Living kidney donor safety
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Aims of the thesis

As mentioned in the introduction, the number of living kidney donation procedures is increasing. At the same time, the living donor population has changed, reflecting the need to increase the donor pool. The prevalence of risk factors for future renal function impairment, such as old age, weight excess or hypertension, has hereby increased over the years. This puts emphasis on the need for a donor screening and follow-up regimen that ensures and monitors donor safety on short as well as long-term. The aim of this thesis is to improve our understanding of vulnerability of the healthy kidney to renal function impairment, in order to contribute to a donation regimen that reconciles optimal use of the donor pool with optimal long-term donor safety. Considering the clinical context of donation, it is of the greatest importance to delineate factors that can identify subjects at risk for post-donation renal function impairment already before donation. This requires insight in the determinants of vulnerability of the kidney in healthy subjects and poses the challenge of identifying such determinants. For clinical purposes, we aim to identify factors that put people who wish to donate at risk for clinically relevant renal function loss after donation. Hereby, we hope to work towards maintaining donor safety in the future.

The Kidney – Inside & Out…

To address abovementioned issues, we travel from inside a healthy kidney to renal outcome after donor nephrectomy. To enhance our understanding of vulnerability of healthy kidneys, we start with exploring intrinsic characteristics of the healthy kidney as a proof of principle that the normal biological variation between healthy individuals bears impact on renal susceptibility to damage. Intrinsic renal factors may have their effect on renal outcome and determine a priori renal vulnerability well before the trigger for renal function loss or onset of disease. Next, we focus on age and body mass index as factors that potentially influence short-term and long-term renal outcome. We measure renal hemodynamics, not only as a sophisticated tool to determine and monitor renal function, but also because renal hemodynamic adaptation is one of the central features of the adaptive response in the remaining kidney after nephrectomy.
Outline of the Thesis

Chapter 1 – ACE activity and susceptibility to renal damage

The normal biological variability between healthy individuals may be relevant for the susceptibility to renal damage. Plasma and tissue levels of angiotensin-converting enzyme (ACE) vary considerably between healthy subjects. Previous studies have shown that renal ACE activity is higher when renal damage is present and that a higher renal ACE activity during renal disease is associated with more severe renal damage [1]. Furthermore, pharmacologic inhibition of ACE reduces proteinuria and renal damage, to a larger extent than can be expected from the concomitant reduction in blood pressure [2-4]. However, it is unknown whether the higher renal ACE levels in renal disease are cause or consequence of the damage. In this chapter, we investigate whether individual differences in renal ACE activity in renal tissue in healthy rats are relevant for the renal susceptibility to inflicted damage. To test this, we measured renal ACE activity in renal biopsy prior to induction of renal damage by adriamycin, and analysed for the association between renal ACE levels in the healthy condition and the ensuing renal damage.

Chapter 2 – Renal function decline with age

With ageing, functional changes occur within the kidney. In the general population, renal function is known to decline slowly over the years. Kidney donors however represent a part of the population that is in very good health. Does renal function decline in this group of subjects or is it preserved? Reports are conflicting, and recently it was reported that the age-related renal function decline might even not apply to women [5]. Therefore, in chapter 2, we present data on the cross-sectional association between age and renal function in our donor population, for men and women separately, analysing the impact of age on glomerular filtration rate and effective renal plasma flow.

Chapter 3 – Prediction of post-donation renal function

Generally, it is believed that pre-donation renal function provides a reasonable estimate of post-donation renal function. In this chapter, we investigate whether the prediction of post-donation renal function in the living kidney donor can be improved by taking pre-donation renal functional reserve into account. The healthy kidney usually has a considerable functional reserve. This means the kidney can adapt to increased (metabolic) demands of the body and, moreover, that loss of renal mass does not necessarily lead to a corresponding loss of renal function. Reserve capacity can be tested by measuring the renal hemodynamic response to different stimuli, such as a protein load or dopamine infusion [6-10]. In our centre, we use low-dose dopamine, an amino-acid solution and their combination [11]. Low-dose dopamine predominantly induces efferent vasodilation; infusion of amino-acids leads to predominantly afferent stimulation and the combination of both substances induces a large increase in both GFR and ERPF in the healthy kidney. This is assumed to be a reflection of renal hemodynamic reserve capacity. Remnant renal function after unilateral nephrectomy does not amount to exactly 50% of the two-kidney values prior to nephrectomy, but is usually higher because the remnant kidney addresses its reserve capacity [12]. It would be logical to assume therefore, that measurement of pre-donation reserve capacity could improve the prediction of post-donation renal function. This hypothesis is tested in chapter 3.
Chapter 4 – BMI modulates post-donation renal filtration

Changes in body composition are known to occur over a lifetime. Healthy adults in the general population show an increase in body weight of several kilos per decade [13]. Excess body weight is a risk factor for progressive renal damage in several renal conditions as well as in the general population and after nephrectomy [14-18]. Overweight elicits hyperfiltration in the kidney, as apparent from higher glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and filtration fraction (FF) [19]. This renal hemodynamic pattern is assumed to be a pathogenetic factor in long-term renal function loss, and could therefore be a target for intervention. Donor nephrectomy elicits profound changes in renal hemodynamics in the remaining kidney. It is unknown whether body weight still modulates renal hemodynamics under these circumstances. In chapter 4, we therefore first investigated the impact of BMI on short-term post-donation filtration fraction. Second, we investigated long-term changes in renal hemodynamics in relation to changes in body weight. In morbidly obese patients, hyperfiltration has been shown to be partly reversible after weight loss following bariatric surgery [20]. Whether changes in body weight in a more physiological range are associated with corresponding changes in renal hemodynamics has not been investigated. This question was therefore addressed in our longitudinal study.

Chapter 5 – BMI and age affect post-donation renal reserve capacity

The kidney has a substantial functional reserve capacity that is assumed to be relevant for preservation of renal function after loss of renal mass. In line with this, in a small population of kidney donors, renal reserve was significantly decreased after living kidney donation [23], suggesting that the remaining kidney indeed addresses its renal hemodynamic reserve after contra-lateral nephrectomy. Thus, differences in reserve capacity might be relevant. In overweight patients with hypertension, a decreased renal reserve capacity was reported in comparison to normotensive patients [21]. Theoretically, reserve capacity could be reduced by older age or weight excess – due to pre-existent hyperfiltration – but in healthy prospective donors, we could not detect an effect of age or BMI on renal reserve capacity before donation [22]. However, it is unknown whether age and BMI have impact on renal reserve after nephrectomy. In this chapter, we therefore investigated post-donation renal reserve in a large cohort of kidney donors and analysed for the effect of age and BMI as potential determinants of reserve capacity.

Chapter 6 – Long-term follow-up: adaptive capacity in elderly donors

Adaptation of the remaining kidney after living kidney donation is considerable and involves hemodynamic as well as tubular adaptation and responses. The short-term effects of older age and higher BMI on post-donation renal function and renal reserve have been addressed in chapters 3 and 5. Long-term renal outcome is addressed in chapter 6. In this chapter, we specifically focus on a role for older age as a possible risk factor for worse long-term renal outcome.
Chapter 7 – Effect of using eGFR for donor screening on acceptance rates

Prospective living kidney donors have to meet strict criteria to be eligible to donate. In most centres, renal function has to be at least 80 ml/min/1.73 m² [24]. However, the usual measurements of renal function are subject to limitations, regarding their accuracy and reliability. The gold standard for renal function measurement is clearance of inulin or isotopes, such as iothalamate, but many centres do not have the availability of such measurements. Regarding creatinine clearance, the reliability has been questioned because of frequently occurring inaccuracies due to collection errors [25]. Thus, several centres currently rely on so-called renal function equations, such as the MDRD (Modification of Diet in Renal Disease study equation) [26], providing an estimated GFR (eGFR). Moreover, the eGFR is currently automatically provided by many laboratories when serum creatinine is measured. Whereas eGFR is advocated because of cheap and easy use, it considerably underestimates true GFR in subjects without renal disease or with normal renal function. In chapter 7, we applied a Bayesian approach for the interpretation of eGFR in healthy subjects, taking into account the low a priori probability of renal function impairment in a healthy population. Such an approach could prevent subjects from being abusively labelled as having suboptimal renal function.
References


