

Round-1

Answering Reviewers

Reviewer 1

Good overview of obesity and hypertension influencing living donor kidney transplantation. For readability i suggest to create 2 tables to summarise the review of the literature of the 2 topics (obesity and hypertension). You propose a scoring system or criteria to evaluate the living donor long term outcome. In my opinion you should mention the Canadian study of Shantier M more in detail in your manuscript to provide the reader an exemple. Because as you mention, until today no other scoring systems exist. By doing that you are offering a tool to the readers but also important is to mention the limitation of this tool (small study, suboptimal after 1 year, ...).

Answering the reviewer

- 1- Manuscript edited according to side comments written in the word file by the reviewer

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. noted no differences in delayed graft function or graft survival in marginal (aged and hypertensive) donors compared with standard criteria donors. [6]** On the other hand, when Thukral et al. examined the outcome of 69 marginal living kidney donors 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.[7] 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** (LD). 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 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. estimated that between 2013 and 2014, the prevalence of obesity in the United States was 35% among men and 40.4% among women. [13] Up till now, several studies have failed to find a significant difference between obese versus non-obese kidney donors as regards health outcomes following donation (Table 1). Rea et al. 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/m²) living donors compared to those obtained from the matched non-obese donors, there was no significant difference in the iothalamate GFR or microalbuminuria between the two groups at the 12-month mark following donation. [14] Similar results were reported by Tavakol et al. and Thukral et al. [15] [7]

They divided the patients according to their BMI into high and low BMI groups with the cutoff value at 30 kg/m². 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 months 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/m². [19]

Hypertension and Living Kidney Donation

Currently, hypertension (HTN) is not considered an absolute contraindication for kidney donation and related studies show no significant difference in outcome between normotensive donors and those with blood pressure levels of 140/90 mmHg and normal kidney function (Table 1). [29]

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 24,533 donors, including 2,265 with pre-donation HTN. The risk of end stage kidney disease (ESKD) was 6.21-fold higher for donors undergoing antihypertensive therapy even with controlled pre-donation blood pressure. [36] Also, in kidney transplant (KT) 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. 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. [38]

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 LD long-term outcome. Recently, Shantier, M et al demonstrated that LKDPI modestly predicts graft survival in 645 donors in Canadian cohort, but these results need external validation. [45] 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?

Reviewer 2

Comments on Hypertension and Obesity in Living Kidney Donors As authors rightly point out, there is a relative scarcity of kidney donors to match the yearly increasing waiting list for a graft. Non-living donors are not enough to supply the demand even in Spain, with more than 40 donors per million population, leaving as the most suitable solution to look for more living donors. Long term follow-up of living kidney donors has shown that after the early postoperative period, the risks to the donors are manageable if the acceptance criteria for donation strictly preclude a person to donate if he/she has some morbidity potentially causing kidney disease. Hypertension and diabetes and their related partner, obesity, are main etiologies of chronic kidney disease and are very prevalent in western societies. The manuscript addresses this topic: Is it safe for an obese or a hypertensive subject to donate one kidney and “long term survive to tell it”? The paper is concise and well written but it does not give not enough assurance to the reader that authors are pro or con with the donation. I think it is necessary to state that the nephrectomy could be riskier for an obese donor in comparison with another person with a proper body mass index, that a nephrectomy could induce maladaptive hyperfiltration in the remnant kidney in a subject with a clear risk factor for chronic kidney disease as hypertension is and many of the today-obese subjects will be tomorrow-diabetics, both potentially capable of threatening long-term kidney disease-free survival. In summary, I think that the manuscript needs to be very stronger precluding obese or hypertensive subjects to be considered as potential living kidney donors as hepatologists and liver surgeons rejecting potential living liver donors suffering of steatohepatitis

Answering the reviewer

Patient with higher BMI (31.6 ± 5.6 kg/m²) 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. found a significant relationship between increasing BMI and the rate of kidney insufficiency after kidney donation. African American kidney donors with BMI ≥ 35 kg/m² had the highest rate of losing eGFR at a mean follow-up of 7.1 years. [28] 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/m² 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]

Answering the editor

- 1- Authors' Contributions added
- 2- References edited
- 3- All references are relevant
- 4- A table is added

Round-2

Response to Reviewer

Reviewer:

I think it is necessary to state that the nephrectomy could be riskier for an obese donor in comparison with another person with a proper body mass index, that a nephrectomy could induce maladaptive hyperfiltration in the remnant kidney in a subject with a clear risk factor for chronic kidney disease as hypertension is and many of the today-obese subjects will be tomorrow-diabetics, both potentially capable of threatening long-term kidney disease-free survival. In summary, I think that the manuscript needs to be very stronger precluding obese or hypertensive subjects to be considered as potential living kidney donors as hepatologists and liver surgeons rejecting potential living liver donors suffering of steatohepatitis (Transplantation: February 15th, 2007 - Volume 83 - Issue 3 - p 257-262. doi: 10.1097/01.tp.0000250671.06456.3f).

Response:

Thank you for your comment. We added the mentioned reference and integrated the following sentences in the conclusion part: "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 of steatohepatitis.^[46] Along those lines, hypertension 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".