Chapter four

Association between BMI and renal hemodynamics after donation
After donor nephrectomy, relative hyperfiltration occurs with overweight on the short-term and with weight gain on the long-term

Submitted

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Abstract

Overweight and weight gain are associated with renal risks. Hyperfiltration may be a mechanism behind overweight-associated renal risk. It is unknown whether the impact of BMI on renal hemodynamics is sustained after living donor nephrectomy, nor what the effect of weight gain is. Therefore, we analyzed, first, the short-term association between BMI and filtration fraction and, second, whether weight gain influenced long-term renal filtration and adaptation after donor nephrectomy.

We studied 266 consecutive living donors. Renal function was measured as the clearance of iothalamate (GFR) and hippuran (ERPF), 4 months before and 2 months after donation. Filtration fraction (FF) was calculated as (GFR/ERPF)*100; BMI was divided into normal weight (<25); overweight (25-30) and obesity (≥30 kg/m²). In 60 donors long-term renal function measurements were available at a follow-up of 7±4 years.

Nephrectomy elicited adaptive increases in the remaining kidney’s GFR (+28±15%) and ERPF (+32±14%) and post-donation FF decreased slightly (all p≤0.001). Post-donation FF was significantly higher with overweight and obesity compared to normal weight. Long-term after nephrectomy, body weight increased from 74±13 kg to 79±13 kg. GFR and ERPF further increased by 10±14% and 14±13%, respectively (p≤0.001). The amount of weight gain correlated with the increase in GFR (R=0.38, p≤0.01) and FF (R=0.40, p≤0.001), but not ERPF.

The impact of BMI on renal hemodynamics is maintained short-term after nephrectomy. Long-term changes in body weight affect renal adaptation, with an increase in filtration fraction in donors who gained weight. Post-donation weight gain may pose an extra burden on the remaining kidney.
Introduction

Excess body weight is a risk factor for progressive renal damage in the general population as well as in renal disorders in native kidneys and in renal transplant recipients [1-7]. The mechanisms underlying the increased long-term renal risk in overweight subjects have not been completely elucidated, but are likely to include the effects of co-morbid conditions such as hypertension and insulin-resistance [8,9]. Moreover, weight excess is associated with an unfavourable renal hemodynamic profile, including hyperfiltration and elevated filtration fraction [10-12]. The latter is assumed to reflect elevated glomerular pressure and is a predictor of progressive renal damage in animal models and in transplant recipients [13].

An increased risk for proteinuria and long-term renal damage has been reported in obese subjects after nephrectomy for several indications [14]. This may be relevant for living kidney donors, since a large proportion of the donor population is overweight and, moreover, an increase in body mass index (BMI) over several years’ time has been reported to occur after nephrectomy [15,16]. Unilateral nephrectomy elicits profound renal hemodynamic adaptation in the remaining kidney. Whether weight excess still exerts its unfavourable effects on renal hemodynamics under these circumstances is unknown.

The pathogenetic role of renal hemodynamic factors in the renal risks of weight excess is relevant as these are potentially accessible to intervention by blockade of the renin-angiotensin-aldosterone system. Yet, the obvious preventive measure would be weight loss, which ameliorates co-morbid conditions such as hypertension and insulin resistance [17,18]. Data on a small population morbidly obese subjects that underwent bariatric surgery showed that massive weight loss (mean loss of 48 kilos) was associated with partial reversibility of the renal hemodynamic abnormalities [18]. Whether changes in body weight in a more physiological range also modulate renal hemodynamics, however, has not been investigated.

To investigate whether weight excess is associated with an unfavourable hemodynamic profile after nephrectomy, we first investigated renal hemodynamics in relation to BMI in 266 consecutive living kidney donors, early after kidney donation. Second, to analyse the impact of changes in body weight, we analysed longitudinal data on renal hemodynamics in a subgroup of 60 donors in whom long-term follow-up data were available, in association with the concomitant changes in body weight over time.

Methods

The study population consisted of 266 consecutive living kidney donors (age 49±11 years [mean ± standard deviation], 56% female, with a BMI of 25.9±4.0). All donors who underwent the prospective screening program in our centre with subsequent donation between 1984 and 2006 were included in the present analysis. Individuals with renal disease, overt diabetes or latent diabetes, identified by an abnormal oral glucose tolerance test, were excluded from donation. Physical examination in donors accepted for the program did not reveal abnormal findings. Blood pressure was measured non-invasively during the renal function measurements by Dinamap® (Critikon, Tampa, FL, USA) in a semi-supine position, after at least ten minutes of rest. Blood pressure was either normotensive or prehypertensive according to the JNC VII guidelines (≤140
systolic and ≤90 diastolic) [19] or regulated with a maximum of one antihypertensive drug (19 subjects). Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure. According to our centre’s routine protocol, renal function was measured 4 months before and 2 months after donation as described below. BMI was calculated (weight/length$^2$) before and after donation from measurements performed on both days of renal function measurements. Procedures were conducted in accordance with the Helsinki declaration and donors consented with the use of their clinical data for these research purposes.

**Renal hemodynamic measurements**

Routinely, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured by constant infusion of low-dose radio-labelled tracers, $^{125}$I-iothalamate and $^{131}$I-hippurate, respectively. Subjects were seated in a quiet room in a semi-supine position. After drawing a blank blood sample, the priming solution containing 0.04 ml/kg body weight of the infusion solution (0.04 MBq of $^{125}$I-iothalamate and 0.03 MBq of $^{131}$I-hippurate per ml saline) plus an extra of 0.6 MBq of $^{125}$I-iothalamate was given, followed by constant infusion at 12 ml/h. To attain stable plasma concentrations of both tracers, a 2 hour stabilization period followed, after which measurements started. Clearances were measured over the next 2 hours and calculated as (U*$V$/P) and (I*$V$/P), respectively. $U^*$ represents the urinary excretion of the tracer, $I^*$ represents the infusion rate of the tracer and $P$ represents the tracer value in plasma at the end of each clearance period. This method corrects for incomplete bladder emptying and dead space, by multiplying the urinary clearance of $^{125}$I-iothalamate with the ratio of the plasma and urinary

<table>
<thead>
<tr>
<th>1A. Pre-donation</th>
<th>Total (n=266)</th>
<th>Normal (n=119)</th>
<th>Overweight (n=110)</th>
<th>Obese (n=37)</th>
<th>p-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49±11</td>
<td>48±12</td>
<td>50±10</td>
<td>49±8</td>
<td>NS</td>
</tr>
<tr>
<td>Male / female ratio</td>
<td>118 / 148</td>
<td>47 / 72</td>
<td>56 / 54</td>
<td>15 / 22</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>25.9±4.0</td>
<td>22.5±1.7</td>
<td>27.1±1.3</td>
<td>33.0±3.2</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92±9</td>
<td>90±9</td>
<td>92±9</td>
<td>95±8</td>
<td>≤0.001</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>115±20</td>
<td>110±15</td>
<td>117±22</td>
<td>126±20</td>
<td>≤0.001</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>434±81</td>
<td>427±76</td>
<td>440±85</td>
<td>440±82</td>
<td>NS</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>26.7±3.2</td>
<td>25.9±2.7</td>
<td>26.8±3.4</td>
<td>28.7±3.0</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1B. Short-term post-donation</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>93±9*</th>
<th>91±9</th>
<th>95±8*</th>
<th>94±9</th>
<th>≤0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>73±13*</td>
<td>70±11*</td>
<td>74±14*</td>
<td>80±14*</td>
<td>≤0.001</td>
<td></td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>286±51*</td>
<td>280±53*</td>
<td>290±50*</td>
<td>293±48*</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>25.7±2.8*</td>
<td>25.2±2.6*</td>
<td>25.9±2.8*</td>
<td>27.1±2.8*</td>
<td>≤0.001</td>
<td></td>
</tr>
</tbody>
</table>

* p≤0.001 and # p≤0.05 short-term after donation versus pre-donation by paired t-test.
clearance of \(^{131}\)I-hippurate. The day-to-day variability for GFR is 2.5\% [20]. The filtration fraction (FF) was calculated as the ratio of GFR and ERPF and expressed as percentage (GFR/ERPF*100).

**Long-term follow-up of hemodynamic measurements**

For sixty donors, long-term follow-up measurements were available. Data were from donors who presented at their own initiative for follow-up (twelve donors, measurements performed between 1989 and 1999) and from two recently initiated studies concerning 5-year follow-up (37 donors) and 10-20-year follow-up (eleven donors). Measurements for these recent studies were performed in 2007; analyses are currently ongoing; all donors provided written informed consent.

**Statistical analyses**

Data are presented as mean ± standard deviation, unless stated otherwise. BMI was classified as normal weight (BMI <25 kg/m\(^2\)), overweight (BMI 25-30 kg/m\(^2\)) or obese (BMI ≥30 kg/m\(^2\)). Correlations were analysed by univariate analysis (Pearson). Differences were analysed by t-tests and analysis of variance (ANOVA) followed by post-hoc analysis. Statistical analyses were performed by using SPSS version 14.0 software (SPSS Inc., Chicago, IL, USA). A p-value ≤0.05 was considered statistically significant.

**Results**

Data of the 266 donors are shown in table 1. Mean age at donation was 49±11 years and mean body mass index (BMI) was 25.9±4 kg/m\(^2\). Kidney donation reduced GFR and ERPF to 64±7\% and 66±7\% of their pre-donation values (p≤0.001). Filtration fraction was slightly but significantly lower short-term after donation. The population characteristics in table 1 are also shown with a break-up according to normal weight (119 donors), overweight (110 donors) or obesity (37 donors). With overweight and obesity, mean arterial pressure, GFR and FF were significantly higher compared to normal weight donors, both before and short-term after donor nephrectomy.

**Filtration fraction and body mass index**

BMI was similar before and early after donor nephrectomy. On continuous univariate analysis, FF positively correlated to BMI, before (R=0.29; p≤0.001) as well as short-term after donation (R=0.24; p≤0.001). Figure 1 shows pre- and post-donation FF for normal weight, overweight and obese donors separately. Both before and early after donor nephrectomy, filtration fraction was higher with increasing BMI (either ANOVA p≤0.001). Compared to donors with normal BMI (post-donation FF 25.2±2.8\%), FF was significantly higher for both overweight (post-donation FF 25.9±2.8\%) and obese donors (post-donation FF 27.1±2.8\%; post-hoc analyses; all p≤0.05).

**Other determinants of short-term post-donation filtration fraction**

Besides BMI, other univariate determinants of pre-donation FF were age (R=0.15; p≤0.01) and MAP (R=0.15; p≤0.01). After donation, the association between age and FF was of borderline significance (R=0.11; p=0.07). Post-donation FF did not correlate to post-donation MAP. On multivariate regression analysis, FF before donation was independently predicted by both age (β=0.12; p=0.06) and BMI (β=0.28; p≤0.001) with R\(^2\)=0.11 and p-value of the model ≤0.001. MAP did not reach statistical significance. Short-term after donation, BMI was the only statistically significant predictor of FF in multivariate analyses.
Longitudinal data: association between changes in body weight and changes in renal hemodynamics

For sixty donors, long-term follow-up data were available. There was no difference in age at donation, BMI at donation or short-term post-donation renal function in donors available versus lost to follow-up. Mean follow-up was 7±4 years after donation, with a range of 1.5 to 21 years. Donor characteristics are presented in Table 2. Mean age at follow-up was 53±10 years, 33% were male. In a mean of seven years’ time, mean body weight had increased by 5.3±5.8 kg, with a range of -8 to +26 kg (p≤0.001 compared to pre-donation). This led to a rise in BMI of 1.7±1.9 kg/m² (range -2.6 to 7.8 kg/m²; p=0.001). The extent of weight gain correlated positively with the duration of follow-up (R=0.51; p≤0.001). Table 2 also presents renal hemodynamic values short-term and long-term after donor nephrectomy. In the remaining kidney, GFR, ERPF and FF were significantly increased between the evaluation early after donation and long-term follow-up.

The change in body weight during follow-up correlated positively with the concurrent change in GFR (R=0.40; p≤0.001) and FF (R=0.38; p≤0.005), but not with ERPF. Scatter-plots showing the individual values and regression lines for changes in body weight (x-axes) with GFR (right panel) and FF (left panel) are given in Figure 2. Analysing the effect of changes in BMI on renal adaptation provided similar results (data not shown).

Discussion

In this study on modulating effects of body mass index on renal hemodynamics after donor nephrectomy, we found, first, that the unfavourable effect of a higher body mass index on renal hemodynamics was sustained after donor nephrectomy in 266 donors, notwithstanding substantial adaptive renal hemodynamic changes in the remaining kidney. Second, on longitudinal analysis in a sub-group of sixty donors, we found that changes in body weight corresponded to long-term changes in renal hemodynamics.

The magnitude of the early adaptive changes in GFR and ERPF, as well as

<table>
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<tr>
<th>Donors with long-term follow-up (n=60; 67% female)</th>
<th>Short-term after donation</th>
<th>Long-term after donation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46±11</td>
<td>53±10</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74±13</td>
<td>79±13</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.8±4.2</td>
<td>26.5±4.2</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Number (%) with overweight (BMI ≥25 kg/m²)</td>
<td>23 (38%)</td>
<td>35 (58%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>73±11</td>
<td>83±13</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Effective renal plasma flow (ml/min)</td>
<td>295±49</td>
<td>321±53</td>
<td>≤0.001</td>
</tr>
<tr>
<td>FF (GFR/ERPF; %)</td>
<td>25.1±2.6</td>
<td>26.1±2.7</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

Table 2. Long-term changes in body weight and renal hemodynamics.

Abbreviations; FF, filtration fraction; GFR, glomerular filtration rate (¹²⁵I-iothalamate); ERPF, effective renal plasma flow (¹³¹I-hippuran); NS, not significant (paired t-test).
the slight decrease in FF, are in line with prior, smaller, studies [21], suggesting that our data are representative for donor populations in general. We are the first to show that BMI still modulates renal hemodynamics after nephrectomy, in spite of substantial adaptive changes in renal hemodynamics. Apparently, the impact of BMI on renal hemodynamics is robust, as also indicated by our findings in transplant recipients [13]. Our data raise the possibility that renal hemodynamic factors play a pathogenetic role in the long-term risk of obesity-related renal damage after unilateral nephrectomy, as reported by Praga et al. [14]. It should be noted however, that we only studied kidney donors, whereas in Praga’s population, nephrectomy was performed for urological disorders, known to bear a worse prognosis, possibly due to compromised status of the remaining kidney.

The pathogenic potential of an elevated filtration fraction, corresponding to elevated glomerular pressure has been extensively shown in animal studies of progressive renal disease [22-25]. It could be argued that the impact of BMI on filtration fraction in our study was relatively small, with a difference of just 1.9% between lean and obese subjects. This might be insufficient to be pathogenetically relevant. However, differences in filtration fraction of a similar magnitude were recently shown to predict renal graft loss, independent from blood pressure and proteinuria [10]. Further support is provided by intervention data in native kidney disease, where a decrease in FF at onset of antihypertensive treatment of 2.5% as opposed to 1% predicted a difference in the efficacy of long-term renoprotection [26] and corresponding observations have been made in diabetic nephropathy.

**Figure 1. Filtration fraction is higher in relation to higher BMI before as well as short-term after donor nephrectomy.**

Data are provided as box and whiskers: median (line in box), 25-75 percentiles (box) and fill ranges (whiskers). Filtration fraction was obtained as (GFR/ERPF)*100. BMI is subdivided as follows: normal weight: BMI <25 (119 donors); overweight: BMI 25-30 (110 donors) and obesity: BMI ≥30 kg/m² (37 donors). Before (left panel) as well as after donation (right panel), filtration fraction was significantly higher with increasing BMI, as analysed by ANOVA. * p≤0.001. Abbreviations: BMI, body mass index.
[27]. Thus, small differences in FF can apparently bear relevance to renal prognosis.

Our data on longitudinal follow-up confirm the long-term adaptive capacity in the remaining kidney after donation. As expected, both glomerular filtration rate and renal plasma flow showed an increase on long-term as compared to early post-nephrectomy data. Remarkably, the long-term changes in renal hemodynamics correlated to long-term changes in body weight and body mass index. Apparently, the association between BMI and renal hemodynamics is dynamic. Chagnac et al. have shown that obesity-induced hyperfiltration can be corrected by weight loss after gastroplasty [18], providing proof of principle of the reversibility of obesity-associated renal hemodynamic changes. A massive reduction in BMI from 48 to 32 kg/m² led to a reduction in GFR by 35 ml/min (p=0.01), and in FF by 2% (p=0.07). We demonstrate that spontaneous changes in body weight of just a few kilograms bear significant impact filtration rate and filtration fraction. Changes in body composition are known to occur over a life time. In the general population, a mean increase in body weight of approximately seven kilos per decade was shown longitudinally [28], quite comparable to the weight gain in our donor population. Furthermore, a post-donation increase in BMI was recently reported in kidney donors [16], indicating that our findings may be representative and relevant for a large population of kidney donors.

For the purpose of intervention, it is important to note that weight loss is usually difficult to obtain. Blockade of the Renin Angiotensin Aldosterone System (RAAS) has been suggested to be beneficial to the renal risks of overweight, as the renal hemodynamic response to RAAS-
blockade was strongly associated with increasing BMI and more pronounced in overweight and obese subjects [29,30]. RAAS blockade may thus be effective in protecting against long-term renal consequences of overweight, in particular as RAAS blockade also reduces blood pressure. It should be mentioned however, that non-hemodynamic consequences of weight excess such as insulin resistance and dyslipidemia may also contribute to obesity-related renal damage, and require specific treatment.

A limitation to the interpretation of our longitudinal data is the heterogeneity in duration of follow-up, so interference by age-related effects on renal hemodynamics cannot be excluded. An additional limitation is the small number of donors with overt obesity, which limits generalizability of our data to populations were obesity is much more common, as in the United States. It should be mentioned however, that the renal risks of overweight are not limited to overt obesity [5,6].

Our findings may gain importance in the near future, considering the increasing prevalence of weight excess, with also an increasing number of living kidney donors being overweight or obese. Fortunately, so far long-term follow-up of living kidney donors provides no evidence for progressive renal deterioration [31,32]. However, today's kidney donors differ from the donors in the past. In many centres, screening protocols have become more liberal, accepting donors with both obesity and hypertension, which are no longer absolute contraindications for donation [15]. Long-term follow-up is warranted to monitor the safety of these changes in donation policy.

In conclusion, the impact of BMI on renal hemodynamics is maintained after donor nephrectomy despite considerable adaptive renal hemodynamic changes. Moreover, longitudinal spontaneous changes in body weight were associated with corresponding changes in long-term renal hemodynamics. Post-donation weight gain may pose an extra burden on the remaining kidney and should preferably be prevented. This needs to be emphasized in donor screening, evaluation and follow-up.
References


