Post nephrectomy renal function: donor nephrectomy vs. radical nephrectomy

Renalna funkcija posle nefrektomije: donorska nefrektomija vs. radikalna nefrektomija

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Abstract

Background/Aim. Monitoring the renal function following donor nephrectomy (DN) or radical nephrectomy (RN) due to kidney tumors is considered essential. The aim of this study was to compare pre-operative and post-operative renal function in patients who underwent DN in relation to patients who underwent RN due to renal malignancy. **Methods.** A retrospective case-control study was performed, which included 199 patients divided into two groups: group 1 (105 patients) were patients who underwent DN due to living-related/unrelated kidney transplantation, while group 2 (94 patients) was a control group, and included patients who underwent RN due to clear cell renal cell carcinoma in the T1bNoM0 clinical stage, where this surgical procedure was the final form of treatment. **Results.** Pre-operative estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease−Epidemiology Collaboration (EPI) equation (eGFR EPI) in the DN group was 94.95 mL/min/1.73 m², while in the RN group, it was 71.00 mL/min/1.73 m². Patients who underwent RN tend-ed to have eGFR EPI below 60 mL/min/1.73 m² after ten years of follow-up compared with patients who underwent DN. In the DN group, the average eGFR EPI was 80.40 mL/min/1.73 m², and in the RN group, it was 56.00 mL/min/1.73 m². A higher incidence of diabetes mellitus (DM) and arterial hypertension (AH) was also observed in the DN group of patients compared to the RN group (AH: 44.3% vs. 21.3%; DM: 22.6% vs. 9.6%, respectively). **Conclusion.** Comparative monitoring of these two groups showed that in both groups, the recovery of the renal reserve was achieved one year after nephrectomy due to the known adaptive mechanisms. Even though the initial renal reserve in a kidney donor is reduced after living kidney transplantation (nephrectomy, permanent loss of renal mass), kidney donors recover kidney function within the first year after surgery due to the adaptive mechanisms.

Key words:
glomerular filtration rate; kidney neoplasms; kidney transplantation; nephrectomy; tissue donors; treatment outcome.

Apstrakt

Uvod/Cilj. Posle donorske nefrektomije (DN) ili radikalne nefrektomije (RN) zbog tumora bubrega, praćenje bubrežne funkcije je od suštinskog značaja. Cilj rada bio je da se uporedi preoperativna i postoperativna bubrežna funkcija posle DN, u odnosu na bolesnike koji su bili podvrgnuti RN zbog maligniteta bubrega. **Metode.** Retrospektivnom studijom slučaj-kontrole obuhvaćeno je 199 ispitanika podeljenih u dve grupe: I grupa (n = 105) bili su ispitanici kojima je urađena DN zbog transplantacije bubrega živog srodnog/nesrodnog donora, dok je II grupa (n = 94) bila kontrolna grupa i obuhvatala je bolesnike kojima je urađena RN zbog svetloćelijskog karcinoma bubrežnih ćelija u kliničkom stadijumu T1bNoM0, gde je ta hirurška procedura bila i konačni vid lečenja. **Rezultati.** Preoperativno, procenjena stopa brzine glomerulske filtracije [*estimated glomerular filtration rate* (eGFR) prema jednačini *Chronic Kidney Disease−Epidemiology Collaboration* (EGFR EPI)] u grupi bolesnika sa DN iznosila je 94,95 mL/min/1,73 m², a kod bolesnika sa RN 71,00 mL/min/1,73 m². Bolesnici koji su bili podvrgnuti RN imali su tendenciju da eGFR EPI nakon deset godina praćenja ostane ispod 60 mL/min/1,73 m², u poređenju sa osobama koje su bile podvrgnute DN. Kod ispitanika I grupe (DN) prosečna eGFR EPI iznosila je 80,40 mL/min/1,73 m², a kod ispitanika II grupe (RN) 56,00 mL/min/1,73 m². Primećena je i veća učestalost pojave dijabetesa melitusa (DM) i arterijske hipertenzije (AH) u grupi posle DN u

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odnosu na grupu posle RN (AH: 44,3% vs. 21,3%; DM: 22,6% vs. 9,6%). **Zaključak.** Uporednim praćenjem obe grupe, može se primetiti da se, poznatim adaptivnim mehanizmima, kod njih ostvaruje oporavak bubrežne rezerve posle prve godine od nefrektomije. Bez obzira na to što se kod transplantacije bubrega živog davaoca kod davaoca bubrega smanjuje inicijalna bubrežna rezerva (zbog nefrektomije, trajnog gubitka renalne mase), davaocima bubrega se, zahvaljujući adaptivnim mehanizmima, funkcija bubrega oporavlja unutar prve godine od hirurške intervencije.

Ključne reči:
glomerulska filtracija; bubreg, neoplazme; transplantacija bubrega; nefrektomija; tkivo, davaoci; lečenje, ishod.

Introduction

Most of the world's leading kidney transplant centers focus their attention on donor/recipient selection, the transplantation process itself, post-operative follow-up of renal transplant patients, and long-term outcomes in recipients [1–6]. The situation is similar in Serbia [7]. However, in recent years, special attention has been given to living kidney donors due to long-term follow-up of these patients after nephrectomy and because, when compared with the general population, they have an increased occurrence rate of some diseases, such as ischemic heart disease [8, 9].

Donor selection and monitoring are not of crucial importance only as far as the quality of the kidney given to the recipient is concerned. From the medical point of view, it is of the utmost importance that we have not consciously or permanently caused impaired health of the donor, *primum non nocere*. Initially, donor nephrectomy (DN) inevitably leads to a decrease in renal function, manifested by increased proteinuria and blood pressure [9, 10]. Since kidney donors are "medically chosen" healthy individuals, and a reduction in the total reserve of kidney function occurs after the planned DN, the question arises of whether we are making patients out of healthy individuals this way. Making a good choice about whether one is an optimal kidney donor is a very important fact for the donor's long-term health. According to the studies published so far, renal function following DN expressed as glomerular filtration rate (GFR), decreases annually on average by -0.42 mL/min/1.73 m^2 [11–14]. Following DN, there is an immediate decrease in renal mass by 50% and in the estimated (eGFR) as well, which later reaches approximately 70% of the pre-donation value [11–13].

The aim of this study was to compare pre-operative and post-operative renal function in patients who underwent DN in relation to patients who underwent radical nephrectomy (RN) due to renal malignancy.

Methods

We conducted a retrospective observational, analytical, case-control study, which included 200 patients treated and followed up for ten years (2010–2020) at the Clinic for Nephrology and the Clinic for Urology of the Military Medical Academy in Belgrade, Serbia. The patients were divided into two groups: group 1 (105 patients) were patients who underwent DN due to related living-donor kidney transplantation, while group 2 (94 patients) was a control group and included patients who underwent RN due to clear cell renal cell carcinoma (ccRCC) in the T1bNoM0 clinical stage [tumor (T), node (N), metastasis (M) staging system], where this surgical procedure was the final form of treatment and, thereafter, patients were considered cured. The control RN group of patients was chosen with the assumption that it was their first malignancy, that their comorbidities included mild to moderate hypertension, and that those were the patients who suddenly, in a very similar way, diminished their kidney function after nephrectomy as well as donors. After the nephrectomy, patients were followed up for at least ten years.

As far as donors are concerned, these healthy people underwent the recommended medical screening before the intervention, i.e., the evaluating laboratory diagnostic tests, in order to exclude the patients with comorbidities that could significantly disrupt the renal functional reserve (diabetes mellitus, malignant hypertension, the existence of untreated malignancy, obesity, etc.). Thus, it could be stated that these were "medically chosen" individuals who, with their consent and the consent of the Ethics Committee of the Military Medical Academy, Belgrade (04/2019, from May 13, 2019), wanted to help their loved ones with organ donation.

In study participants, the GFR was used to monitor the remaining renal function, which is directly proportional to the reserve of the basic morphological and functional unit of the kidney, i.e., the nephron. Serum creatinine-based estimation equations [eGFR, Chronic Kidney Disease−Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) Study] were used to estimate the GFR, which is also a recommendation based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [13–15]. This way, patients' renal function was assessed using the data obtained from their pre-operative and post-operative laboratory parameters (urea, creatinine, urine).

The statistical analysis was conducted using the IBM SPSS Statistics 26.0 computer program. All continuous variables were described as the median [interquartile range (IQR) between 25th and 75th percentile] or mean ± standard deviation, according to the data distribution (Shapiro-Wilk test). The categorical variables were expressed as percentages and examined using the χ^2 test. Comparisons of nonparametric variables between two groups were performed by the Mann-Whitney U test. All analyses were evaluated at the level of statistical significance of $p < 0.05$. The research was approved by the Ethics Committee of Military Medical Academy, Belgrade, Serbia (date of approval May 13, 2019). All patients signed the informed consent.

Results

In the DN group, there were 38.1% males and 61.9% females (Table 1). In the RN group, there were 67% males and 33% females; statistically, there was a significant difference between these groups in terms of gender representation ($p < 0.001$). The average age was statistically significantly higher in the DN group, 55.6 years, than in the RN group of patients, 46.9 years (Table 1).

The median serum creatinine (Table 2), before surgery, was statistically significantly lower in the DN group (69 umol/L) compared with the RN group (92 umol/L) ($p < 0.001$). After a 10-year follow-up, there was a deterioration in serum creatinine in both groups. In the group 1, the median value of serum creatinine was 76.5 umol/L, while in the group 2, it was 115 umol/L. Compared to the increase in serum creatinine, the increase was around 10.8% in the group 1, in contrast to the group 2, where the increase was around 25%.

Compared to the pre-operative GFR value (Tables 3 and 4), it was statistically significantly higher, 94.9 mL/min/1.73 m^2 ("lower" renal functional reserve), in the DN group than in the RN group of patients, 71 mL/min/1.73 m^2 ($p < 0.001$). After ten years of follow-up, in the RN group, we observed that regardless of the formula used to calculate eGFR, it did not exceed 60 mL/min/1.73 m^2. Moreover, following our two groups of patients, we noticed an interesting fact – in the DN group, after 10 years of follow-up, there was a higher prevalence of hypertension (44.3% in the group 1 and 21.3% in the group 2, $p < 0.001$) and diabetes (22.6 % in the group 1, and 9.6% in the group 2, $p = 0.022$), compared to the RN group of patients (Table 5).

Table 1

Baseline characteristics of the patients who underwent nephrectomy

Variable	Group 1	Group 2	*p*-value
Number of patients	105	94	
Gender (male/female)	40 (38.1) / 65 (61.9)	63 (67.0) / 31 (33.0)	< 0.001*
Age at the time of intervention (years)	55.63 ± 7.35	46.93 ± 12.99	< 0.001**
Follow-up period (years)	11.47 ± 5.17	11.05 ± 2.01	0.419**

Values presented as numbers (percentages) or mean ± standard deviation.
*χ^2; **Independent Samples Test.
Group 1 included patients who underwent donor nephrectomy; Group 2 (control group) included patients who underwent radical nephrectomy due to clear cell renal carcinoma in the T1bNoMo clinical stage (TNM – tumor, node, metastasis staging system).

Table 2

Serum creatinine (sCR) in the patients who underwent nephrectomy

Time of sCR determination	Group 1	Group 2	*p*-value*
Before surgery	69.00 (59.00–78.00)	92.00 (76.50–112.00)	< 0.001
6 months after surgery	78.50 (66.00–89.25)	120.00 (101.50–134.25)	< 0.001
1 year after surgery	72.00 (64.25–88.00)	99.00 (89.00–113.75)	< 0.001
5 years after surgery	72.00 (65.50–89.00)	101.25 (90.00–118.25)	< 0.001
10 years after surgery	76.50 (70.00–86.00)	115.00 (98.00–117.00)	< 0.001

*Mann-Whitney test; values presented as median with interquartile range (25–75th percentile).
Group 1 included patients who underwent donor nephrectomy; Group 2 (control group) included patients who underwent radical nephrectomy due to clear cell renal carcinoma in the T1bNoMo clinical stage (TNM – tumor, node, metastasis staging system).

Table 3

eGFR EPI in the patients who underwent nephrectomy

Time of eGFR EPI determination	Group 1	Group 2	*p*-value*
Before surgery	94.95 (83.12–102.82)	71.00 (59.00–91.75)	< 0.001
6 months after surgery	81.70 (66.35–95.22)	54.00 (47.00–63.75)	< 0.001
1 year after surgery	86.60 (69.22–97.20)	66.00 (58.00–74.00)	< 0.001
5 years after surgery	83.35 (69.00–91.97)	61.50 (53.42–69.00)	< 0.001
10 years after surgery	80.40 (63.60–86.40)	56.00 (48.50–60.00)	< 0.001

Values presented as median with interquartile range (25–75th percentile).
*Mann-Whitney test.
eGFR EPI – estimated glomerular filtration rate according to the Chronic Kidney Disease−Epidemiology Collaboration (EPI) equation; Group 1 included patients who underwent donor nephrectomy; Group 2 (control group) included patients who underwent radical nephrectomy due to clear cell renal carcinoma in the T1bNoMo clinical stage (TNM – tumor, node, metastasis staging system).

Table 4

eGFR MDRD in the patients who underwent nephrectomy

Time of eGFR MDRD determination	Group 1	Group 2	*p*-value*
Before surgery	95.10 (79.02–105.65)	68.00 (59.00–91.00)	< 0.001
6 months after surgery	79.35 (65.10–93.25)	54.00 (47.00–63.00)	< 0.001
1 year after surgery	83.40 (67.75–96.30)	66.00 (58.00–74.00)	< 0.001
5 years after surgery	80.20 (67.10–89.50)	60.50 (53.25–69.00)	< 0.001
10 years after surgery	81.00 (63.08–84.05)	57.00 (49.50–61.00)	< 0.001

Values presented as median with interquartile range (25–75th percentile).
*Mann-Whitney test.
eGFR MDRD – estimated glomerular filtration rate according to the Modification of Diet in Renal Disease (MDRD) Study equation; Group 1 included patients who underwent donor nephrectomy; Group 2 (control group) included patients who underwent radical nephrectomy due to clear cell renal carcinoma in the T1bNoMo clinical stage (TNM – tumor, node, metastasis staging system).

Table 5

The incidence of arterial hypertension (AH) and diabetes mellitus (DM) in the patients who underwent nephrectomy, 10 years after surgery

Parameter	Group 1	Group 2	*p*-value*
AH	47 (44.3)	20 (21.3)	0.001
DM	24 (22.6)	9 (9.6)	0.022

Values presented as numbers (percentages).
*χ^2-test.
Group 1 included patients who underwent donor nephrectomy; Group 2 (control group) included patients who underwent radical nephrectomy due to clear cell renal carcinoma in the T1bNoMo clinical stage (TNM – tumor, node, metastasis staging system).

Discussion

The decrease in renal mass was accompanied by a consequent decrease in renal function, regardless of the reason that led to it; however, there were differences in the extent of renal reserve recovery. Inevitably, after unilateral nephrectomy in both groups, there was a loss of 50% of renal mass. The loss of renal mass occurs abruptly, immediately after the surgical intervention, i.e., renal mass and function fall to approximately half the pre-nephrectomy value. After a very short time, the remaining contralateral kidney begins to compensate for the loss of renal function through the so-called adaptive mechanisms [1, 11, 12, 15, 16].

It would be ideal to do a study with completely identical groups by age, gender, and previous diseases. Since the aim of our study was to assess renal function after nephrectomy, donor, or after radical due to RCC, we took two groups that share nephrectomy. In our study, the first group was comprised of healthy people in whom we performed a DN after assessing the total renal reserve in order to help a relative/non-relative (husband/wife); the second group of respondents were patients who underwent nephrectomy for medical reasons; acquired kidney failure is common in both groups. This decrease in GFR is directly dependent on the associated factors such as patient age, gender, pre-operative GFR, pre-operative presence of hypertension, hyperlipidemia, and diabetes [17, 18]. Certain adaptive mechanisms depend on pre-operative factors, which relate to the patients in both groups and certainly affect the degree of post-operative GFR recovery [19, 20]. Along with the decrease in the number of func-

tional nephrons, the remaining nephrons hypertrophy in order to try to maintain the homeostasis of fluids and electrolytes in the body. Over time, recurrent and afterward chronic hyperfiltration, which is the result of a partial increase in glomerular pressure, leads to renal damage and/or accelerated exacerbation of the existing renal damage [21–24]. These short-term and long-term structural and functional adaptations of residual renal tissue must be taken into consideration when predicting the possibility of recovery and the final outcome in a patient with a single kidney.

In a study of renal function following a traumatic kidney loss, it has been reported that the remaining kidney recovered up to 70% of the initial GFR strength due to the adaptive mechanisms. It should be pointed out that any loss of nephrons, regardless of the reason, poses a risk of end-stage renal disease. For this reason, the patients who underwent RN due to a kidney tumor or DN are at risk of renal failure – chronic kidney disease (CKD). It is known that the surgical treatment of renal tumors increases the rate of CKD and that the chosen surgical method (classical or laparoscopic surgery) has a direct impact on post-operative renal function [14, 25–28]. RN has to be done regardless of the status of the contralateral kidney, but DN is not acceptable in case of the ill-functioning contralateral kidney (better kidney remains to the donor). DN is performed if the renal reserve is preserved, and a kidney with a smaller renal reserve is always taken.

Fehrman-Ekholm et al. [29] published a follow-up study concerning DN in 2001, which followed a total of 403 donors. In this study, it was stated that three donors developed stage 4 chronic renal failure, while one donor ended up with

stage 5 renal failure that required an active hemodialysis treatment. During the 12-year follow-up period, the mean GFR was 72 mL/min/1.73 m^2. It turned out that the prevalence of hypertension in these patients was not different from the same prevalence in the general population. In another study, Ellison et al. [30] showed that the frequency of the need for dialysis after DN was only 0.04%.

A study published in 2015 by Gazel et al. [31] followed a total of 200 patients, out of whom 70 patients underwent DN, and 130 patients underwent RN due to kidney tumors. After dividing the patients into groups with GFR below 60 mL/min/1.73 m^2 and those with GFR above 60 mL/min/1.73 m^2, they noticed that the GFR values of patients who underwent RN had a significantly stronger tendency to remain less than 60 mL/min/1.73m^2, compared to those patients who underwent DN ($p < 0.001$). Moreover, at the end of the follow-up period, approximately 20 months later, the decrease in GFR was 33.70% in the RN group and 34.29% in the DN group, and this difference was not statistically significant ($p = 0.783$).

Due to the adaptive hyperfiltration, the residual kidney after unilateral nephrectomy has a relatively rapid recovery within 6–12 months after nephrectomy [32–34]. It has been shown that the effective kidney flow increases by about 30% after only seven days after surgery and remains elevated for a longer period of time (> 10 years) [1–4]. It has also been found that after surgery, the residual mass and function have a remarkable ability to compensate for the loss [22–24]. In the published papers concerning healthy kidney donors, compared with the general population or appropriate controls, no differences were found in urinary albumin excretion, GFR, hypertension prevalence, quality of life, survival rate, and the risk of end-stage renal disease occurrence during a long-term follow-up [11, 12, 15].

If the value of serum creatinine was the only analyzed parameter in our patients after 10 years, in the group 1, we could observe an increase in serum creatinine by about 10.8% in contrast to the group 2, where the average increase in serum creatinine was 25%, which was directly related to the reduced functional reserve (in the group 1, GFR was higher than 80 mL/min/1.73 m^2, while in the group 2, GFR maximum was 60 mL/min/1.73 m^2). In two studies, the reduction in GFR following DN was 20–25% [20, 21]. In the aforementioned study published in 2015 by Gazel et al. [31], this reduction was 34.29%.

Regardless of the used formula, when comparing GFR after one year and after ten years after surgical treatment, it can be concluded that definitive recovery by the so-called adaptive mechanisms occurs within that first year and is practically maintained during the follow-up period of 10 years for both groups. The values of GFR EPI postoperatively after the first year were as follows: in the group 1, 86.60 mL/min/1.73 m^2 (69.22–97.20 mL/min/1.73 m^2) and in the group 2, 66.00 mL/min/1.73m^2 (58.00–74.00 mL/min/1.73 m^2), while the values of eGFR EPI after 10 years were as follows: in the group 1, 80.40 mL/min/1.73 m^2 (63.60–86.40 mL/min/1.73 m^2) and in the group 2, 56.00 mL/min/1.73m^2 (48.50–60.00 mL/min/1.73 m^2). The GFR

recovery was better achieved in the group 1. That raises the question of whether the existence of malignancy, even if localized, affected the existing adaptive mechanisms.

In the group 1, after 10 years of follow-up, hypertension was present in 47 patients (44.3%), and in the group 2, in 20 patients (21.3%), which represents a statistically significant difference ($p = 0.001$). The difference in the numbers could be partially explained by the fact that mild and moderate hypertension was not a contraindication for donation in the group 1. Thus, in elderly patients and those who already suffered from mild to moderate hypertension, their condition only worsened in relation to the pre-operative one. On the other hand, the group 2 mainly consisted of younger people and males, so hypertension was not expected. After 10 years, in the group 1, diabetes was present in 24 patients (22.6%), and in the group 2, in 9 patients (9.6%), which is a statistically significant difference ($p = 0.022$).

In the group 1, even though these were carefully selected patients, it turned out that although statistically older, they had a better GFR than those in the group 2. The group 2 consisted of statistically younger patients diagnosed with RCC, predominantly males, without prior selection and exclusion of those with poorly regulated hypertension, diabetes, long-term history of smoking, and extreme obesity [35].

Limitations of the study

The limitations of this study are the retrospective follow-up model, as well as age and gender differences between investigated groups.

Conclusion

In the study group of healthy patients, one year after the intervention, the expected recovery of renal function was achieved after DN thanks to adaptive mechanisms, and a similar renal reserve was maintained after ten years of follow-up.

Comparing the group after DN with the group after nephrectomy due to RCC, we see that after ten years of follow-up, renal function was preserved in the first group after DN, unlike in the group after RN.

It can be concluded that our group of kidney donors was a carefully medically selected group of patients in whom, during the retrospective 10-year follow-up period, it was shown that the renal reserve did not worsen. That certainly confirms that a careful medical selection of "healthy" donors is conducted in our country. Thus, the principle of *primum non nocere* has been preserved.

A long-term evaluation of healthy kidney donors indicates that there is a decrease in creatinine clearance by about 30% (GFR) after 6–12 months post-DN, with a negligible risk of developing end-stage renal disease after kidney donation.

In subjects after DN after 10 years, there were more of those who had *de novo* diabetes compared to patients after RN due to RCC. The aforementioned could be explained by the fact that in the group 2, the patients were younger, while in group 1, older, marginal donors and patients with predia-

betes were accepted. The greater presence of diabetes in the group 1 after ten years after nephrectomy certainly accounted for obesity. It could be said that the donors "relaxed" after having fulfilled a great emotional goal by donating a kidney to their loved ones.

The patients who underwent RN in our hospital were younger males with a higher value of serum creatinine and, consequently, a lower volume of GFR pre-operatively. The inclusion of patients in the RN group is a forced choice, *per se*. In this group of patients, apart from monitoring the possible occurrence or recurrence of malignant disease, the risk factors that can accelerate CKD and other chronic diseases can be carefully reduced or treated through regular examinations.

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