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MINIREVIEWS

Hypertension and obesity in living kidney donors

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Abstract

Over the past few decades, the shortage in the kidney donor pool as compared to the increasing number of candidates on the kidney transplant waitlist led to loosening of kidney donors' acceptance criteria. Hypertension and obesity represent risk factors for chronic kidney disease, both in native kidneys and those in kidney transplant recipients. While great progress has been made in kidney transplantation from living donors to benefit the recipient survival and quality of life, progress has been slow to fully risk-characterize the donors. This review critically reassesses the current state of understanding regarding the risk of end-stage kidney disease in those donors with obesity, hypertension or both. Accurate risk assessment tools need to be developed urgently to fully understand the risk glomerular filtration rate compensation failure in the remaining kidney of the donors.

Key Words: Living donor; Kidney; Obesity; Hypertension; Living kidney donors

Core Tip: Hypertension and obesity represent risk factors for chronic kidney disease, both in native kidneys and those in kidney transplant recipients. While great progress

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has been made in kidney transplantation from living donors to benefit the recipient survival and quality of life, progress has been slow to fully risk-characterize the donors. This review critically reassesses the current state of understanding regarding the risk of end-stage kidney disease in those donors with obesity, hypertension or both.

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INTRODUCTION

According to a recent United Nation Organ Sharing update, there are more than 110000 candidates on the kidney transplant waitlist, with the number growing every year[1]. Kidney transplant is the standard of care for patients with end-stage kidney disease (ESKD) and there is an increasing demand for organs available for transplantation[2].

Over the past few decades, the noted shortage in the kidney donor pool as compared to the increasing number of candidates on the kidney transplant waitlist has made it necessary to loosen the kidney donors' acceptance criteria. Looking at the deceased donors' side, the American Society of Transplantation validated the expanded criteria for kidney donation to include "marginal factors" such as donation from hypertensive and aged deceased donors, those being historically declined by transplant centers[3-5]. Martínez-Vaquera *et al*[6] noted no differences in delayed graft function or graft survival in marginal (aged and hypertensive) donors compared with standard criteria donors. On the other hand, when Thukral *et al*[7] examined the outcome of 69 marginal living kidney donors (LKD) after donation, they found a statistically significant increase in blood pressure, mean body mass index (BMI) and drop in mean estimated glomerular filtration rate (eGFR); moreover, up to 22.3% developed diabetes mellitus during the follow-up period. While the risk of reduction in eGFR may be lower in kidney donors than in those after nephrectomy after cancer, even careful donor selection cannot fully mitigate the risk[8]. Therefore, the decision of accepting expanded-criteria donors is still highly individualized through non-specific local criteria and practice pattern, with many aspects of the medical, legal and ethical domains remaining uncertain[9]. There is even more uncertainty when it comes to living donors. The approval of "marginal" living donors, a group with relative contraindications, remains a grey zone in many transplant centers. Some of those relative contraindications include donors who are elderly, hypertensive, obese, with a history of malignancy, or potential transmissible infections[10]. The inevitable dilemma of harming donors on the one hand, but saving the lives of kidney failure subjects on the other is a difficult compromise to make[11]. Despite the seriousness of the issue, when foreseeing multiple combined relative contraindications in living donors, the donor's and recipient's outcomes remain pressingly understudied. The aim of current review is to highlight the current state of understanding regarding the risk of ESKD in donors with obesity and hypertension (HTN) and need to develop a validated living kidney donor profile index (LKDPI) to mitigate this risk.

OBESITY AND LIVING KIDNEY DONATION

Obesity is considered a worldwide pandemic and disease of the modern post-industrial age[12]. Flegal *et al*[13] estimated that between 2013 and 2014, the prevalence of obesity in the United States was 35% among men and 40.4% among women. Up till now, several studies have failed to find a significant difference between obese *vs* non-obese kidney donors as regards health outcomes following donation (Table 1). Rea *et al*[14] found that despite the increase of arterial hyalinosis and marked tubular vacuolization noticed in the biopsies of the transplanted kidneys from 553 obese (BMI > 30 kg/m^2) living donors compared to those obtained from the matched non-obese donors, there was no significant difference in the iothalamate GFR or microalbu-

Table 1 Summary of studies addressing outcome of hypertensive and obese living kidney donors post-donation

Ref.	Donors (*n*)	Follow up period	Obesity pre-donation	Hypertension pre-donation
Thukral *et al*[7]	65	5 yr	26% had BMI > 25 at the time of donation. Significant increase in BMI and drop in eGFR at 5-year follow up. 22.3% later developed DM as well	49.3% with no h/o prior HTN. Significant increase in mean SBP, DBP and number of HTN medications in patients with prior HTN at 5-yr follow-up
Tavakol *et al*[15]	98	Donors from 1967-2003 compared to two-kidney controls 2005-2006	16 obese donors (BMI > 30) with none having DM at the time of donation. No significant difference in decrease in GFR in obese *vs* non-obese groups. Obese patients had more proteinuria and albuminuria on multivariate analysis	No patient had HTN at donation. Significantly, more obese patients developed HTN
Serrano *et al*[17]	3752	10-40 yr	652 obese donors (17%, BMI > 30). Intra operative time longer in obese. No significant difference in short- (< 30 d) and long- (> 30 d) term readmission. No difference in GFR and ESRD development in obese patients	Significant difference in long term development of DM and HTN in obese patients
Rea *et al*[14]	49	340 d	49 obese donors (mean BMI 37.6 ± 5.0) *vs* 41 non-obese donors (mean BMI 24.8 ± 2.2). No significant difference in pre-and post-donation serum creatinine and micro-albuminuria	
Kerkeni *et al*[16]	189	9.28 yr	No significant increase in post-operative complications. High BMI patients (mean BMI 26.8) maintained normal renal functions and didn't developed proteinuria as compared to lower BMI patient (mean BMI 25.2 kg/m^2) and this difference was not significant	
Lafranca *et al*[18]	14 studies, 1192 donors	Systematic review	Operation duration and conversion rate from Laproscopic to open procedure was significantly higher in high BMI group (BMI > 30). No significant difference in decrease in eGFR, peri-operative complication rates	
Praga *et al*[27]	73	> 12 mo (13.6 ± 8.6 yr)	Significant difference in development of renal insufficiency and proteinuria in obese patients (BMI > 30) as compared to non-obese patient even after multiple regression analysis	
Nogueira *et al*[28]	39	7.1 ± 1.6 yr	Significant difference in decrease in eGFR from baseline in obese patients (BMI > 35 kg/m^2)	
Ozdemir *et al*[37]	2265	15 yr		6.21-fold high risk of ESRD in 15 yr in patients with pre-donation HTN controlled on medications
Quadri *et al*[44]	129689	5 yr	Among those with age < 50 yr, pre-existing HTN + obesity (BMI > 30 kg/m^2) were associated with a 24-fold increased risk of no eGFR compensation of the remaining kidney over 5 yr post-donation	

BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HTN: Hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; DM: Diabetes mellitus; ESRD: End-stage renal disease.

minuria between the two groups at the 12-mo mark following donation. Similar results were reported by Tavakol *et al*[15] and Thukral *et al*[7]. Regarding the safety during operation and the incidence of post-operative complications, most of the literature does not show any significant difference between obese and non-obese kidney donors. Kerkeni *et al*[16] studied the data of 189 LKD by dividing them according to their BMI into the following groups: overweight (33% with BMI 25-30), moderately obese (21% with BMI > 30), and markedly obese (10.5% with BMI > 35 kg/m^2). No significant difference was found between their BMI and the incidence of perioperative complications. A more recent study conducted by Serrano *et al*[17] reported the outcome of 3752 donor nephrectomies; 17.5% of these were obese donors with BMI > 30 kg/m^2. They found that intra-operative time was longer for obese donors; however, there was no difference in intra-operative or postoperative complications. Finally, Lafranca *et al*[18] conducted a meta-analysis that included 14 studies comparing the operative outcome and length of hospital stay in about 6000 LKDs who underwent laparoscopic donor nephrectomy. They divided the patients according to their BMI into high and low BMI groups with the cutoff value at 30 kg/m^2. Overall, the meta-analysis showed no significant difference between the two groups regarding the duration of the operation, the incidence of conversion to open surgery, warm ischemia duration, estimated blood loss, length of hospital stay after the procedure or the amount of peri-operative complications, such as bleeding, wound complications, urinary tract infections, reoperation or readmission[18]. It is to be noted, however, that all the

aforementioned studies had a short follow-up period of up to 12 mo and none of them addressed the possible long-term complications for the obese donors after a single nephrectomy. In light of donor shortage, various centers have considered accepting candidates with BMI > 30 kg/m^2[19].

From a different perspective, the association between obesity and the development and progression of chronic kidney disease has been demonstrated in numerous studies [20-23]. Higher BMI was shown to be directly related to the presence and deterioration of proteinuria in individuals without kidney disease[20,21]. It is also considered an independent risk factor for the development of ESKD[24-26]. Addressing the long-term outcome, Praga *et al*[27] have studied the effects of unilateral nephrectomy after a mean of 13.6 ± 8.6 years. Patient with higher BMI (31.6 ± 5.6 kg/m^2) had a greater risk for the development of proteinuria and kidney insufficiency, with proteinuria appearing after 10.1 ± 6.1 years of donation. The onset of kidney insufficiency was 4.1 ± 4.3 years after the appearance of proteinuria[27]. Mirroring these results, Nogueira *et al*[28] found a significant relationship between increasing BMI and the rate of kidney insufficiency after kidney donation. African American kidney donors with BMI ≥ 35 kg/m^2 had the highest rate of losing eGFR at a mean follow-up of 7.1 years. While the International Forum for the Care of the Live Kidney Donor advised that accepting obese candidates as potential kidney donors should be individualized according to acute and long-term risks, they still discourage donations from those with BMI > 35 kg/m^2 and recommend weight loss prior to donation[29-31]. This practice was also adopted by the KDIGO Clinical Practice Guideline on the Evaluation and Care of LKD [32]. Neither the Canadian nor the European Association of Urology provides any recommendations for the acceptance of obese candidates as potential kidney donors [33,34].

HTN AND LIVING KIDNEY DONATION

Currently, HTN is not considered an absolute contraindication for kidney donation and related studies show no significant difference in outcome between normo-tensive donors and those with blood pressure levels of 140/90 mmHg and normal kidney function (Table 1)[29]. The decision for donation should be made according to the manageability of HTN, the presence of other co-morbidities, and the overall health of the LKD[35]. The most recent KDOQI US Commentary of the KDIGO Clinical Practice Guideline on the Evaluation and Care of LKD states that donors with HTN that can be controlled with one or two medications to < 140/90 mmHg and without end-organ damage could be considered for LKD[32].

However, pre-donation HTN still carries a significant risk for the LKD when considering long-term outcomes. A recent study drawing on data from the Medicare and Medicaid Services databases for the period between 1999 to 2016 has analyzed 24533 donors, including 2265 with pre-donation HTN. The risk of ESKD was 6.21-fold higher for donors undergoing antihypertensive therapy even with controlled pre-donation blood pressure[36]. Also, in kidney transplant recipients, HTN has been shown to be a significant risk factor for the development of delayed graft function and even graft failure[37]. Mustian *et al*[38] analyzed the odds for causes of non-approval in LKD candidates in a single-center database between 2012 and 2017 and found out that donor HTN was associated with four-fold increase in odds of non-approval, with every 10-mm Hg increase in systolic blood pressure resulting in 30% increase odds of non-approval. Theoretically, the combination of HTN and obesity in LKD candidates carries significant short- and long-term risks and potential complications[39]. HTN and obesity embodies two of the four main components of metabolic syndrome and is most concerning when present in LKD donors with minimal kidney reserve[40]. Various transplant centers have a lower threshold to exclude obese, hypertensive donors[41]. The British guidelines recommend that overweight or obese candidates should be otherwise healthy to be considered for kidney donations[42]. Also, the Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI) guidelines adopt similar recommendations[43]. Our own preliminary experience, presented in plenary session as oral presentation at the 2020 American Transplant Congress in Philadelphia, PA suggested the concurrent HTN and obesity have major and additive adverse impact on compensatory GFR rise in living donors over 5 years [44]. At this time, there is no scoring system or criteria to evaluate the living donors long-term outcome. Recently, Shantier *et al*[45] demonstrated that LKDPI modestly predicts graft survival in 645 donors in Canadian cohort, but these results need external validation. Perhaps the time is ripe to formulate a risk profile index suited to

assess medium and long-term outcomes in those potential LKD with less-than-ideal health status, to enable truly informed consent for the potential donors and their families. For now, nonetheless, the nagging question remains — are we turning short-term saviors into long-term victims? Living donor safety is an ultimate goal in kidney transplantation. Some data indicate that hepatologists and liver surgeons decline potential living liver donors suffering of steatohepatitis[46]. Along those lines, HTN and obesity are risk factors for CKD progression and other comorbidities. Setting clear cut-off values for BMI and blood pressure limits, translated into guidelines, to turn down kidney donors is a serious issue that merits serious consideration.

CONCLUSION

In summary, donor's safety is an ultimate goal in living kidney transplantation. Some data indicate that hepatologists and liver surgeons decline potential living liver donors suffering from steatohepatitis[46]. Along those lines, HTN and obesity are risk factors for CKD progression and other comorbidities. The knowledge is still evolving about the long-term outcomes and complications of accepting kidney donors with pre-donation HTN and high BMI, both with regard to the donors' and recipients' sides. The urge to minimize the gap between the number of donors and candidates on the kidney transplant waitlist has led to a tendency to utilize more medically complex marginal living donors while we are lacking standardized assessment of the risks for these subjects. Setting clear cut-off values for BMI and blood pressure limits, translated into guidelines, to turn down kidney donors is a serious issue that merits serious consideration. Future research should be focused on the assessment of the only expandable pool of candidates, those with living donation.

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