groups advocate for assessment of a patient's suitability for kidney transplantation on an individualized basis considering metabolic fitness and surgical feasibility. However, unwarranted bias in wait listing continues to exist due to arbitrary BMI limits, and bariatric surgery often needs to be considered. However, before bariatric surgery is routinely recommended based on BMI alone to ESKD patients seeking kidney transplantation, robust evidence from prospective studies of improvements in patient focused outcomes and long-term safety is required [31].

Could robotic transplants address the issue?

Robotic surgery shows promise as a solution to the problem of body size impeding kidney transplantation. Several studies have demonstrated significantly fewer, and often no, site infections in obese, robotic transplant recipients [32-34]. Outcomes up to 5 years post robotic-assisted transplantation have also been studied. Median BMI in the robotic cases was significantly higher than on the open controls (BMI; 42.3 (31.1-64.3) vs 36.8 (30.0-51.1)), yet there was no difference in patient and graft survival or transplant rejection at 5 years between groups [33]. Similarly, using data from the UNOS registry in the US from patients with BMI >40 kg/m^2, with higher BMI in the robotic transplant group compared to open surgery, there was no difference in patient or graft survival, or kidney function at 3 years post transplant [34].

Is it time to limit body weight bias in kidney transplantation?

Bariatric surgery does lead to effective weight loss in patients with ESKD, but is not without risk and, of course, does not guarantee transplantation. Benefits may only outweigh the risks when the end goal of transplantation is achieved. In order to avoid potentially unwarranted weight loss surgery, referral to a specialist centre for robotic surgery should be considered in patients whose BMI is > 40kg/m^2; this may help reduce the current trend towards bariatric surgery. With robust pre-transplant recipient assessment, sound medical management, risk assessment and modern era immunosuppression, weight loss prior to

transplantation is unlikely to further improve outcomes, and can increase the time on dialysis prior to transplantation. Certainly, when individualized assessment and cardiovascular disease risk assessment does not preclude transplantation, listing should occur without reference to BMI, provided all other listing assessment criteria are met.

This area is ripe for new research to address many of the conundrums faced. First, there is a need to continue to evaluate outcomes from robotic transplant procedures. Second, further evaluation of frailty and functional capacity, independent of body size, on transplant outcomes is needed. This may pave the way for clinical trials using nutrition and exercise interventions pre-transplant, with a focus on more patient-centered outcomes, rather than BMI, to optimise metabolic health prior to kidney transplantation.

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