Reduced glomerular filtration rate due to loss of nephron mass may be an independent risk factor for atherosclerosis

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Abstract

Background. Whether living with reduced nephron mass (RNM) poses a risk to humans is the subject of ongoing controversy. The aim of this study was to discover whether or not RNMs are associated with greater atherosclerotic plaque burdens.

Methods. Using the post-operative abdominal CT scans of 739 nephrectomized patients [NP; 315 women and 424 men; mean age 64.5 ± 15.0 years; observation period 4.9 ± 5.7 years (3675.9 patient-years)] and of an age- and a gender-matched control group, a retrospective observational and case–control study was conducted. The V600 calcium scoring method was used to determine the aortic calcium volume score (ACS) and thus the APB.

Results. The ACS was 0.47 ± 0.77 mm³ in the NPs compared with 0.41 ± 0.69 mm³ in the control group (P <0.0001). The ACS and the glomerular filtration rate (GFR using the CKD-EPI formula) after nephrectomy correlated inversely (P = −0.3652; P <0.0001), and the ACS and the time since nephrectomy correlated positively (P = 0.2919; P <0.0001). In linear regression models, age, time interval and GFR after nephrectomy proved to be independent factors of influence on ACS (P <0.05 each). Including the control group, age, GFR after nephrectomy and nephrectomy were independent factors of influence on the ACS. The factor GFR after nephrectomy explains ~10.7% in NPs, and 28% of the variance of the ACS in all patients.

Conclusions. The factors ‘low GFR’ and RNM are risk factors for greater atherosclerotic plaque burden. Patients with RNM should undergo regular control examinations to monitor arterial blood pressure and treat hypertension if it occurs.

Keywords: angiolysin; arterial hypertension; calcium scoring; glomerular filtration rate (GFR); medullipin

Introduction

After renal ablation, there is compensatory growth of the remaining renal tissue in animal models [1–3], but not glomerular neogenesis [4]. The glomerular filtration rate, mean glomerular blood flow [3] and glomerular pressure [5] increase and cause hyperfiltration [6,7]. In the first phase of glomerular hypertrophy, there is epithelial cell expansion, then mesangial cell expansion [8], and finally glomerulosclerosis [7,9], which leads to proteinuria, hypertension and renal failure [10].

Whether living with only one kidney or generally with decreased nephron mass poses a risk to humans is the subject of ongoing controversy [10,11]. The increase in urinary protein, the reduction of renal function [12], and the increase in blood pressure after a live kidney donation [13] need not necessarily result in lower life expectancy [14], although this might actually be expected [15] in view of the extent of the effects on blood pressure [13]. Ultimately, the aetiological cause of the rise in blood pressure is unclear. Assuming the validity of the data on blood pressure, in this study, we replaced blood pressure as a target variable with the atherosclerotic plaque burden of the abdominal aorta in a completely new approach that was made technically possible by the introduction of a new method of calcium scoring in computer tomography [16]. For this purpose, we selected patients for whom a nephrectomy was performed for urological reasons. These were mainly tumour patients who require CT follow-ups for the rest of their lives after surgical treatment.

The objective of this study was to find out whether this method yielded proof of an increased risk of atherosclerosis in patients with reduced glomerular filtration rate due to loss of nephron mass.

Materials and methods

Patients

The study included 739 patients who underwent a nephrectomy because of a tumour (n = 704) or other urological diseases (n = 35), and for whom at least one post-operative CT was available. There were 315 women and 424 men with a mean age of 64.5 ± 15.0 years (range 0.56–93.6 years). As a control group, we used the examinations of 739 patients, 315 women and 424 men with a mean age of 64.5 ± 15.0 years (range 0.4–93.6 years). As the retrospective observational study had no influence on conducting
either the CT scan or further treatments, approval of the local ethics commission was not needed. The study was conducted in full compliance with the provisions of the Declaration of Helsinki in the version of October 2008.

**Study design**

The study was a retrospective observational study with a time component—due to the varying intervals between nephrectomy and the CT scan used for determining the calcium score—and a case–control study. The group of nephrectomized patients was compared with a control group consisting of 739 patients. Simple random matching was carried out by age with assignment precision of 1 year and by gender. The controls stemmed from a pool of 1520 patients who had not undergone nephrectomy. Due to the peculiar age and gender distribution of the nephrectomized patients, double matching could not be performed.

**Criteria for inclusion**

Criteria for inclusion in the study were a nephrectomy that was carried out on a known date and at least one multi-slice CT scan of the abdomen made afterwards that was available as a DICOM file in the hospital picture acquisition and communication system (PACS) system. The mean interval between nephrectomy and the latest CT scan was 4.97 ± 5.7 years (range 0–73.2 years). For the control group, there had to be at least one abdominal CT scan that had been made for any reason. Most of the patients had tumours (n = 281), liver disease (n = 229) and vascular disease (n = 133). Other illnesses were given for 96 patients.

**Criteria for exclusion**

Of the 1002 patients for whom a nephrectomy between 1999 and 2010 could be proven based on the file or a radiology examination, 263 were excluded from the study. For 178 patients, there was no post-operative abdominal CT scan; for 36 patients, it was not possible to reconstruct the nephrectomy; based on these coefficients the plaque burden at age 64, the average age at the time of nephrectomy, was defined as 100%, and the plaque burdens of patients older than 64 were allotted to this value. The relative plaque burdens subject to the time interval after nephrectomy were calculated analogously.

In the fourth step, simulations of various linear and non-linear functions were made to describe the correlation between ACS, age and interval since nephrectomy, or the factor nephrectomy; based on these coefficients of determination, the method of linear regression was deemed acceptable.

Then, in the fifth step, within the group of nephrectomized patients, initially including all variables as covariates and then in a forward stepwise variable selection procedure in which all variables with probability values >0.10 were excluded, various linear regression models were fitted to the dependent variable V600.

Finally, in the sixth step including all patients, those who were nephrectomized and those who were not, initially including all variables as covariates and then in a forward stepwise variable selection procedure in which all variables with probability values >0.10 were excluded, various linear regression models were fitted to the dependent variable V600.

The variables included in the models were the ACS, the interval between nephrectomy and the latest CT follow-up, glomerular filtration rate before nephrectomy and at the time of the latest CT follow-up, age, and gender. Information on other risk factors such as hypertension or diabetes was not available.

The statistical analysis was done using SPSS 15 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.00 (Graph Pad Software, San Diego, CA, USA). P <0.05 was considered statistically significant.

**Results**

**Age distribution of patients**

Figure 2 shows the age distribution of the patients. It is a non-normal distribution skewed to the left and steep on the right. The median age was 66.83 years, greater than the mean. The skewness was –1.091; the kurtosis was 1.790.

**Interval between nephrectomy and CT scan**

The interval between nephrectomy and the most recent CT scan used for calcium scoring was 4.97 ± 5.7 years. Here, as well, the distribution was not normal. The median was 4.005 years (range: 0.003–40.373 years), noticeably less

**Scanners used and image analysis**

The examinations were conducted using Somatom Sensation Open 20, Somatom Definition Flash, Somatom plus 4, Somatom Emotion 2, Somatom Sensation 64, and Somatom Sensation 16 spiral CT scanners (Siemens Healthcare, Erlangen, Germany) and Lightspeed VCT XT 64, LightSpeed 16, LightSpeed QX/i 4 spiral CT scanners (General Electric, Milwaukee, WI, USA). Most scans used collimation of 5, 3 or 2.5 mm, while the other scans had thinner collimation. A finding of ‘single kidney’ in the CT scan was always verified by a consensus of two experienced, board-certified radiologists (JP and BG). The calcium scoring of the aorta (ACS) was made without knowledge of the objective of the study.

**ACS**

For segmenting the hard plaque of the aorta, the V600 method was chosen, which can be used irrespectively of whether contrast medium is applied or not [16]. To do so, the calcium volume of the aorta on the segment from the upper edge of the celiac trunk to the bifurcation was determined at a General Electric image processing workstation (AW 4.4, GE, Milwaukee, WI, USA) by discarding the data on volume above the trunk and caudal to the bifurcation and separating the spinal column from the aorta manually. Clips were segmented and discarded, as were the origins and courses of the unpaired visceral arteries. Other calcifications, such as granuloma of the liver or concrements of the gall bladder, were discarded manually. Finally, a density threshold of 600 HU was introduced, and the remaining volume was determined automatically (Figure 1).
than the mean. The total ‘observation period’ after nephrectomy was 3675.9 patient-years.

Glomerular filtration rates

The GFRs of the patients in the nephrectomy group were $77.12 \pm 27.9 \text{ mL/min/1.73 m}^2$ before, and $60.59 \pm 28.36 \text{ mL/min/1.73 m}^2$ after nephrectomy (Wilcoxon test; $P < 0.0001$), whereas the clearances in the control group were $78.60 \pm 20.82 \text{ mL/min/1.73 m}^2$ (Mann–Whitney test; $P > 0.05$).

V600 scores

The ACS was $0.4675 \pm 0.7727 \text{ mm}^3$ in the group of nephrectomized patients, statistically significantly higher than the score of $0.4130 \pm 0.6942 \text{ mm}^3$ in the control group ($P = 0.0359$). The Wilcoxon test for comparison of the pairs also resulted in a statistically significant difference ($P < 0.0001$). The group of nephrectomized patients had fewer patients for whom no calcification of the aorta was found (130 of 739) than the control group, with 152 of 739 patients. However, this difference was not statistically significant (chi-square test; $P = 0.1077$). The odds ratio was 0.8244, with a 95% confidence interval of 0.6566–1.035.

Dependence on age of the V600 score of the aorta

The ACS increases with age, as shown in Figure 3. While hardly any calcification can be seen in patients <40 years
of age, except for some nephrectomized patients, the score then increases rapidly. For women, the increase of the ACS begins at a noticeably later age but eventually reaches levels similar to those of men.

Increase in the V600 score after nephrectomy

Figure 4 shows the ACS in relation to the interval between the CT scan and the nephrectomy. The ACS increases over time since nephrectomy ($P < 0.0001$, one-way ANOVA, with post-test for linear trend). The time after nephrectomy and ACS correlated with a Spearman $\rho = 0.2919$ ($P < 0.0001$).

Correlation of glomerular filtration rates and V600 score

In the nephrectomized patients, there was an inverse correlation between the V600 score of the aorta and the creatinine clearance after nephrectomy, with a Spearman $\rho = -0.3652$ (confidence interval from $-0.2581$ to $-0.4402$, $P < 0.0001$).

Comparison of age-dependent plaque burden increments in patients with and without a nephrectomy

The relative age-dependent plaque burden increments, related to the plaque burden at age 64, the average age at the time of the nephrectomy, were calculated, as shown in Figure 5. The differences between the group of nephrectomized patients compared with the control group were statistically significant ($P = 0.0085$; two-way ANOVA).

Predictors for aortic calcification in the group of nephrectomized patients

Independent predictors for the ACS were age ($\beta = 0.373$; $P < 0.0001$), time after nephrectomy ($\beta = 0.294$; $P < 0.0001$), and the factor ‘reduced nephron mass’ (RNM) in terms of low GFR after nephrectomy ($\beta = -0.107$; $P = 0.014$) (Table 1). The factor ‘RNM’ explains ~10.7% of the variance of the ACS. The factor ‘RNM’ pushed the factor ‘difference between creatinine clearances before and after nephrectomy’ out of the models.

Predictors for aortic calcification among all patients

Remaining independent predictors for the V600 score were age ($\beta = 0.353$; $P < 0.0001$), the factor ‘reduced nephron mass’ in terms of low GFR ($\beta = -0.280$; $P < 0.0001$), and the factor nephrectomy ($\beta = 0.106$; $P < 0.0001$) (Table 1).

Discussion

This study shows for the first time that the arterial plaque burden increases disproportionately after nephrectomy, subject to the time interval since nephrectomy and to the remaining GFR. ‘Reduced nephron mass’ in terms of low creatinine clearance values proved to be an independent risk factor for the progression of atherosclerosis. It explains ~10.7% of the variance of the ACS of nephrecto-
Several weaknesses of this study must be taken into consideration when interpreting the data. Firstly, it is a retrospective study which, as a case–control study, reaches level II–2 according to the USPSTF classification and level 3b according to the Centre for Evidence Based Medicine of the University of Oxford. Secondly, for many patients, no information was found on other cardiovascular risk factors such as nicotine consumption, cholesterol level, etc. While it may be assumed that these risks are randomly distributed across the two groups of patients, we do not have the data to support this assumption. Thirdly, we must point out the bias that about half of the nephrectomized patients were operated in our urology department, but clearly, fewer patients in the control group were treated in the urology department. The relatively high rate of patients from our vascular surgery department in the control group leads to the assumption that the effect of nephrectomy on the atherosclerotic plaque burden is possibly underestimated. Be that as it may, the results will ultimately have to be confirmed in prospective studies with stronger evidence.

However, it should be noted that the results appear to be highly plausible in view of the known effects of nephrectomy on blood pressure [13]. It is not yet known today the extent to which the aortic plaque burden is increased by arterial hypertension or the extent to which conclusions can be drawn about future cardiovascular events. However, it is clear that not only arterial hypertension itself but also arteriosclerosis as a direct result of hypertension can be responsible for causing these events [18], and as the case may be, arteriosclerosis as a direct result of a low GFR. The indirect correlation between arterial hypertension and the number of cardiovascular events of high blood pressure has been well documented [15]. The methodological consideration that cardiovascular events should be predictable not only based on the coronary plaque burden [19,20] but also based on the basis of calcification of other vascular areas is also plausible, although not yet documented.

Since 1898, when Tigerstedt and Bergmann [21] prepared a watery extract from the kidney that had hypertensive effects, the kidney has been considered the central organ for regulating blood pressure. Paessler and Heinecke [22] found, after resecting 5/6 of the kidneys to create renal failure, that blood pressure rose by ~15 mmHg, and they were the first to prove that left ventricular hypertrophy ensued as a result. This was followed by the epochal experiments by Loesch in the 1920s and by Goldblatt in the 1930s, in which renal ischaemia was shown to be a hypertensive mechanism [23], which led directly to the discovery and purification of angiotensin and renin and to an understanding of their interaction in this blood pressure- and volume-regulating system of the body [23]. Just shortly after that, in 1940, Page et al. reported on the regression of vascular changes in the fundus oculi of hypertensive patients from oral administration of extracts of raw kidney, brought about by its pronounced effect in lowering blood pressure [24]. There are two substances carrying the blood pressure-lowering effects. They are localized in the renal medulla [25]. These two hormones, which were later called medullipin [26] and angiolysin [27], have not yet been chemically characterized [28], although they, in addition to sodium nitroprusside, are among the strongest antihypertensive and vasodilatory substances whose existence has been proven [27]. With this in mind, it appears conceivable that blood pressure can be transplanted with a kidney [29], in both directions, from genetically hypertensive donors to normotensive recipients and from normotensive donors to hypertensive recipients [30]. In view of the fact that the factor ‘nephrectomy yes or no’ remains in the models despite the presence of the factor ‘GFR after nephrectomy’, we pose the hypothesis for explaining the increase in blood pressure after a nephrectomy and the disproportionate plaque burden that the capacity of the antihypertensive hormonal mechanism of the kidneys is impaired by a nephrectomy.

There are some studies that indicate that patients with CKD have a greater risk of experiencing a cardiovascular event than would be expected based on the data of the Framingham study [31]. There is also evidence that these patients have a higher incidence of peripheral arterial occlusive disease including cerebrovascular disease and of congestive heart disease [32]. Since the patients we studied did not initially have a chronic disease of the renal parenchyma, but rather the nephrectomies were performed due to renal cell carcinoma in otherwise healthy kidneys, it could be speculated based on this study whether chronic kidney disease is even a condition for an increased risk of arteriosclerosis or whether it might be sufficient to have a low GRF due to reduced nephron mass. The discovery of the mechanism and quantification of the significance of

### Table 1.

<table>
<thead>
<tr>
<th>Predictor of ACS</th>
<th>B</th>
<th>P</th>
<th>β</th>
<th>Standard error</th>
<th>95% confidence interval</th>
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<tbody>
<tr>
<td>Nephrectomized patients (n = 739)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>&lt;0.0001</td>
<td>0.373</td>
<td>0.002</td>
<td>0.016</td>
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<td>Time after nephrectomy</td>
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<td>&lt;0.0001</td>
<td>0.294</td>
<td>0.005</td>
<td>0.034</td>
</tr>
<tr>
<td>GFR after nephrectomy</td>
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<td>0.014</td>
<td>−0.107</td>
<td>0.001</td>
<td>−0.005</td>
</tr>
<tr>
<td>All patients</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
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<td>&lt;0.0001</td>
<td>0.353</td>
<td>0.001</td>
<td>0.015</td>
</tr>
<tr>
<td>GFR after nephrectomy</td>
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<td>&lt;0.0001</td>
<td>−0.280</td>
<td>0.001</td>
<td>−0.009</td>
</tr>
<tr>
<td>Nephrectomy yes or no</td>
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<td>&lt;0.0001</td>
<td>0.106</td>
<td>0.055</td>
<td>0.106</td>
</tr>
</tbody>
</table>

ACS, aortic calcium score; B, parameter vector; β, standardized matrix B; P, significance; GFR, glomerular filtration rate.
the supposed mechanisms such as low GFR or arterial hypertension must be the subject of prospective studies.

Despite the fact that the effect of a nephrectomy on the atherosclerotic plaque burden is probably underestimated, we want to warn against drawing premature conclusions from our study. For treating malignant renal disease, nephrectomy and partial renal resection remain the method of choice.

There is currently no alternative procedure in sight, and especially for live kidney donors, there is still no ultimate proof that a nephrectomy has a long-term, lifespan-reducing effect. The increase in blood pressure leading to a higher risk of aortic calcification is believed to be able to be treated so effectively today that any potentially higher risk of cardiovascular events can be safely avoided [33]. The only recommendation that we give is that regular follow-up examinations should be conducted after a nephrectomy so that any existing or arising arterial hypertension can be adequately treated.

In summary, this study shows that, consistent with existing knowledge of the increase in blood pressure after nephrectomy, there is also a disproportionate increase in the aortic plaque burden. This is level IIb evidence, which so effectively today that any potentially higher risk of cardiovascular events can be safely avoided [33]. The only recommendation that we give is that regular follow-up examinations should be conducted after a nephrectomy so that any existing or arising arterial hypertension can be adequately treated.

Conflict of interest statement. None declared.

References


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