BODY SIZE AND OUTCOMES IN DIALYSIS AND TRANSPLANT PATIENTS – DOES IT MATTER?

Mehmet Sukru Sever

Istanbul School of Medicine, Turkey

Corresponding Author: Mehmet Sukru Sever, M.D. Istanbul School of Medicine, Turkey

Abstract

The terminologies of “body size”, “body mass index (BMI)”, “body weight”, “large BMI” and “obesity” are controversial for defining the effects of “adiposity” or “fat excess” on the outcomes of dialysis and transplant patients. However, probably these terminologies will be continued to be used in the future as well, because of being older and simpler terminologies.

In the general population obesity is a powerful risk factor for cardiovascular morbidity and mortality, while, it conferred a survival advantage to dialysis patients. However, this may be a oversimplification, since obesity may still be a risk factor in non-sarcopenic hemodialysis patients.

Obesity is associated with early post-transplant adverse effects (i.e. delayed graft function, graft failure, wound infections, also transplant costs) and unfavorable graft and patient survival. However, thanks to safer immunosuppressive protocols, recently graft and patient survival is similar in obese as those of the non-obese patients. On the other hand, morbid obesity may still be a cause of unfavorable patient and graft survival.

Since obese transplant recipients have better life expectancy as compared to wait-listed hemodialysis patients, they should be transplanted as well, while morbidly obese patients should be asked to lose weight before being placed in the waiting lists.

Keywords: obesity, large body mass index, outcome, hemodialysis patients, transplant recipients

Introduction – The Terminology

In the literature, most often, the terminologies of “body size”, “body mass index (BMI)” and “body weight” are used interchangeably. Furthermore, vast majority of the studies use “large body size” and “obesity” for describing the effects “adiposity” on the outcomes of dialysis patients and transplant recipients. However, all these terminologies are controversial and, importantly, large BMI and obesity may not be the right wordings for this theme, because BMI is an imperfect metric of fat excess in Chronic kidney disease (CKD) [1]. So the question is: which is the right terminology?

It has been suggested that abdominal obesity, measured by the waist circumference may be better associated with cardiovascular risk in many studies. As an example, in a prospective cohort study on 537 dialysis patients,

aged mean 63 years, waist circumference predicted all cause and cardiovascular disease (CVD) mortality, whereas BMI showed an inverse relationship with these outcomes [2]. This controversial finding clearly underlines that abdominal obesity does not always overlap with high BMI. In a WHO report it has been emphasized that measurement of abdominal adiposity (e.g. waist circumference, waist–hip ratio and waist–height ratio) are associated with CVD risk factors and incident CVD events [3]. “On the other hand, universal cut-off points for BMI and waist circumference are not appropriate for use worldwide given the ethnic or population-specific differences in disease risk for any particular anthropometric measure; while, there may be general a consistency in the cut-off points of waist–hip ratio for predicting CVD risk [3]”. Despite all these concerns, probably BMI will continue to be used in the future because it is an older and simpler terminology

[4]. For the sake of simplicity, throughout this review, I will assume that high BMI or obesity simply coincides with high waist circumference, and I will use these terms interchangeably. Also, since devastating weakness is almost always associated with an unfavorable prognosis, most of this review will be dedicated to the effects of obesity/adiposity on the outcomes.

Obesity and Outcomes – General Population

In the general population obesity is a powerful risk factor for morbidity and mortality. It is very well described that obesity is associated with CVD; however, it is rarely considered that obesity is also associated with many other diseases; such as osteoarthritis and even various neoplasia (including, colon, endometrial and breast cancer) [5]. On the other hand, it is not clear whether these concerns are valid for end stage renal disease (ESRD) patients, because no randomized trial, testing the health benefits of intentional weight loss in this population has been performed so far. Therefore, most of the information on this patient population comes from observational studies.

Obesity and Outcomes – Dialysis Patients

In an analysis of the USRDS database, the incidence of obesity were analyzed in more than 660.000 incident adult dialysis patients [6]. The patients were initiated permanent dialysis between 1995 to 2002. Their BMI was calculated with the height and estimated dry weight collected from the Centers for Medicare and Medicaid Services Form. This study showed a significant increase in obesity both in general population and in dialysis patients; however, the slope of increase in dialysis patients far exceeded the increase in general population [6]. This finding underlines that the nephrologists will be faced with more and more obese dialysis patients in the future [7].

Although obesity is assumed to be an unfavorable prognostic indicator in the general population, interestingly, it conferred a survival advantage to human beings till the 19 th century, in eras when food scarcity and infection limited human life to shorter than 40–50 years [8]. Apparently, obese persons were better nourished, and characterized by better immune response against devastating chronic infectious

and other diseases, which were more frequent and major causes of death in that particular time period. Then, it can be speculated that, the same protective effect may apply to cancer, heart failure and ESRD patients as well, all of which are devastating illnesses. A USRDS analysis investigated the correlation between body size and outcomes in 418.000 patients over a 2-years average follow-up time [9]. For the purpose of that particular analysis, BMI was divided into 8 categories between 19 to 37. It was found that high BMI was associated with increased survival, even at extremely high BMI, after adjustment for demographic, laboratory, and comorbidity data. High BMI was also associated with a reduced risk of hospitalization in all categories [9]. Similar results have been published in peritoneal dialysis patients as well [10]. However, a recent Japanese registry study, which included 120.000 dialysis patients, pointed out some other interesting findings. This study evaluated the association of basal BMI with mortality and morbidity after a 1-year period [11]. The cases were stratified either by BMI into 4 quartiles or by serum creatinine levels into 3 tertiles. It was shown that obesity paradox occurs in HD patients only when obesity is simply defined by BMI. However, when patients were subdivided by serum creatinine levels in each BMI category, in patients with high serum creatinine, obesity was found to be a risk factor for all cause death similar to general population. Thus, it was concluded that it is not the loss of body fat, but loss of muscle mass (sarcopenia), being responsible from unfavorable outcomes; and obesity may still be a risk factor in non-sarcopenic HD patients. Early identification and intervention for sarcopenia by assessing serum creatinine levels may be more important to improve poor clinical outcomes in prevalent HD patients [11].

Obesity and Outcomes – The Transplant Recipients

Similar to dialysis patients, there is an epidemic of obesity among the kidney transplant recipients over time; there is a decreasing trend in the number of normal weight and underweight patients, while prevalence of obese and morbidly obese patients show a considerable increase [12]. Many studies have underlined unfavorable effects of

obesity both in the short and long term on various parameters after transplantation.

Short term adverse effects include wound infections, delayed graft function, graft failure, CVD and also transplant costs [4, 13–15]. Unfavorable long term risks of obesity have been described as well. For example, an interesting report analyzed the associations of BMI with post-transplant cardiac risk in more than 1,000 patients [15]. Values of BMI were ranked into quartiles, and cumulative post-transplant incidences of congestive heart failure (CHF), atrial fibrillation (AF), myocardial infarction (MI) and a composite of these cardiac diagnoses were assessed. It was found that 5-year cumulative incidence of any cardiac diagnosis rose from 8.6% to 29.3% across the lowest to highest BMI quartiles. Although the rate of MI did not differ by BMI quartile, high BMI was associated with an increased cardiac risk, especially of CHF and AF [15].

Obesity may have adverse effects on graft and patient survival as well. A recent systematic review and meta-analysis on the effects of obesity on kidney transplantation outcomes investigated 21 studies, which included 9296 cases [16]. Overall, graft loss at one year and five years was more favorable in non-obese patients. On the other hand, when studies were subdivided as those published before and after 2003, this beneficial effect was valid only for the studies published before 2003, but not with those afterwards. A very similar pattern was also noted for patient survival; better outcomes in non-obese patients were found in studies only published before 2003. Therefore, 3 major conclusions were drawn: 1. There is (or was) an excess risk for graft loss and death in obese transplant recipients; 2. This increased risk is mostly confined to studies performed before 2000, i.e. before the introduction of safer and more effective immunosuppressives; and 3. In the past, obesity was a risk factor for graft loss and death by CVD and all-cause mortality; however, today, the graft and patient survival is similar as those of the non-obese patients [16].

So the critical question is; can this conclusion be valid for all stages of obesity? The answer is certainly no. A UNOS registry analysis evaluated the outcome of transplantation in super obese (BMI > 50) patients. This study has noted significantly worse patient and graft outcome in super obese patients as compared to

any other BMI class in the early and late period after transplantation [17]. Then the second question comes; what is the upper limit of BMI that transplantation can be performed relatively safely? Unfortunately, this is not clear. However, since Bennett et al. [18] has reported a survival advantage of transplantation over dialysis even in the morbidly obese population, it is not possible to define a contraindication for transplantation considering BMI alone.

Management of obese transplant candidates in the waiting lists

Since many studies have shown detrimental effects of obesity early after transplant operation, many transplant physicians are hesitant for transplanting obese cases. Indeed, a recent survey in US has shown that “most centers asked their patients to lose weight so that their BMI was no greater than 35” [4]. However, since there is a definite survival benefit of transplantation as compared to patients who remain in the waiting list, even morbid obesity should not be a reason for excluding obese dialysis patients from the waiting lists. A recent registry analysis from US including more than 200,000 patients between 1995 to 2007 found that risk of death was significantly lower in transplant recipients compared to wait-listed candidates in various BMI strata, confirming that still morbidly obese patients should be transplanted [19]. ERBP guideline [20] recommends that “... patients with a body mass index > 30 kg/m² should reduce weight before transplantation”. However, then it adds “There is no consensus on whether obesity should be an exclusion criterion for kidney transplantation and policies differ among transplant centers.” Finally, it has been underlined that “the guideline development group could not make a statement regarding the acceptance or refusal for kidney transplantation based on obesity itself” [20].

To conclude, many studies have shown increased risk of morbidity and mortality of transplantation in obese patients in the early post-transplant period. Although graft and patient survival figures are controversial, obese patients have increased risk of CVD in the long term as well. So, the question is; should we continue to transplant obese dialysis patients? The answer is certainly YES if they have live donors, because transplantation offers better outcomes as compared to dialysis, even in mor-

bidly obese patients. The real controversy stands for management of obese dialysis patients if they do not have live donors. Since there is a scarcity of organs, it has been argued that "... these limited organs should be offered to the persons, who will benefit most" [21]. 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", which suggests that non-obese patients should take priority in the waiting lists. On the other hand, considering that obese patients also benefit from transplantation as compared to those in the waiting lists, this argument may give rise to many ethical concerns and puts responsibility on the shoulders of the nephrologists.

It is the personal opinion of this author that obese patients should have the same chance with their non-obese counterparts for deceased donor renal transplantation, while morbidly obese patients should be asked to lose weight before being placed in the waiting lists.

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Резиме

ГОЛЕМИНАТА НА ТЕЛОТО И РЕЗУЛТАТИТЕ КАЈ ПАЦИЕНТИТЕ НА ДИЈАЛИЗА И СО ТРАНСПЛАНТАЦИЈА – ВАЖНО ЛИ Е?

Мехмет Шукру Север

Факултет за медицина во Истанбул, Турција

Терминологиите на „големината на телото“, „индекс на телесна маса (БМИ)“, „телесна тежина“, „голем БМИ“ и „дебелина“ се контроверзни за утврдување на ефектите на „дебелината“ или „вишокот масти“ врз резултатите кај

пациентите на дијализа и со трансплантација. Сепак, веројатно тие ќе се користат во иднина, затоа што се постари и поедноставни терминологи.

Кај општата популација дебелината е моќен фактор на ризик за кардиоваскуларен морбидитет и морталитет, додека таа им дава предност во преживувањето на пациентите на дијализа. Сепак, ова може да е преголемо упростување, бидејќи дебелината сè уште може да биде фактор на ризик кај несаркопенични пациенти со хемодијализа.

Дебелината е поврзана со раните несакани ефекти на посттрансплантот (на пример, одложена функција на графтоот, слабост на графтоот, инфекции на раните, исто така, и трошоците за трансплантација) и неповолното преживување на графтоот и на пациентите. Сепак, благодарение

на побезбедните имunosупресивни протоколи, неодамнешните преживувања на графтоот и на пациентите се слични и кај дебелите пациенти и кај пациенти што не се дебели. Од друга страна, морбидната дебелина сè уште може да биде причина за неповолно преживување на пациентот и на графтоот.

Бидејќи дебелите примачи на трансплант имаат подобар животен век во споредба со пациенти што се на список за чекање за хемодијализа, и ним треба да им се направи трансплантација, додека од морбидно дебелите пациентите треба да се побара да ја намалат тежината пред да бидат ставени на списокот на чекање.

Клучни зборови: дебелина, голем индекс на телесна маса, резултат, пациенти на хемодијализа, примач на трансплант