

## Impaired kidney function in rats six months after unilateral nephrectomy – an old story, a new perspective

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### ABSTRACT

**Aim** Despite of routinely practised living kidney transplantation, data on consequences and impact of unilateral nephrectomy on the quality of life and health of donors are scarce. The aim of the present study was to examine long-term changes and function of the remnant kidney after unilateral nephrectomy in an animal model.

**Methods** Thirty six female Sprague – Dawley rats at 4 months of age were randomized into the three groups: unilaterally nephrectomized, sham operated and naïve rats. The nephrectomy was done at inclusion in the experiment and their blood was taken at inclusion and six months thereafter.

**Results** There was a significant increase in serum creatinine concentrations six months after unilateral nephrectomy ( $39.7 \pm 0.8$   $\mu\text{mol/l}$ ) in comparison with the sham operated ( $30.1 \pm 1.1$   $\mu\text{mol/l}$ ) and the naïve rats ( $26.3 \pm 3$   $\mu\text{mol/l}$ ) ( $p \leq 0.001$ ). Serum sodium levels remained unchanged ( $p = 0.116$ ). Blood haemoglobin concentration did not differ between the three groups ( $p = 0.115$ ).

**Conclusion** Although it has been very well established that kidney possesses huge capacity to compensate severe loss of renal mass, our results implicate that renal function undergoes significant deterioration with time after unilateral nephrectomy. Fortunately, in everyday clinical practice we do not see severe renal dysfunction in patients with a single kidney. However, prolongation of the human life span in the future could face us with renal impairment in living kidney donors. Future examination of specific biomarkers in our rat model (e.g. growth factors) could support our findings.

**Key words:** unilateral nephrectomy, kidney function, creatinine

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## INTRODUCTION

The development of kidney transplantation has made a great success in the therapy of end stage renal disease (ESRD). It has provided a better life quality (1) and improved survival of patients with ESRD compared to the outcomes of patients on dialysis treatment (2). The shortage of cadaver kidney donors and simultaneously increased demand for kidney transplantation has led to a rise in need for living-donor kidney donation (3,4). Kidney recipients from living donors have many advantages over cadaver kidneys, such as longer allograft and recipient survival, fewer postoperative complications and better renal function (5-7). However, data on the consequences of a living kidney donation and its impact on the quality of life and health of the donors are scarce. The mechanisms by which the remnant kidney compensates severe loss of organ mass, such as unilateral nephrectomy, are very well known and it is generally accepted that one can live with a single functional kidney (8,9). Difficulties occurring in long term follow up human studies are responsible for the lack of data in regard to functionality of remaining kidney and its contribution to the living donors' quality of life. Previous studies have shown that the loss of one kidney is normally compensated by the other, healthy kidney (10). The remaining kidney undergoes structural and functional changes in order to maintain homeostasis of fluid and solutes in the organism (11). Numerous studies have followed short- and long-term consequences of live kidney donation but they were mostly conducted as single-centre studies, on a relatively small sample of donors. They have reported that the short- and long-term morbidity and mortality of living donors are reasonably low (10,12). Perioperative complications are the same as in all operative procedures. Most common are minor complications, such as post-operative bleeding, wound and other infections, whereas major complications, such as post-operative death, are rather exceptional (13). Some studies reported higher incidence of arterial hypertension and proteinuria among kidney donors years after unilateral nephrectomy (14), but it still remains unclear whether these were consequences of the nephrectomy or normal ageing process. Survival and the risk of ESRD in carefully screened kidney donors appear to be similar to those in the general population (15). In contrary,

Sui et al. demonstrated high incidence of renal carcinoma in uninephrectomized rats 7 months after nephrectomy, which has been associated with enhanced IGF-1 signalling pathway (16).

The aim of present study was to examine the long-term changes and function of the remnant kidney after unilateral nephrectomy. For that purpose an animal (rat) model of unilateral nephrectomy was utilized. Because of the short life span, animal models are good for the long-term follow up, which is often a problem in human studies. Here we present the data on creatinine, sodium and potassium serum concentration, and haemoglobin content in red blood cells after the first 6 months postnephrectomy.

## MATERIALS AND METHODS

### Experimental Animals

The Sprague – Dawley rats were purchased from Harlan Inc. (Italy) and housed at the animal care facility of the School of Medicine J. J. Strossmayer University of Osijek. All experimental procedures conformed to the European Guidelines for the Care and Use of Laboratory Animals (Directive 86/609) and were approved by the Ethics Committee of home institution and authorized by the Ministry of the Republic of Croatia. Rats were housed in a temperature-, humidity-, and light-controlled room with free access to tap water and fed *ad libitum* with a commercially prepared pelleted diet. Total of 36 female rats (12 rats per group) were introduced to the experiment at 4 months of age.

### Experimental groups and protocol

In the present study animals were divided into the three groups: nephrectomized rats, sham operated rats, and naïve rats. Sham operated rats and naïve rats were used as controls.

Before the rats were subjected to surgery their blood was taken for further analysis. Afterwards they were divided into the three groups and accordingly unilaterally nephrectomized, sham operated or remained intact. Halves of removed kidneys from nephrectomized rats were immediately frozen at -80°C or *formalin-fixed* and paraffin-embedded as routine. Part of the serum was also put on -20 °C for future analysis. Animals are kept at the animal care facility for 12 months. After a six month period and before the sacrifice their blood will be taken for analysis. Kidneys

from all three groups of rats are going to be collected and prepared for histology, WB or rtPCR one year after inclusion into the study.

### Unilateral nephrectomy

Rats were anesthetized by 75 mg/kg of ketamin (Ketanest S 25 mg/mL, Pfizer, New York, SAD) and 0.5 mg/kg of midazolam (Midazolam Torrex 5 mg/ml, Torrex Chiesi Pharma, Beč, Austrija). After becoming unresponsive to noxious stimuli, they were subjected to the surgery. A small lumbar incision was made, and the left kidney was removed. In sham operated animals, the left kidney was exposed and gently manipulated but left intact.

### Blood and serum analysis

At this stage of the experiment we have taken the blood from the animals two times, at the time of inclusion into the study and after a six month period. The blood was taken by incision of the tail vein, collected in appropriate tubes (with/without anticoagulants) and immediately delivered to the routine diagnostic laboratory at University Hospital Center Osijek where the full blood count and the biochemical analysis of the serum were performed.

### Histology and light microscopy

The tissue samples from rats that were first included into the protocol and sacrificed one year later were fixed in 4% formaldehyde and paraffin embedded. 5- $\mu$ m thick sections were then mounted on glass slides and depleted of paraffin with xylene. Following, the sections were counterstained with hematoxylin/eosin, Mallory or PAS and analysed by a light microscope.

### Statistics

Statistical analysis was performed by using SigmaPlot (ver. 11.0, Systat Software Inc., SSI, San Jose, California, SAD) and SPSS (ver. 16.0, SPSS Inc., Chicago, IL, USA) programs. Values are presented as mean $\pm$ S.E.M. or as median followed by maximum and minimum values. For the comparison between the two measurements paired t-test or Wilcoxon's test were used. To compare between more than two different groups one-way ANOVA or Kruskal-Wallis test were utilized and post-hoc Holm Sidac or Dunn's when appropriate.

## RESULTS

As this is an ongoing study and experimental animals were introduced into the protocol at various

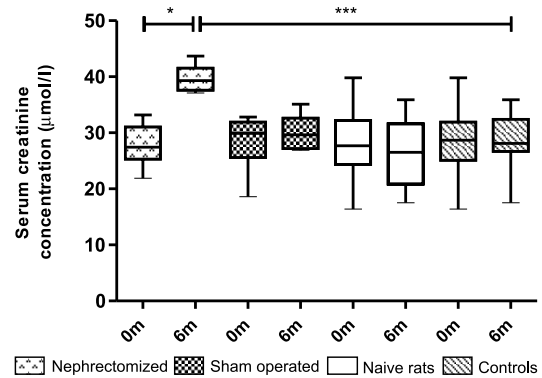
time points, initial measurements refer to all included rats (n=36), whereas the results of repeated measurements refer only to those rats that have been in the protocol for at least 6 months (n=23).

There was a significant increase in serum creatinine concentration after a 6 month period when compared to the initial serum creatinine concentration (n=6, p=0.031). However, there was no significant change in serum creatinine levels in the control groups of rats, neither in sham operated (n=7, p=0.106) nor in naïve rats (n=5, p=0.875) during the 6 month period (Figure 1).

Initial serum creatinine concentration did not differ between the three groups (nephrectomized rats 27.8 $\pm$ 1.1  $\mu$ mol/L, n=12; sham operated rats 28.5 $\pm$ 1.3  $\mu$ mol/L, n=12, and naïve rats 27.8 $\pm$ 1.8  $\mu$ mol/L, n=12; p=0.935). Taking the controls together, their initial serum creatinine concentrations (28.1 $\pm$ 1.1  $\mu$ mol/L, n=24) did not differ from the basic creatinine concentrations found in nephrectomized rats (p=0.880) (Figure 1).

A significant increase in serum creatinine concentrations was found six months after nephrectomy in unilaterally nephrectomized rats (39.7 $\pm$ 0.8  $\mu$ mol/L, n=9) compared to sham operated (30.1 $\pm$ 1.1  $\mu$ mol/L, n=9) and naïve rats (26.3 $\pm$ 3  $\mu$ mol/L, n=5; p=0.173) (p<0.001). There was no significant difference in serum creatinine concentrations in sham operated rats compared to naïve rats.

There was no significant correlation between initial serum creatinine level and creatinine concentration measured after the 6-month period, neither in all the rats (n=18, Kendall's tau B =-0.243, p=0.16) that have been in the protocol for over 6 months, nor for the certain subgroups, unilaterally nephrectomized rats (n=6, Kendall's tau B



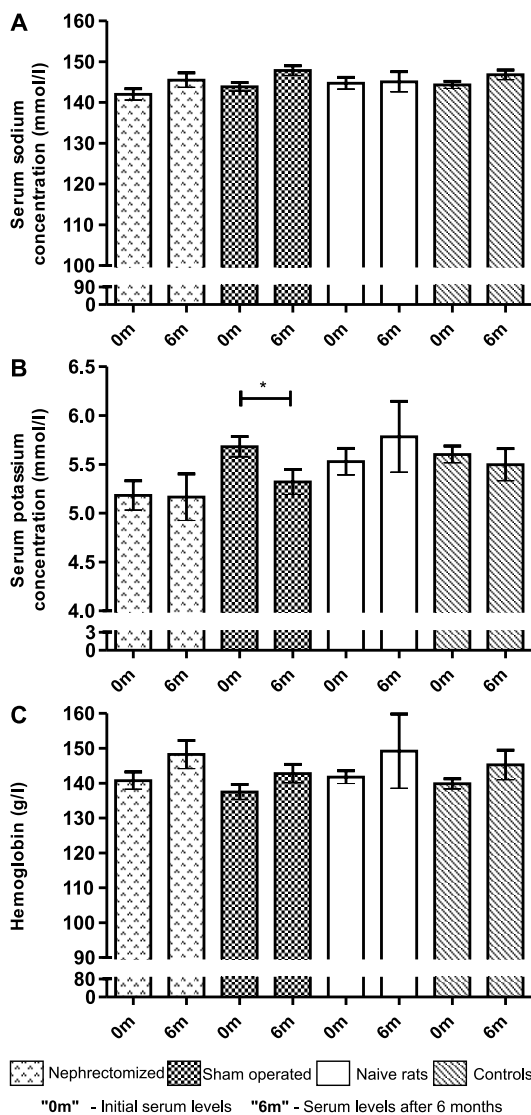
**Figure 1. Serum creatinine concentration at the time of inclusion into the study and after a 6-month period in nephrectomized rats, sham operated rats, naïve rats, and in control groups presented together**

(\*p=0.031; \*\*\* p<0.001; 0m, initial serum creatinin level; 6m, serum creatinin level after six months)

=0.2,  $p=0.573$ ) and controls ( $n=12$ , Kendall's tau B = -0.412,  $p=0.063$ ).

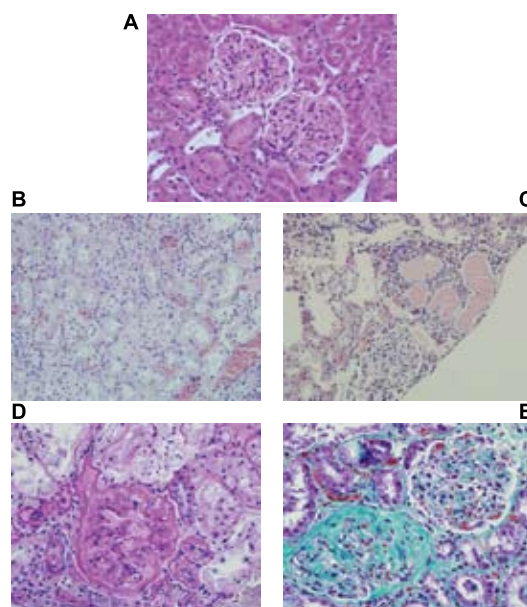
There was no statistically significant difference in serum sodium concentration when initial values were compared to the values measured after six months in each experimental group or between the groups ( $p=0.116$ ). Furthermore, serum haemoglobin concentration did not differ between the three groups of rats ( $p=0.115$ ), or within any of experimental group (Figure 2). However, six months after the introduction into the study serum potassium level was significantly decreased in sham operated rats ( $p=0.006$ ) (Figure 2).

Histological analysis of the remnant kidney one year after unilateral nephrectomy showed that approxi-



**Figure 2. Serum level of sodium (A), potassium (B), and haemoglobin (C) at the inclusion into the study and after a six month period**

(\* $p=0.006$ ; 0m, initial serum creatinin level; 6m, serum creatinin level after six months)



**Figure 3. Histology of an extracted kidney at the time of inclusion into the protocol (A) and the remnant kidney one year after uninephrectomy (B-E) showing normal glomerulus (HE x400) (A), focal sclerosis (HE x200) (B), appearance of "thyroidization" and lymphocyte infiltration (HE x200) (C), completely sclerotic glomerulus (PAS x400) (D) found next to an intact glomerulus (Malory x400) (E) (Ksenija Marjanović, 2011)**

mately 1/8 of the total glomeruli number was sclerotically changed unlike the kidney taken during uninephrectomy a year before. In the remnant kidney small focal changes with an appearance of "thyroidization" accompanied by lymphocyte infiltration of the interstitium were also observed (Figure 3).

The remnant kidneys from nephrectomized rats were 50% heavier than their counterparts extracted by nephrectomy a year before and 25% heavier than the kidneys found in the control rats (Figure 4).



**Figure 4. Compensatory enlargement of remnant kidney (upper kidney). The weight of remaining kidney was 25% higher than of the kidneys found in the control rats (Mate Moguš, 2011)**

## DISCUSSION

Severe reduction of renal mass, such as unilateral nephrectomy for the purpose of kidney donation, results in anatomical and functional changes in the remaining kidney in order to compensate the occurred loss (17,18). The compensatory enlargement of the remnant kidney after unilateral nephrectomy is a well known fact described in the 19<sup>th</sup> century (19). It has been accompanied by pathological changes that lead to reduced renal function, although the weight of the kidneys has not been a true index of the rate of dysfunction (20). In accordance with this, the remnant kidney in our experiment was significantly heavier than those found in the control groups of rats, and the histological analysis of the remnant kidney showed that about 1/8 of the total number of kidney glomeruli had degenerative changes such as glomerulosclerosis. Furthermore, unexplained lymphocyte infiltration was found in the remnant kidney one year after unilateral nephrectomy, which could suggest immune involvement in the postnephrectomy changes. Previous experiments demonstrated that the growth of remaining kidney starts as early as the day following the nephrectomy (21), and the rate of enlargement increases by the time, reaching 121% after 150 days (22). Compensatory growth leads to an increased weight (23,24) and volume (25) of the remaining kidney. Although each part of the nephron – glomeruli (25,26), proximal (27) and distal convoluted tubules and cortical collective duct (28) can be affected by the compensatory growth, it occurs primarily in the cortex, especially in the proximal convoluted tubules (29). The nature of this growth is rather hypertrophic than hyperplastic (29) and it has been shown that in rats it can vary with age at the time of nephrectomy (30-32). The predominant cause of the observed changes is the increased workload on nephron caused by hyperfiltration, which is followed by increased release of growth factors that induce cell growth.

Our results are consistent to a previous report that the serum creatinine concentration was twice as high as in the sham operated rats 10 months after uninephrectomy (16). Studies of physiological maturation of the kidney demonstrated that senile loss of rats' glomeruli begins first after 350 days of age (33). Therefore, reduced renal function found in this study can only be attributed to the nephrectomy itself. Furthermore, that is

confirmed by the absence of any changes in renal function in the control groups of rats with both kidneys. Most of the other authors performed neonatal nephrectomy, unlike in human living donation. Conversely the age of rats in our experiment, at the time of nephrectomy, corresponded to mature age in terms of a finished growth and functional development, which makes this model more similar to the real life human living donation. Our results have confirmed again that an adult kidney tends to grow compensatory despite the fact that differentiated nephrons are relatively quiescent in a mature adult kidney (34).

The main purpose of functional changes occurring in the remaining kidney is maintenance of water and electrolyte homeostasis (35). Changes in renal hemodynamics, such as an increased renal blood flow (36,37) and decreased renal vascular resistance (38) caused by renal cortical vasodilatation (39), play an important role in functional adaptation. Rise in glomerular blood flow allows the increase of the glomerular filtration rate and the filtered load of water and solutes for excretion, and the rise in blood flow to nephron segments increases solute delivery and thereby enhances the excretion of substances derived from tubular secretion (17). The major functional adaptation following unilateral nephrectomy is a dramatic and progressive increase of the mean nephron glomerular filtration rate which is similar to the compensatory changes in renal mass (39,40). Compensatory adaptations in tubules allow a rise in fractional excretion of water and solutes mostly by a decrease in their fractional reabsorption (sodium and water), increase in their secretion (potassium) (41-43) or by accelerated flow of tubular fluid (urea) (43,44).

In this experiment, sodium concentration did not change within 6 months from uninephrectomy, which was expected as the renal function measured by creatinine appoints only a mild dysfunction (cca. 20% enhanced creatinine and 40% decreased glomerular filtration rate). Accordingly, chronic renal failure patients do not present with sodium concentration disturbances until the terminal stage, in some cases not even then. However, previous experiments have shown that the renal sodium and potassium handling was affected earlier in uninephrectomized rats than in the control rats (43). Higher initial serum potassium level found in the

sham operated rats from this study when compared with nephrectomized and naïve rats can only be explained by the blood haemolysis during the sample handling. Haemoglobin concentration was similar in all three groups and did not vary from the preoperative values, indicating that significant erythropoietin loss does not occur by that time.

Consistent to the previous reports, the results of this study have confirmed limitations of the renal functional reserves. It should be taken into consideration that remnant kidney is jeopardized by

at least two processes. First, kidneys are normally ageing. Compensatory events present the second threat to the remnant kidney. Flow increment burdens the kidney by enhancing glomerular pressure, thus leading to glomerular sclerosis. Rat model confirms the need for precaution in considering living kidney donation as a non-dangerous procedure in terms of future donor kidney function.

#### ACKNOWLEDGMENT/DISCLOSURES

Competing interests: none declared.

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## Oštećena bubrežna funkcija u štakora, šest mjeseci nakon jednostrane nefrektomije – stari problem iz suvremene perspektive

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### SAŽETAK

**Cilj** Unatoč rutinskoj primjeni transplatacije bubrega od živih donora, podaci o posljedicama i utjecaju jednostrane nefrektomije na kvalitetu života i zdravlje donora su oskudni. Cilj ovog istraživanja je, na životinjskom modelu, ispitati dugoročne posljedice i funkciju preostalog bubrega nakon jednostrane nefrektomije.

**Metode** 36 ženki štakora soja Sprague-Dawley, u dobi od 4 mjeseca, bili su randomizirano u tri grupe: (a) unilateralno nefrektomirani, (b) lažno operirani i (c) kontrolni štakori. Nefrektomija je učinjena prilikom uključenja u pokus, a krv za analizu uzeta je dva puta (prilikom uključenja i nakon šest mjeseci).

**Rezultati** Nakon šest mjeseci zabilježen je statistički značajan porast razine kreatinina kod unilateralno nefrektomiranih ( $39.7 \pm 0.8 \mu\text{mol/l}$ ), u usporedbi s lažno operiranim ( $30.1 \pm 1.1 \mu\text{mol/l}$ ) i kontrolnim štakorima ( $26.3 \pm 3 \mu\text{mol/l}$ ) ( $p \leq 0.001$ ). Koncentracija natrija bila je nepromijenjena ( $p = 0.116$ ). Hemoglobin u krvi nije se razlikovao između grupa ( $p = 0.115$ ).

**Zaključak** Iako je općepriznata činjenica da bubrežni posjeduje veliki kapacitet za kompenzaciju gubitka bubrežne mase, naši rezultati ukazuju da nakon unilateralne nefrektomije s vremenom može doći do značajnog narušavanja funkcije preostalog bubrega. Srećom, u svakodnevnoj kliničkoj praksi ne susrećemo teže oblike bubrežne disfunkcije kod pacijenata s jednim bubregom. Tendencija produženja životnog vijeka kod ljudi mogla bi nas u budućnosti suočiti s bubrežnom disfunkcijom kod živih donora. Nova istraživanja na ovom životinjskom modelu, uz korištenje visokospecifičnih bubrežnih biomarkera, mogla bi u budućnosti ponuditi nove odgovore.

**Ključne riječi:** unilateralna nefrektomija, bubrežna funkcija, kreatinin