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
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 adaptive 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 hu-
mans. 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,
creation excretion more than doubled (increased from 31.5 to
66.3 μEq/min). In parallel, they observed a sharp and sta-
tistically 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 to-
total peripheral vascular resistance and found how it increased
from 3634 to 5229 dyn s cm–5. Interestingly, when they cre-
ated 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 re-
cal circulation resistance was lower than the total body cir-
culation resistance, and (ii) the increase in total vascular re-
sistance 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) concen-
tration tripled after unilateral nephrectomy and that ANP block-
ade 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 plas-
ticity. This phenomenon may be associated with one situation
reported by Gonzalez Rinne et al.: a GFR increase after living kid-
ney 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 tempt-
ing 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 sit-
uation of a kidney decreasing its GFR in a recipient who has a
smaller BSA than their donor may be the reverse of compen-
satory 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 hy-
pertrophied 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 periph-
eral vascular resistance and whether morphological and func-
tional 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 con-
continues to grow after birth, no new nephrons are being formed
[25]. Therefore, maternal factors during intrauterine fetus devel-
opment and preterm birth are considered critical factors that in-
fluence 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 variabil-
ity 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 num-
ber and glomerular size [29, 25]. The study in LKD further em-
phasized the underappreciated loss of nephrons due to reab-
sorption 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 mini-
mum of at least 70–80 mL/min/1.73 m2, which is required for ap-
proval 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 glomeru-
lomegaly and not the glomerular hypertension [32]. This find-
ing 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 recipi-
ents, 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 liv-
ing 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, suggest-
ing that BSA mismatch involved a different mechanism from re-
nal 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/m2 but disappeared af-
ter donation for those with a BMI ≥25 kg/m2. This result demon-
strates that kidney adaptability is not uniform between individ-
uals: some individuals may still have a renal reserve, while oth-
ers may not. The long-term consequences of lacking renal re-
serve 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 il-
ustrates in humans the phenomena that was observed decades
ago in animal models of kidney transplantation.
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