Moderator’s view: Pretransplant weight loss in dialysis patients: *cum grano salis*

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**ABSTRACT**

A high Body Mass Index (BMI) predicts delayed graft function, all cause and cardiovascular death after transplantation but such risk excess is apparently confined to patients included in studies performed before 2000. Perhaps with the exception of morbid obesity (BMI > 40), clinical outcomes in transplanted obese patients are definitely better than in listed dialysis patients who don’t receive a renal transplant. Furthermore the new Scientific Registry of Transplant Recipients (SRTR) risk calculator incorporates BMI into the prediction model of the global risk for the graft’s and patient’s survival appropriately framing the risk of obesity in a multidimensional risk context. In the aggregate, available knowledge suggests that clinical decisions on weight loss before transplantation should be context specific. Renal transplant patients from living donors have substantial better survival in comparison to well matched dialysis patients listed for the same intervention at all BMI categories. Therefore renal transplantation in obese patients with a living donor may be prioritized. The attitude of fully informed obese patients at accepting the risk driven by transplantation, the experience of the surgical team with obese patients (including also robotic surgery) are of obvious importance. Renal transplantation should be timely considered when reasonable attempts at weight loss failed or appear overtly unrealistic. Transplantation in morbidly obese patients with BMI > 40, a category where the survival advantage of transplantation vs dialysis is probably small and still uncertain, particularly so in African-Americans, should be deferred until significant weight loss is achieved.

**Keywords:** obesity, dialysis, transplantation, weight loss, CKD

Obesity is one of the major drivers of the current epidemics of chronic diseases worldwide, from cardiovascular disease to osteoarthritis and neoplasia, including colon cancer and endometrial and breast cancer [1]. Although still insufficiently emphasized, chronic kidney disease (CKD) is a very relevant element in the wide-ranging list of chronic diseases driven by obesity and it is perhaps the most common cause of this condition at population level. As of 2012, in the United States Renal Data System (USRDS), type-2 diabetes and hypertension, two risk factors largely attributable to overweight and obesity, ranked as the most frequent causes of kidney failure [2], the combined prevalence of end-stage renal disease (ESRD) secondary to these risk factors being about 1200 patients per million population, a rate about three times higher than that attributable to glomerular and hereditary diseases combined (~400 patients per million population). In the years between 1995 and 2002, the average body mass index (BMI) in the dialysis population in the USA rose at twice as fast rate (from 25.8 to 27.9 kg/m²) as in the contemporary general population (25.7 to 26.7 kg/m²) [3]. Over the same years, the number of bariatric surgery interventions in American dialysis patients more than tripled [4].

Kidney transplantation is indisputably the best renal replacement therapy for ESRD and the superiority of this treatment over dialysis applies to high-risk conditions including diabetes [5], liver disease [6] and heart failure [7]. Even though we still lack state-of-the-art, detailed risk–benefit analyses in obese dialysis patients, pressure to transplant obese patients is increasing. In 2006 the prevalence rate of dialysis patients with mild obesity (BMI 30–35 kg/m²) in the waiting list for renal transplantation was 14%, while the corresponding figure in 2011 was 20% and...
WEIGHT LOSS IN THE OBESE DIALYSIS POPULATION: AN UNCERTAIN SCENARIO

Good medical practice demands dietary and drug treatments be applied only when there is evidence that they may be beneficial or, in the lack of a proper trial, evidence exists that they do not cause harm. By the same token, it is good clinical practice to precede elective surgical interventions by minimization of treatable risk factors. As alluded to before, obesity is an unquestionable public health priority and a powerful risk factor in the general population [1]. However, experimental proof that obesity is also a risk factor for adverse clinical outcomes in the ESRD population is lacking because no randomized trial testing the health benefits of intentional weight loss in this population has been performed so far. This lack of specific knowledge makes decisions about obesity treatment in ESRD highly problematic and opinion and experience, rather than evidence-based decisions, dominate the scene. This is so also because reverse epidemiology, i.e. the apparently paradoxical inverse association between mortality and the BMI, is a hallmark of ESRD. Analyses performed in renal registries [8] in large, high-quality clinical databases [9] and in international studies [10] documented that BMI associates in an inverse fashion with mortality. Reverse epidemiology is not peculiar to ESRD but extends to other chronic diseases, e.g. chronic heart failure [11], some investigators oppose the use of the ‘reverse epidemiology’ concept [12]. As a matter of fact, in dialysis patients in the Netherlands the association of the BMI with the death risk has a shape superimposable on that observed in the age- and sex-matched general population [13]. Although formally correct, the term ‘reverse’ may generate the false perception that this inverse relationship underlies a proven causal link [12]. Obesity conferred a survival advantage to human beings till the 19th century, i.e. in epochs when food scarcity and infection limited human life to ∼40–50 years [14], and in theory the same protective effect may apply to high-risk chronic conditions like cancer, heart failure and ESRD. In descriptive analyses made by the USRDS in morbidly obese ESRD patients submitted to bariatric surgery, the 3-year survival rate after such an intervention was ∼78% [4], which prima facie (i.e. in a crude analysis) would compare favorably with the expected survival rate (∼60%) of ESRD patients with a BMI >30 kg/m² in another analysis in the same database in 2004 [15]. However, as alluded to before, with the lack of proper trials testing the effect of intentional weight loss in the dialysis population, such a conclusion is unwarranted. Furthermore, the BMI is an imperfect metric of fat excess in CKD [16]. The adoption of a metric reflecting abdominal obesity, the waist circumference, rather than an inverse relationship, reveals a linear, direct association between this parameter and all-cause and cardiovascular mortality in the dialysis population [17], which perfectly coincides with findings in a worldwide extended case–control study of patients with myocardial infarction [18].

In this uncertain scenario, clinical policies about intentional weight loss interventions in obese patients who are candidates for renal transplantation vary widely within and between countries and recommendations in clinical guidelines differ to an important extent.

WEIGHT LOSS BEFORE TRANSPLANTATION: THE PRO AND THE CON VIEWS

Starting from common ground, the two opponents of this Polar View agree on at least four important points. Both contenders emphasize (i) that in studies performed so far obesity was measured by the BMI, which is an inappropriate metric of fat excess, (ii) that the wide range of BMI cut-offs adopted for entering dialysis patients into a renal transplantation program in US centers is unjustified, (iii) that the risk of wound infection, acute rejection, delayed graft function and frequent hospitalization in obese G5 CKD patients has a negative influence for quality evaluation of transplant centers and creates financial problems to transplant programs, eventually discouraging transplantation in the obese and (iv) that weight loss should be considered in obese patients, the dissent being on the optimal timing, which is before transplantation for Krista Lentine [19] and after transplantation for Randal Detwiler [20]. Furthermore, the two contenders adopt the same philosophical approach, i.e. utilitarianism, a philosophy whose fundamental axiom dictates that ‘it is the greatest happiness of the greatest number that is the measure of right and wrong’. Krista Lentine remarks that ‘Kidney transplants are a scarce resource, and the number of persons awaiting transplants increasingly out-paces supply’. The utilitarian assumption is that if the society has to distribute limited financial resources, due to the diminishing marginal utility of money, generally giving it to the person who is more likely to have an improvement in well-being is the best decision. Thus, in order to guarantee the maximum benefit to the greatest number of patients, only those patients who achieve a target BMI should be transplanted. The utilitarian approach of Krista Lentine assumes that available evidence offers sufficient support to the hypothesis that pretransplant weight loss is beneficial. The evidence upon which she bases her view is mainly formed by two large observational studies based on the USRDS [21] and the Scientific Registry of Transplant Recipients (SRTR) [22], respectively. These retrospective cohort studies show direct, graded...
associations of BMI with delayed graft function, with also a ‘U-shaped’ relationship between the 10-year risk of death and graft loss in the first of these two studies. In addition to these robust studies, Krista Lentine discusses also an audit of 1107 transplant recipients at St Louis University and a systematic review of 26 studies showing that the 5-year incidence of cardiac events increases linearly across BMI quartiles [23]. Overall, these studies make a strong case for obesity being an adverse prognostic factor for the risk of renal and cardiovascular events. Of note, the relationships between BMI and cardiac events in transplant patients in Lentine’s audit and the accompanying systematic review [23] are directionally opposite to the BMI–mortality relationship in hemodialysis patients [24], which remains almost perfectly inverse notwithstanding statistical adjustment for an impressive series of 18 potential confounders. This change in directionality of the link between BMI with clinical outcomes after renal transplantation fits well with biological and clinical knowledge that restored renal function has substantial health benefits, thereby establishing epidemiological links between BMI and outcomes close to those seen in the general population [1]. Another crucial element in Krista Lentine’s review is a sound criticism of a large observational study [25] showing that weight loss in patients listed for renal transplantation but eventually not transplanted for up to 6 years increases the risk of death. Being listed and not receiving a renal transplant may underlie a relatively higher-risk situation. Furthermore, the health effects of non-intentional changes in nutritional and biological parameters (like in the observational study just mentioned [25]) radically differ from intentional ones. In this respect, blood pressure is a case in point. Hypertension is a robustly inverse death predictor in observational studies in the dialysis population [26], while intervention studies with anti-hypertensive drugs in the same population, including also trials in patients with heart failure, show that intervention with these drugs produces an important reduction in the death risk [27].

Randal Detwiler shares the utilitarian approach of his pro counterpart but interprets in a causal manner the observational data indicating that weight loss in patients listed for transplantation (but not transplanted) rather than decreasing the risk of death, actually increases it [25], and other data in the USRDS showing that weight loss in listed obese patients who eventually are transplanted is neutral with regard to post-transplant mortality or graft loss [28]. He quotes a recent meta-analysis showing that the excess risk for graft loss and death in obese transplant patients is confined to studies performed before 2000, i.e. before the introduction of safer and more effective immunosuppressive regimens [29]. He is skeptical that effective weight loss and exercise programs can be successfully put in place in dialysis patients listed for renal transplantation and remarks that clinical outcomes of renal transplantation in obese dialysis patients are definitely better than in listed patients who do not receive a renal transplant [30]. Perhaps the most convincing argument against weight loss before transplantation by Randal Detwiler is that transplant physicians should not treat obesity as a risk factor different from others with equivalent or greater risk like diabetes or hepatitis C infection. He makes the sound reflection that the new US SRTR risk calculator incorporates BMI into the prediction model for renal transplant and patient survival and that it is therefore the resulting individual risk rather than BMI per se that should dictate decisions about the prioritization of clinical policies to adopt (like weight loss programs) in patients listed for renal transplantation.

**Box 1 Tentative list of clinical research priorities**

- Studies in listed dialysis patients investigating the prognostic power of fat mass and muscle mass as estimated by specific metrics (bioelectrical impedance analysis, creatinine-based equations) and on metrics of abdominal obesity (waist circumference) on clinical outcomes post-transplantation (delayed graft function, acute rejection, graft loss, all-cause and cardiovascular mortality).
- Randomized clinical trial testing the effect of pretransplant intentional weight loss on transplant outcomes in patients with various degrees of obesity, from mild to very severe.
- Cost–benefit and cost-effectiveness analyses comparing weight loss interventions before versus post transplantation.
- Studies testing the effectiveness of transplant policies based on global risk prediction for graft and patient outcomes based on models including the BMI (or other obesity metrics) versus policies considering obesity per se.
- Prognostic studies in listed obese patients with evidence of coronary heart disease.
- Intervention studies preventing hyperfiltration in obese transplant recipients (by ACEIs and ARBs) who cannot lose weight.

**STRIKING A BALANCE**

As for many other fundamental questions that clinicians face in everyday practice [31], for the issue debated in this Polar View, there is no sufficient evidentiary basis for formulating firm conclusions. Furthermore, surgical technology and interventions are evolving rapidly and may soon offer safer opportunities for both weight loss before transplantation and for transplantation in the obese dialysis patient. Laparoscopically adjustable gastric banding safely enabled sufficient weight loss to gain eligibility for kidney transplantation in a small series of patients [32], while robotic renal transplantation in a series of 28 obese patients abated the risk of wound infection when compared with perfectly matched patients who underwent traditional surgical transplantation [33].

These moderators believe that even though weight loss before transplantation may be difficult to achieve and may not be risk-free, the issue should be openly discussed with obese transplant candidates. Efforts focusing on patient education have an as yet unexploited potential for improving clinical outcomes in dialysis patients and effective weight loss programs are in place in some major transplant centers both in the USA and in Europe. On the other hand, cost-effectiveness studies in obese dialysis patients...

CONFLICT OF INTEREST STATEMENT

None declared.