Clinical Kidney Journal, 2022, vol. 15, no. 5, 841–844

https://doi.org/10.1093/ckj/sfab267
Advance Access Publication Date: 11 December 2021
Editorial Comment

EDITORIAL COMMENT

Kidney glomerular filtration rate plasticity after transplantation

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ABSTRACT

Since the first living donor kidney transplantation about six decades ago, significant progress has been made in terms of extending allograft survival. However, to date, only a small number of studies have compared the functional changes of the donated kidney to that of the remaining kidney. Although relatively small, the study by Gonzalez Rinne *et al.* demonstrated the adaptive capacity of the transplanted kidney in 30 donor–recipient pairs. The glomerular filtration rate (GFR) in both donors and recipients was obtained 12 months after transplantation and the authors identified three scenarios: (i) where donors had a higher GFR than recipients; (ii) where donors had a lower GFR than recipients; and (iii) where donors had a similar GFR to recipients. The mechanisms mediating GFR adaptability after kidney transplantation seem to be associated with body surface area (including sex differences in body surface area). Microstructural analysis of human and animal models of renal physiology provides some clues to the physiological adaptation of the transplanted organ. The nephron number from endowment and age-related loss and the adaptive ability for compensatory glomerular hyperfiltration likely play a major role.

Keywords: body surface area, donor, GFR, kidney transplantation, recipient

Living donors were the first source of kidney donation [1, 2] and remain a significant source of kidney allografts in many geographical areas [3]. Yet, since its beginnings living kidney donation has raised concerns regarding the potential consequences of donation to the donor. Kidney function and in particular glomerular filtration rate (GFR) of donors has been closely monitored since the first donations [1, 2, 4]. Over time, there has developed a large body of evidence that the remaining kidney compensates for the donated kidney without any significant adverse consequence for the donors [5–7]. However, some studies have highlighted a slightly increased risk of end-stage kidney disease for donors compared with healthy non-donors [8, 9]. Subsequently, a new interest emerged in studying the kidney function of donors, and more recently, its association with kidney function in the recipients.

Several studies have identified both living-donor and recipient characteristics associated with post-transplantation GFR [10–13]. Briefly, sex, body surface area (BSA) or kidney volume of the donor is associated with the GFR of the recipient. The physiological basis for these associations is likely to be mediated by the microstructure of the donated kidney. A recent study of 2293 donor–recipient pairs showed that the presence of more interstitial fibrosis and tubular atrophy (IFTA), more arteriolar hyalinosis and larger nephron size assessed on implantation biopsies predicted the long-term death-censored allograft loss [14]. Similarly, increased IFTA or a larger glomerular volume predicted the short-term (median 4.4 months post-transplant) decline in donor's estimated GFR <60 mL/min/1.73 m^2 [15]. The importance of kidney quality as determined by microstructural biopsy measures is evident; however, there have not been many studies

Received: 7.12.2021; Editorial decision: 8.12.2021

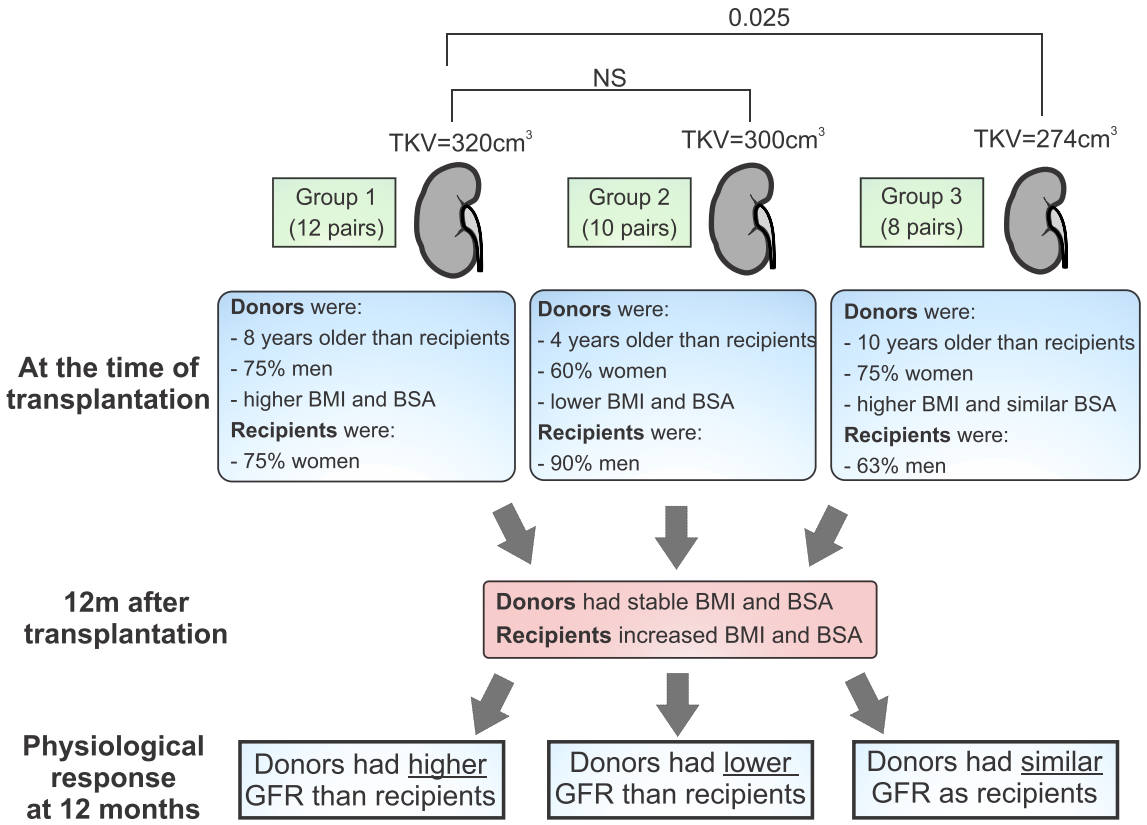

FIGURE 1: Conceptual summary of how donor and recipient pre-surgery characteristics affect physiological response 12 months following transplantation. TKV, total kidney volume; NS, not significant.

comparing the differential functional performance of kidneys of varying quality from the same source in two different hosts (donor and recipient) following transplantation.

In the present issue of *Clinical Kidney Journal*, Gonzalez Rinne *et al.* illustrate, in a very straightforward manner, host differences in the adaptative capacity of kidneys from the same source. In 30 pairs of living kidney donors (LKDs)/kidney transplant recipients, they compared the GFR of the donor and the recipient 12 months after transplantation. Figure 1 shows the summary of the main findings in their study. Group 1 with predominantly male donors had a larger total kidney size than the predominantly female donors in Group 3. One year following the transplantation, donors largely maintained their body mass index (BMI) and BSA, whereas recipients had an increase in both BMI and BSA. The effects of baseline characteristics, predominantly in terms of sex comparisons between donors and recipients, resulted in three situations: (i) a higher GFR in the donor than in the recipient ($n = 12$), (ii) a higher GFR in the recipient than in the donor ($n = 10$) and (iii) a similar GFR in the donor and in the recipient ($n = 8$). They found that both sex- and BSA-mismatching between donor and recipient influenced the evolution of GFR after kidney transplantation.

Physiologically, these results were expected and are consistent with the results from Tent *et al.* [16], who demonstrated that the early and long-term GFR of recipients from LKDs depended on BSA matching and not on sex independent of BSA differences. The highest GFR in recipients after kidney transplantation was observed among those with a higher BSA than their donor. In multivariate analysis, sex was not associated with this variation. In the present study, Gonzalez Rinne *et al.* confirm BSA mismatch as a determinant of post-transplantation GFR.

BSA has long been considered as an important parameter in the interpretation of GFR. It was proposed in 1928 by McIntosh *et al.* [17] to index GFR to 1.73 m^2. Yet, as soon as 1949, Tanner [18] had concerns about the use of BSA as an indexation parameter, which may lead to 'spurious correlation' with BSA. Indexing GFR to BSA is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [19], but the physiological and mathematical relevance is still debated and alternatives are proposed [20]. In the present work, BSA was used as an estimator of 'metabolic demand'. Metabolic demand is a 'black box' that may, as in the present study, represent the 'GFR need' for a given organism. The rationale for using BSA as a surrogate of metabolic demand is debated because body composition may vary between individuals of similar BSA and because the metabolic demand for the kidney specifically is not a well-defined concept. Whatever the correlation is between 'metabolic demand' and BSA, it remains that BSA mismatch is associated with a different evolution of GFR after kidney transplantation. The mechanism by which BSA would be a determinant of GFR change after kidney transplantation is unknown, but a review of glomerular filtration physiology may provide some insights.

Tent *et al.* [16] measured in parallel effective renal plasma flow (ERPF) and GFR, which permits the calculation of filtration fraction (FF). Interestingly, for donors and recipients with an increasing GFR, both ERPF and GFR increased after kidney transplantation and the FF (GFR/ERPF) remained constant. In other words, an increase of ERPF and not an increase in FF was

responsible for the increase of GFR. This further suggests that glomerular filtration pressure was unchanged, avoiding glomerular hypertension. The adaptability of GFR without the need for an increase in FF or filtration pressure is reassuring. It is in line with the observation from Lenihan *et al.* [21], who observed that, among LKDs, changes in filtration surface area and changes in ERPF were sufficient to explain the GFR increase of the remaining kidney after unilateral nephrectomy.

Yet, the trigger of GFR adaptation is still unknown in humans. Animal studies in the 60s and 70s are interesting as they may provide some clues. In 1978, Humphreys *et al.* [22] evaluated the urinary excretion of cation after unilateral nephrectomy in 28 anesthetized mongrel dogs. After unilateral nephrectomy, cation excretion more than doubled (increased from 31.5 to 66.3 μEq/min). In parallel, they observed a sharp and statistically significant decrease in cardiac output (from 2.52 to 1.85 L/min) with an increase in diastolic blood pressure and a decrease in heart rate. The authors further calculated total peripheral vascular resistance and found how it increased from 3634 to 5229 dyn s cm^{-5}. Interestingly, when they created an arteriovenous fistula with a flow equal to the renal blood flow of the removed kidney, cation excretion did not increase after nephrectomy. They concluded that (i) the renal circulation resistance was lower than the total body circulation resistance, and (ii) the increase in total vascular resistance was responsible for the initial natriuretic response of the remaining kidney [22]. Almost 25 years later, Valentin *et al.* [23] observed that atrial natriuretic peptide (ANP) concentration tripled after unilateral nephrectomy and that ANP blockade prevented the rise in cation excretion. The link between ANP, vascular resistance and renal blood flow has never been demonstrated, but may be a mechanism involved in renal plasticity. This phenomenon may be associated with one situation reported by Gonzalez Rinne *et al.*: a GFR increase after living kidney donation.

However, Gonzalez Rinne *et al.* also reported on a group of transplant pairs where GFR was lower in the recipients than in the donors. This observation was particularly true for recipients with a smaller BSA than their donor. At first glance, it is tempting to overlook this observation and consider it 'expected' given the higher probability of kidney damage associated with kidney transplantation in the recipient than in the donor. Yet, this situation of a kidney decreasing its GFR in a recipient who has a smaller BSA than their donor may be the reverse of compensatory hypertrophy. Interestingly, there is some evidence in the literature that compensatory hypertrophy is reversible. In 1991, Churchill *et al.* studied the GFR of rats with transplanted kidneys in various situations. They observed that when a hypertrophied kidney (from a uninephrectomized rat) was transplanted into a rat with a solitary hypertrophied kidney, the GFR and the weight of the transplanted kidney decreased. In contrast, when the hypertrophied kidney was transplanted into a binephrectomized rat, the transplanted kidney remained hypertrophied [24]. This is one of the very rare illustrations of reversible compensatory hypertrophy. Unfortunately, the authors did not evaluate peripheral vascular resistance and whether morphological and functional changes of the transplanted kidney were associated with vascular resistance. Yet, it is in agreement with the observation from Gonzalez Rinne *et al.* that GFR may decrease in part due to a lower 'metabolic demand'.

Nephron endowment is probably a major parameter to be considered in terms of GFR adaptability. It is believed that nephrogenesis only occurs during the gestation period and stops by the 36th week of gestation, and that although the kidney continues to grow after birth, no new nephrons are being formed [25]. Therefore, maternal factors during intrauterine fetus development and preterm birth are considered critical factors that influence the nephron endowment [25]. Studies have also linked low nephron endowment at birth (often presumed based on preterm birth or low birth weight) with chronic kidney disease and hypertension later in life [26–28]. There is a huge variability in the total number of nephrons per kidney, and aging itself is associated with nephron loss. Studies on autopsy kidneys and those in LKDs consistently showed a huge variability in nephron number between individuals, average annual loss of 6000–7000 nephrons, and an inverse association between nephron number and glomerular size [25, 29]. The study in LKD further emphasized the underappreciated loss of nephrons due to reabsorption of globally sclerosed glomeruli [29], such that despite selection on health, the oldest donors (>70 years of age) may have already lost up to 50% of the nephrons they were born with. From the perspective of kidney function, the decline in measured GFR in healthy donors closely follows this decline in nephron number, with the possible exception in these oldest donors [29]. The oldest donors (70+ years old) may actually be selected for donation only because they have some degree of hyperfiltration as evidenced by increased single-nephron GFR [30], which causes their GFR to be above some acceptable minimum of at least 70–80 mL/min/1.73 m^2, which is required for approval for kidney donation. Shorter donors and donors related to their recipients are also both associated with having fewer nephrons [30].

Additional insights include an inverse relationship between nephron number per kidney and average glomerular size, and larger glomeruli also associate with male sex and taller height [31]. Another insight came from a Japanese autopsy study, which demonstrated how in the setting of low nephron endowment, the primary factor involved in GFR maintenance was glomerulomegaly and not the glomerular hypertension [32]. This finding is consistent with the scenario of donors having lower GFR than recipients, because in this scenario, the majority of donors were women and recipients were men. Presumably, smaller glomeruli from female donors hypertrophied in male recipients, with a physiological response that drove a higher GFR in recipients.

Given the finite number of nephrons, it is reasonable to ask whether GFR adaptation recruits the total kidney reserve and leaves the kidney without any further possibility to increase the GFR in response to acute demands. It seems that this is not the case; the transplanted kidney (or the remaining kidney after living kidney donation) keeps its ability to increase the GFR. This capacity of the kidney has long been evidenced by an increase in GFR following dopamine infusion or amino acid infusion, and is known as the renal reserve [33]. In fact, Tent *et al.* observed that renal reserve was still present in transplanted kidneys, suggesting that BSA mismatch involved a different mechanism from renal reserve to increase GFR. Van Londen *et al.* [34] demonstrated that after living kidney donation, renal reserve was still present only for young females with a BMI <25 kg/m^2 but disappeared after donation for those with a BMI ≥25 kg/m^2. This result demonstrates that kidney adaptability is not uniform between individuals: some individuals may still have a renal reserve, while others may not. The long-term consequences of lacking renal reserve are unknown, but some data suggest that the lack of renal reserve may be associated with obstetrical complications [35].

The article by Gonzales Rinne *et al.* poses old questions: it illustrates in humans the phenomena that was observed decades ago in animal models of kidney transplantation.

FUNDING

This study was supported with funding from the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK090358).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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