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Editorial Comment

EDITORIAL COMMENT

Obesity and listing for renal transplantation: weighing the evidence for a growing problem

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Abstract

A 56-year-old female patient was referred to the transplant assessment clinic in July 2016. She started haemodialysis in 2012 for renal failure due to urinary tract infections. She is doing very well on dialysis and has an excellent exercise tolerance without shortness of breath or angina. She has had no infections since starting dialysis and no other comorbidity, except well-controlled hypertension and hyperparathyroidism requiring treatment with cinacalcet. Clinical examination is essentially normal except for truncal obesity with height 167 cm and weight 121 kg, giving her a body mass index of 43.4. Can she be listed for a renal transplant? If not, which target weight should be given to the patient before she can be transplant listed? Which interventions, if any, should be recommended to achieve weight loss?

Key words: body mass index, obesity, renal transplantation

Obesity—a worldwide epidemic

Obesity [1], defined as a body mass index (BMI) in excess of 30 kg/m^2, is clearly on the increase: in 2014, 600 million adults were obese while a staggering 1.9 billion were overweight with a BMI between 25 and 30 [2]. The worldwide prevalence of obesity more than doubled between 1980 and 2014 [2].

In the general population, obesity contributes substantially to the overall burden of disease and has now climbed as a risk factor for chronic diseases from the 10th position to 6th [3]. In Europe, North and South America, Central Asia and parts of Africa, high BMI ranks among the top four risk factors for disease burden, following only high blood pressure, smoking and alcohol use [3]. In comparison, the relationship between BMI and mortality is more complex, whereby there is a U-shaped association between BMI and mortality (people with intermediate BMIs outlive people with higher or lower BMIs) and the nadirs of these curves tend to increase monotonically with age [4].

The renal population is no exception when it comes to trends of BMI and this includes transplant recipients [5]. Between 1995 and 2002, mean BMI of incident dialysis patients in the USA increased from 25.7 to 27.5 kg/m^2 [6]. Similarly, in a recent Italian study the increase in the proportion of obese

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patients was 6–14% in Calabria and 6–16% in Emilia [7]. The fact that use of fast food is widespread and on the increase in our renal patients, despite their above average exposure to dieticians, is both worrying and difficult to understand [8].

BMI—an imperfect tool to measure and monitor obesity

The World Health Organization defines overweight as a BMI of 25 – 29.9 kg/m^2 and obese as a BMI $\geq$30 kg/m^2 [9]. The surgical literature often uses a different classification to categorize particularly severe obesity: severe obesity, BMI >40 kg/m^2; morbid or extreme obesity, BMI of 40–50 kg/m^2; and super obese, BMI >50 kg/m^2 [3]. Interestingly, ethnicity also affects BMI and ethnicity-specific BMI criteria have been proposed [10].

BMI correlates with the degree of body fat in a curvilinear fashion, but many caveats apply: first, the correlation is weaker at low BMIs. In muscular individuals, BMIs that would usually indicate overweight or mild obesity may be spurious, whereas in some persons with sarcopenia (e.g. elderly individuals and persons of Asian descent), a typically normal BMI may conceal underlying 'hidden obesity' [11]. In view of these limitations, some authorities advocate a definition of obesity based on the true percentage of body fat. For men, a percentage of body fat >25% defines obesity, with 21–25% being borderline. For women, >33% defines obesity, with 31–33% being borderline.

How can true body fat be assessed? First, body fat content can be estimated using the Deurenberg formula, but this can overestimate body fat in obese individuals [12]. Options for actual measurement include waist:hip ratio (WHR), skinfold thickness or the use of more sophisticated methodologies such as body impedance. WHR is a good marker of visceral adiposity and does seem to predict cardiovascular mortality both in the general population [13] and in dialysis population [14]. However, none of these considerations have really permeated daily clinical practice and in reality BMI is used almost exclusively [15].

BMI and survival—paradox, poorly understood or just very complex?

In the general population, higher BMI is associated with burden of disease [3]. In contrast, higher BMI is paradoxically associated with survival advantages in haemodialysis patients, including those waitlisted for kidney transplantation [16, 17]. This phenomenon has interested nephrologists ever since the first report by Fleischmann *et al.* [18] in 1999, but the mechanisms underlying this observation remain poorly understood and debated. A recent study on 123 383 American dialysis patients confirmed that higher BMI was associated with lower mortality across all age and dialysis vintage groups [19]. Most authors concur that survival advantage associated with higher BMI in dialysis patients is restricted to those with normal or high muscle mass and that fat mass in itself is not protective [20]. Another interesting caveat in this assumption is that ethnicity may have an influence as well: in Japanese haemodialysis patients, both lean body mass and fat are protective [21]. It is also worthwhile remembering that malnutrition is a strong predictor of poor outcome in dialysis patients and that patients reaching end-stage renal disease represent a small selection of 'survivors' compared with the chronic kidney disease population at large. In this highly selected population, high BMI may associate with other factors that are protective for dialysis patients. Similarly, depression is very common in patients on maintenance dialysis and is associated with weight loss and poor outcomes [22]. It is also interesting to note that biochemical absence or presence of inflammation modifies the effect of BMI on mortality whereby no protective effect with higher BMI are seen in non-inflamed patients [23]. Others have attempted to explain the observation by emphasizing that uremic toxin production rate is relatively higher in patients with low body weight [24]. Interestingly, endothelial progenitor cell density is increased in non-diabetic obesity [25] and this has been invoked to explain the benefit of obesity in inflamed patients [23]. In summary, current concepts point to a role of elevated BMI nullifying the negative consequences of chronic inflammation [23].

Use of BMI in recipient selection—contemporary practice and guidelines

Our own experience suggests that practice is extremely variable internationally, nationally and sometimes even within the same department. Access to transplantation generally varies between centres in the UK in a way that cannot be explained by case mix [26]. Data are scant, but in a 2013 survey carried out via NDTeducational, 29% of respondents indicated that they had a cut-off of >35 kg/m^2 for listing, whereas 27% stated that their BMI cut-off was >30 kg/m^2 [27]. Current guidelines are also relatively vague. The European Renal Best Practice Transplantation Guideline Development Group documented that 'No other guideline body provides recommendations on this topic of BMI and transplant', but recommends that patients with a BMI >30 kg/m^2 reduce weight before transplantation (ungraded statement) [28]. The British Renal Association guidelines state that 'Obese patients (BMI >30 kg/m^2) ... should be screened rigorously for cardiovascular disease and each case considered individually' and that 'individuals with BMI >40 kg/m^2 are less likely to benefit' [29]. Similar recommendations are given by guidelines in Australia/New Zealand [30]. The European Association of Urology guideline states 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 BMI' [31]. It is all the more surprising that some centres remain categorical on this topic. For example, in 2010, MacLaughlin *et al.* [32] subjected patients to a weight loss programme to achieve a BMI of 30 and thus become eligible for transplantation in their centre in London. Lafranca *et al.* [33], in a 2015 paper on the topic, also suggested a categorical BMI cut-off of 30. Finally, it is important to note that factors other than guidelines may affect the way in which BMI affects access to transplantation listing: Gill *et al.* [34] demonstrated that higher BMI is associated with a lower likelihood of transplantation primarily in women and note that underlying perceptions clearly deserve further study.

BMI and post-transplant outcomes

The association of high BMI with post-transplant outcomes has been established through a variety of studies. Meier-Kriesche *et al.* [35] used United States Renal Data System (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. In an analysis of 5684 patients from Australia and New Zealand, recipient BMI was also associated with increased risk of delayed graft function and acute rejection, but a multivariate analysis failed to show any relationship with graft survival [36]. In contrast, a recent meta-analysis by Lafranca *et al.* [33] found a positive effect of

BMI <30 for several of the pooled outcome measurements, including mortality and rejection. Another review and meta-analysis including 11 studies indicated that underweight, overweight and obese recipients had higher mortality [37]. However, Streja *et al.* [38], in an analysis of 10 090 kidney transplant recipients, did not show increased mortality with obese recipients, although there was a trend towards higher graft loss. However, pre-transplant sarcopenia was associated with significant lower patient and graft survival [38]. An increased risk of surgical-site infections in obese patients is also well-established in the literature. A recent systemic review and meta-analysis study by Lafranca *et al.* [33] reported that the incidence of wound infections and wound dehiscence were studied in 13 studies ($N = 4504$ recipients) [5–17] and 6 studies ($N = 3922$ recipients), respectively [4–16]. Of more concern, a study of 869 kidney transplant recipients by Lynch *et al.* [39] reported that the development of surgical site infections was associated with a significant increase in the risk of allograft loss at 3 years [hazard ratio 2.2 (95% confidence interval 1.36–3.55)]. In summary, obesity impacts many interrelated outcomes post-transplant. Obesity does increase the risk of wound infection, but despite several studies and meta-analyses, the situation for graft and patient survival is much less clear and some studies suggest a negative impact of obesity, whereas others do not.

Patient survival in obese recipients—transplantation versus remaining on dialysis

Although obesity is associated with increased post-operative complications, observational studies suggest that transplantation among obese transplant recipients offers survival advantages compared with waitlisted obese transplant candidates. In an analysis of USRDS, Glanton *et al.* [40] looked at the outcomes of 7443 patients who had a BMI >30 kg/m^2 and were waitlisted for transplantation. In this study, mortality for those who underwent transplantation was still half that of patients who stayed on dialysis (3.3 versus 6.6 deaths/100 patient-years, respectively). Interestingly, the beneficial effect of transplantation was lost when BMI was >40 kg/m^2 [40]. Another recent study using data from the USRDS between 1995 and 2007 reported a 48% reduction in the risk of death in patients with a BMI ≥40 kg/m^2 but a ≥66% reduction in patients with BMI 30–39 kg/m^2 [41]. This study also revealed that living donor transplantation was associated with ≥66% reduction in the risk of death in all BMI groups [2]. The survival advantage of transplantation was lower in patients with class III obesity (BMI of 40 kg/m^2), and in some subgroups (i.e. Black patients with a BMI of 40 kg/m^2) transplantation was not associated with a survival benefit compared to treatment with dialysis [41]. Another recent study analysed the UK Renal Registry for patients listed from 1 January 2004 to 31 December 2010 and compared survival between those transplanted and those who remained listed in 17 681 patients. Remarkably, 1- and 5-year patient survival was significantly better in all BMI bands (<18.5, 18.5 – < 25, 25 – <30, 30 – <35, 35 – <40 and ≥ 40 kg/m^2) in the transplant group when compared with those who remained on the waiting list ($P < 0.0001$) [42]. An important cautionary note related to such studies is that overall the number of very obese transplanted individuals was low and that substantial selection bias may be present in that favourable outcomes of transplanted patients with higher BMI may be the result of non-random selection of healthier obese patients that remain unaccounted for in these studies [43].

Pre-transplant weight loss and optimization

A recent case–control study examined post-transplant survival among obese kidney candidates who were temporarily suspended on the list due to their weight (BMI ≥30 kg/m^2); no difference in survival was observed with pre-transplant weight loss [44]. Some authors have gone further and argue that focusing on pre-transplant weight loss is somewhat futile: in a 20-year follow-up of 1810 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 [45]. The authors concluded that 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 [45]. Khwaja *et al.* [46] suggested that patients need to be told that it is not clear whether weight loss on dialysis is safe and that 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 (sarcopenia) [46].

More widely, preoperative optimization of the kidney transplant patient is essential in achieving a favourable outcome. Pre-emptive anaesthetic assessment of such recipients is essential not only for perioperative management but also for a multidisciplinary consensus on the appropriateness of proceeding with transplantation. Live-donor transplantation has a unique advantage not only because interventions to optimize can be planned, but also because the concrete potential for a transplant in the near future can motivate recipients to lose weight. The Society for Bariatric and Obese Anaesthesia has formulated comprehensive guidelines for the preoperative management of the obese patient [47] and it has been noted that anaesthetists can play a crucial role in motivating patients to lose weight when they discuss the obesity-related risks directly with the patient [48].

Bariatric surgery for pre-transplant weight loss

We have previously discussed that common sense, but not current evidence, suggests weight loss pre-transplant in obese recipients. It is also clear from clinical practice that many patients would not be able to achieve any degree of weight loss by conventional means alone and it is not surprising that clinicians consider bariatric surgery. A review of USRDS between 1991 and 2004 revealed 188 patients undergoing bariatric surgery before transplant listing, on the waiting list and after transplantation [49]. The review showed a mean excess body weight loss of 61%, which is lower than age-matched, non-ESRD patients undergoing bariatric surgery. One of the larger case series so far reported 30 patients undergoing gastric bypass and found the intervention safe and effective [50]. Others reported good results with gastric banding [51]. It is tempting to speculate that being on dialysis itself might affect the outcome of bariatric surgery. A very recent study in dialysis-dependent and non-dialysis-dependent patients with chronic kidney disease undergoing bariatric surgery showed increased morbidity in patients on dialysis but no difference in mortality [52]. In summary, we feel that given the uncertainty around pre-transplant weight loss in general it is premature to advocate routine bariatric surgery for obese recipients. Further prospective trials are awaited to establish the efficacy of bariatric surgery as an adjunct to improve renal transplant outcomes for obese patients.

Perioperative and surgical risk

Surgical intervention in an obese individual is generally associated with increased morbidity, although, interestingly, another paradox applies whereby obese patients have been reported to have a better long-term survival [53]. Surgery in the morbidly obese has also significantly developed as a subspecialty in its own right [54]. Any surgical intervention in an obese individual is fraught with technical challenges, including difficulty in exposure of the surgical field (Figure 1), and studies have established the increased incidence of wound complications (superficial/deep infections, dehiscence and fluid collections) when obese patients undergo renal transplantation [39, 55]. It is hypothesized that increased wound complications stem from the larger dead space above the fascia, larger incisions, longer operative time and also from the higher prevalence of diabetes [56]. Delayed wound healing, incisional hernia and deep vein thrombosis have also been shown to be more common [57]. Post-operative inactivity also needs to be considered, and length of stay is increased in obese renal transplant recipients [58]. Not surprisingly, transplanting obese recipients is therefore also more costly [59], which may be a hidden disincentive for transplant centres to accept such patients [5]. Furthermore, obese individuals are more likely to suffer with significant comorbidities such as cardiovascular disease, hypertension and diabetes, resulting in heightened anaesthetic risks [60]. Other specific risks may be particularly relevant in obese patients undergoing renal transplantation; dialysis access can be challenging, particularly in the very obese, as is adequacy of dialysis, and thus these patients may go into surgery less well-dialysed than their non-obese counterparts. Fluid status is more difficult to assess and patients suffering fluid expansion or contraction perioperatively may be more difficult to assess clinically due to their body habitus. Whether an elevated intra-abdominal pressure in the obese has any effect perioperatively or on graft function remains unclear [61]. Other perioperative complications such as renal vein thrombosis, renal artery stenosis and lymphocele formation are inconsistently reported in the literature [62].

Fig. 1. Intraoperative exposure in an obese recipient utilizing the Bookwalter retractor (courtesy of Dr Frank Dor, Imperial College Healthcare Trust, London, UK).

Operative considerations and specific surgical techniques

Obsessive attention to detail in the appropriate choice of the operating table, bariatric equipment and closure techniques should be maintained to prevent morbidity. As wound issues are the main established postoperative complication, extra diligence should be applied during gaining optimum access with

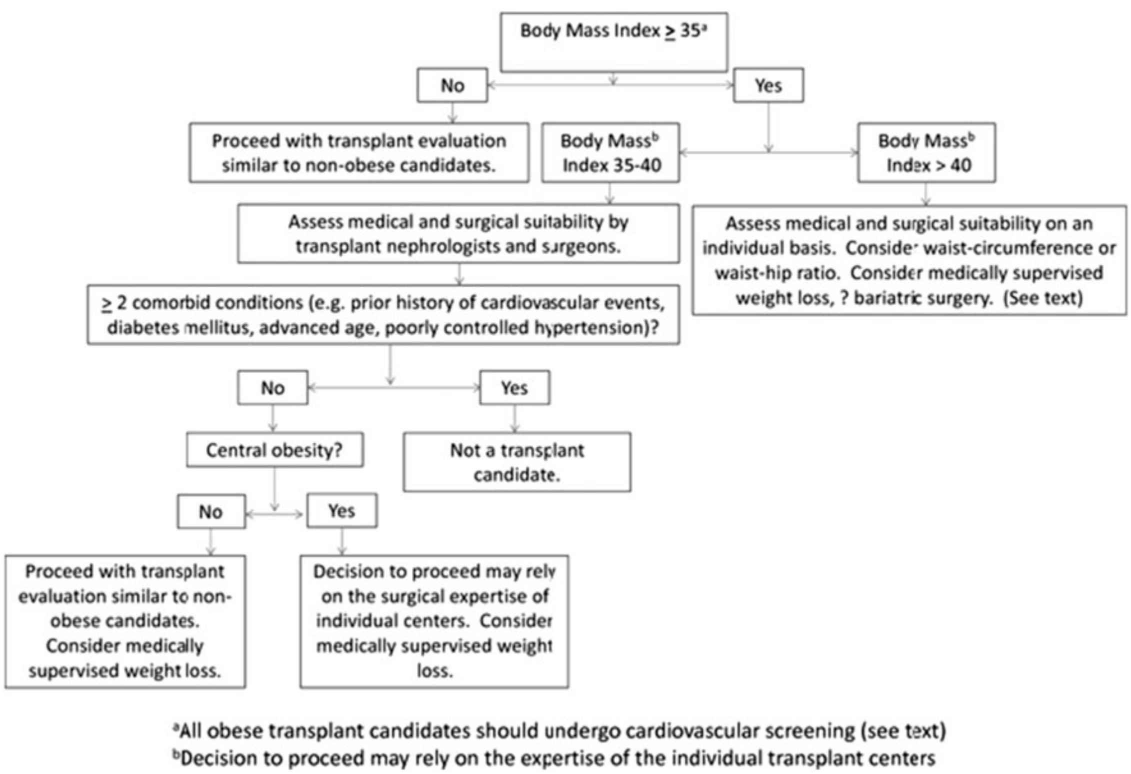

Fig. 2. Algorithm for transplant listing in obese recipients [65] (with permission).

the use of adjuncts such as Omni-tract and Bookwalter retractors. Similarly, closure should be performed in multiple layers to reduce dead-space formation, with the liberal use of suction drains to prevent fluid collections. As modern technology and surgical techniques in obesity surgery and transplantation have advanced, the role of minimally invasive robotic surgery has been explored and may have definite advantages if carried out by experienced teams [63, 64]. Particularly in obese patients, these techniques may yield the maximum achievable benefit, as they naturally reduce surgical insult and reduce the risks of wound complications.

Conclusion

The discussion has for too long focused on the question of whether obesity increases risk (which is undisputed). The appropriate question is whether an obese recipient still benefits compared with dialysis, despite the risk incurred by obesity [42], bearing in mind that it is difficult to identify limits of body composition that preclude clinical benefit from kidney transplantation [5]. It is, therefore, time to treat obesity as one risk factor among many others and not as an independent and additional hurdle for transplant listing. On the other end of the spectrum, nihilism (i.e. listing everybody regardless of the degree of obesity) seems equally inappropriate. Obese recipients, such as the patient in our case vignette, should be offered individualized care plans based on multiple factors, including their comorbidity and risk, living donor availability, sensitization and local expertise. Pham *et al.* [65] suggested an algorithm (Figure 2), whereby the patient in our case vignette should undergo holistic assessment and counselling and attempt to lose weight until a BMI of 40 is achieved. A multidisciplinary approach should involve dieticians and general practitioners to ensure weight loss is feasible and does not lead to sarcopenia. The role of bariatric surgery remains unclear. The transplant community should also consider how to move on from the monodimensional measurement of BMI to more sophisticated assessments of body fat. Finally, it is time for transplant centres to come up with policies on this topic in order to provide transparency for patients, relatives and health care providers.

Conflict of interest statement

None declared.

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