Summary, Discussion and Future Perspectives
Living kidney donation

Living kidney donation is the best available treatment option for patients with end-stage kidney disease (ESRD)\textsuperscript{1,2}. However, because of a persistent donor organ shortage, the selection criteria for potential living donors have been liberalized, which may possibly increase living donor risks\textsuperscript{3,4}. To ensure donor safety while accepting more donors for living donation, more insight is needed in the short- and long-term effects of nephrectomy on the donor. The general aim of this thesis was to help provide this insight, as well as optimizing living kidney donor screening.

Part one: GFR in living kidney donation

In part one of this thesis, we focused on the validity of available methods to estimate glomerular filtration rate. We assessed the use of estimated GFR (eGFR) to predict measured GFR (mGFR) before and after donation, as well as the use of the renal functional reserve (RFR) in living kidney donation. In chapter two, we investigated if pre-donation eGFR can be used for prediction of post-donation mGFR and whether pre-donation eGFR cut-off values can be defined to predict a matching post-donation single kidney mGFR. In this study, we showed that pre-donation eGFR can be used to predict post-donation mGFR and we provide pre-donation eGFR cut-offs for living kidney donors to achieve a desired post-donation single-kidney mGFR. Donors with an eGFR equally or above the calculated cut-off (e.g. an eGFR\textsubscript{CKD-EPI} \geq 94 mL/min/1.73m\textsuperscript{2} to achieve a post-donation mGFR of 50 mL/min/1.73m\textsuperscript{2}) can be accepted for donation, while donors with an eGFR below the cut-off require confirmatory testing as the current living donor guidelines suggest\textsuperscript{5}. While previous studies investigated the use of eGFR in donor screening\textsuperscript{6,7}, this is the first study that takes the effect of nephrectomy into account.

In chapter three, we investigated the use of eGFR to detect renal function decline after donation. We compared slopes of eGFR with slopes of mGFR in 349 living kidney donors. In this study, we found that eGFR was unable to detect the renal function loss in donors with a declining mGFR (28% of all donors). While in general eGFR provides an underestimation of mGFR\textsuperscript{8}, these data implicate that eGFR slopes in living donors should be interpreted with caution. Donors with a declining kidney function, may be missed when using only eGFR for donor follow-up.

In chapter four, we investigate a different method of predicting residual kidney function after donation: the measurement of the renal functional reserve (RFR) by infusion of dopamine. In this chapter, we studied whether overweight female donors of childbearing age had a different RFR compared to non-obese female donors. We found that obese women had a similar RFR before donation, compared to non-obese women, but no residual RFR was detectable after donation.
In chapter five, we investigated the predictive capacity of the pre-donation RFR in more detail and investigated if it can predict GFR after donation. We show that the RFR is a predictor of the short-term increase of GFR after living kidney donation but not of long-term GFR. Therefore the RFR is not a suitable tool in living donor screening.

Part two: Living kidney donation beyond the GFR

In part two of this thesis we focused on renal parameters other than the GFR; the use of tubular compartment function in donors and the development of novel biomarkers to predict donation-attributable risk for the individual donor. In chapter six we investigated whether pre-donation tubular phosphate handling in the donor could predict renal function in the recipient at one year post-transplantation. We measured the tubular maximum reabsorption capacity for phosphate (TmP-GFR) in the healthy donor kidney and found that it is independently associated with recipient kidney function. This is indicates that beyond the GFR, tubular function may also be a predictor in living kidney transplantation.

In chapter seven we investigated the implications of tubular phosphate handling of the donor kidney in the recipient. Recipients often have a (severe) hypophosphatemia in the short-term after transplantation and we demonstrate that this is independently associated with beneficial graft and cardiovascular survival after transplantation.

Another important outcome for the well-being of living kidney donors is chronic pain. In chapter eight we show with a validated questionnaire that approximately 20% of donors have pain complaints after donation, of which 6% require an analgesic. This knowledge can be used in donor counseling and may help to further improve donor decision making.

Overall, it is apparent that more insights are needed into the effects of nephrectomy on the living donor. In chapter nine we propose an approach for the structured collection of biomaterials, functional and clinical data: the design of TransplantLines. TransplantLines is a biobank study covering all aspects of solid organ transplantation, including, but not restricted to kidney donation. Because risks and benefits of donors and recipients are often entwined, they are considered together in this study. TransplantLines may be the basis for hypothesis-generating studies that yield insight in the effects of nephrectomy on the living donor and may help predict the donation-attributable risk.

Discussion and future perspectives

This thesis contributed to ongoing efforts to improve the safety of living donors and donor risk assessment, by investigating several aspects of living kidney donor screening and follow-up. Living kidney donors undergo a rigorous screening prior to donation, but due to a persistent donor organ shortage, the living donor guidelines have been liberalized. This has caused a shift in the characteristics of the living kidney donor population. Compared
with two decades ago, accepted donors are now on average older, have a higher BMI and are more likely to have hypertension\(^{11,12}\). While the absolute risk for end-stage renal disease and premature mortality of living kidney donors are lower than the general population\(^ {13,14}\), donors have increased relative risks compared to selected controls\(^ {3,4}\). This underlines the importance of pre-donation risk assessment in living donors. We evaluated this risk assessment in donor screening and donor follow-up with aspect to the kidney function and other markers for donation-attributable risk.

The measurement of kidney function, expressed as the glomerular filtration rate (GFR, unit: \(\text{mL/min}\), often standardized for body surface area: \(\text{mL/min/1.73m}^2\)), is one of the main components of pre-donation evaluation\(^ {15,16}\). The gold-standard technique for measuring GFR (mGFR) is the calculation of the clearance of an exogenous filtration marker, such as iothalamate\(^ {17}\). These markers are suitable for measuring GFR because they are completely filtrated by the glomerulus and (almost) not excreted, resorbed or metabolized by the tubular compartment. The usability of mGFR in routine care is limited, because it is a laborious and expensive procedure\(^ {16}\). The GFR can also be estimated by using the serum concentration of creatinine, a breakdown product of muscle metabolism\(^ {18}\). Different formulas have been developed to estimate GFR (eGFR) from serum creatinine that adjust for differences in creatinine production by a correcting for sex, age and race, dependent on the formula\(^ {6}\). However, these formulas are influenced by tubular secretion of creatinine\(^ {19}\), body composition and muscle mass and despite correction factors\(^ {18}\), they have a poor performance in subjects with normal renal function\(^ {8,20,21}\), limiting their use in living donors. Alternatively, the renal clearance of creatinine can be calculated using 24-hour urine collections\(^ {18}\). The creatinine clearance is an adequate measure of kidney function, but the method is sensitive to collection errors\(^ {16}\). mGFR, eGFR and the creatinine clearance are all used in living kidney donor screening and follow-up, but methods depend on local practice of the transplant center.

In this thesis, we made efforts towards a more evidence based approach to kidney function assessment in the potential donor that may be applicable in clinical care. We evaluated the performance of eGFR and the creatinine clearance in living kidney donor screening, by comparing them to post-donation mGFR. We show that pre-donation eGFR formulas can predict post-donation mGFR and provide cut-offs to achieve a desired post-donation mGFR. These cut-offs may be used for donor guidelines to select donors that do not require mGFR confirmation of eGFR. We propose a selection algorithm incorporating these thresholds to further improve donor screening (Figure 1). Donors with an eGFR below the cut-off should undergo additional renal function evaluation, preferably by mGFR\(^ {17}\), while donors with eGFR above the cut-off can be accepted without additional renal function measurement.
Figure 1: An algorithm for living kidney donor screening using eGFR

An algorithm for selecting living kidney donors. Clinicians can first determine what post-donation single-kidney GFR is required for a prospective living kidney donor. This is an individualized decision based on donor risk factors (age, ethnicity, co-morbidities). Candidates with an eGFR below cut-off require confirmatory testing. Based on current literature, mGFR is advised as confirmatory test. Candidates with an eGFR above the cut-off or with an mGFR above the individualized cut-off and no relevant contraindications for donation can be accepted for living kidney donation.

After living kidney donation, eGFR is also often used for the follow-up of the donor. Given the low absolute risk for ESRD in living donors, this is thought to be the most viable option for renal follow-up of the donor. However, we show that slopes of eGFR are often not accurate. In cross-sectional analysis eGFR formulas provide an underestimation of mGFR, which is in line with previous literature. But in longitudinal analysis, the slope of all creatinine-based eGFR formulas (CKD-EPI, MDRD study and Cockcroft-Gault equations) did not...
accurately match the slope of the mGFR. Most donors (70% in our cohort) have a benign compensatory mGFR increase after donation\textsuperscript{24,25}, but in donors with a declining mGFR, the eGFR is unable to detect this decline of kidney function. Particularly in older donors, who are at risk to develop progressive GFR loss\textsuperscript{22,26}, mGFR-based donor follow-up is preferable to timely detect potential renal function decline and eGFR is inadequate from a perspective of donor safety. Future studies are needed to design more suitable tools to timely detect progressive renal function decline after living kidney donation. A combination of eGFR and repeated measurements of the 24-hour creatinine clearance, possibly in the context of a risk prediction tool also considering age and race, could be used as an alternative in centers where mGFR is unavailable.

The measurement of the renal functional reserve (RFR) by infusion of dopamine was thought to be a marker of the capacity of the kidneys to adapt after nephrectomy, thus resulting in a GFR beyond 50% of the pre-donation GFR\textsuperscript{27}. Dopamine causes renal vasodilation and thereby could be a predictor of the renal reserve capacity\textsuperscript{28}. Having an adequate RFR may be important for conditions that alter hemodynamics and cause ‘increased renal filtration’, such as obesity\textsuperscript{29,30} or pregnancy\textsuperscript{31,32}. Living kidney donors have an increased risk for adverse pregnancy outcomes\textsuperscript{33} and obese donors have an increased ESRD risk\textsuperscript{24}, which could be explained by utilization of RFR by donation combined with pregnancy/obesity. We show that RFR is lost in young female donors of childbearing age with overweight. These results may provide an explanation for the findings that donors have an increased risk of preeclampsia\textsuperscript{33,35}.

It has previously been reported that the RFR is a predictor of the short-term response after living kidney donation\textsuperscript{36}; now we find that it is not a predictor of long-term GFR. This implicates that the RFR is not a suitable tool in living donor screening. Mechanistically, donors have a compensatory increase of the GFR to approximately 66% of its pre-donation value almost directly after nephrectomy\textsuperscript{24}, which is considered to be a hemodynamic response\textsuperscript{37} (and thus can be predicted by RFR). Most donors continue to have an GFR increase, which is considered to be more structural in nature\textsuperscript{38} (and is not predicted by RFR).

While the GFR is the most used marker for kidney function, the kidney has many functions. Renal tubuli are essential for, among others, electrolyte and fluid homeostasis\textsuperscript{39}. The use of tubular compartment function in donors may be provide additional benefit in the assessment of kidney function in donors. Consequently, markers related to electrolyte homeostasis, including renal phosphate homeostasis, could be indicators of tubular function. Renal phosphate homeostasis is regulated primarily in proximal tubular epithelial cells by sodium phosphate co-transporters NaPi-IIa, NaPi-IIc and PiT-2\textsuperscript{40–42}. The renal tubular maximum
The reabsorption capacity of phosphate per unit of glomerular filtration rate (TmP-GFR) is the maximum renal capacity to reabsorb phosphate and may reflect tubular function, thereby being a functional marker to study “tubular quality” even in the absence of tubular damage markers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). We show that the TmP-GFR is independently associated with recipient GFR, one year after transplantation, which gives an argument for studying tubular function in living donors. Similarly, post-transplantation renal phosphate handling, reflected by the development of hypophosphatemia, could reflect tubular function and thus predict renal outcomes. We show that the development of post-transplantation hypophosphatemia is associated with beneficial graft and cardiovascular outcomes in recipients. This indicates that post-transplantation hypophosphatemia is a sign of good graft function.

Renal function is not the sole outcome of post-operative donor evaluation. Overall medical risk and donor well-being are equally important. Generally living donation leads to an increase in quality of life of the donor, but in the presence of post-operative pain the donor quality of life may even be reduced. Systematic assessment of quality of life, including the presence of both short- and long-term post-operative pain in donors is an essential constituent of living donor follow-up. We find that 20% of living donors experience chronic pain after donation. Interestingly, younger donors more often experienced pain than older donors. These data may contribute to better donor counseling.

From this thesis and from data of other living kidney donation programs, it is apparent that more insights are needed in the effects of nephrectomy. To improve risk prediction, studies into modifiable risk factors, lifestyle and novel biomarkers of renal function are warranted. Also long-term studies of donor-outcomes are necessary to make an adequate risk prediction for living donors. An approach for the study of these factors may be the systematic collection of functional, clinical data and biomaterials in living donors. The TransplantLines biobank and cohort study may be the practical implementation of this goal. TransplantLines is a biobank and cohort study covering all aspects of solid organ transplantation, including but not restricted to kidney donation. From TransplantLines the descriptive follow-up data can be complemented by hypothesis-generating studies that yield mechanistic insight in the effects of nephrectomy on the living donor and may help predict the donation-attributable risk. An important part of living kidney donation that is not covered by this thesis, but may be also answered by the studies coming forth from TransplantLines are the psychological and psychosocial outcomes after donation. Ultimately this information is likely to contribute to improved living kidney donor screening and follow-up, and thereby to qualitatively and quantitatively improved outcomes after living kidney donation.
In conclusion, while living kidney donation may provide benefit to donor and recipient, it may not be without harm (‘Nil prodest quod non laedere possit idem’, Ovid, Tristium Liber Secundus, 2.265-6)\textsuperscript{52}. We show that an adequate assessment of kidney function before and after donation can contribute to reducing this harm, either by eGFR, creatinine clearance or mGFR. We propose to also study other aspects of kidney function, such as the tubular handling of phosphate (TmP-GFR) and show that pain is a relevant adverse effect of living kidney donation. To be able to further study the effects of living kidney donation, we propose a biobank study covering all aspects of transplantation and living donation. This may help predict the donation-attributable risk and to improve living kidney donation outcomes.
References


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