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Factors that Influence Graft Function at 1-Year Posttransplantation and Correlation with Baseline Donated Kidney Function Measured with Radioisotopes

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Abstract

Introduction. Assessment of renal function is a crucial component of donor evaluation. The higher measured donor GFR is independently associated with a better allograft outcomes in living donor kidney transplantation (LDKT). Monitoring graft function and estimation of GFR is a recommended method for patients' follow-up in posttransplantation period. The aim of our study was to investigate the correlation of directly measured GFR of donated kidney with estimated GFR through creatinine-based formulas and to detect impact factors on the graft function at 12 months posttransplantation.

Methods. Fifty LDKT patients (related and non-related donors) with stable renal function in a period of 12 months after transplantation were included in our study. The mean recipient age was 30.7±9.6 years, and donor age 55.45±9.41 years. The mean directly measured donated kidney GFR was 47.61±5.72 ml/min. Graft function was estimated at 3, 6 and 12 months by 3 formulas: Cockcroft-Gault (C-G), MDRD 6 variables and Nankivell. Direct correlation of estimated with measured radiolabeled ^{99m}Tc DTPA GFR was performed. Various impact factors such as donor age, dialysis vintage and different calcineurin inhibitors as a part of immunosupression were evaluated.

Results. Estimated GFR at 12 months with MDRD, Cockroft Gault, and Nankivell formulas was 72.65±22.6, 94.25±36.42, and 81.78±17.89 ml/min, respectively. The highest estimated GFR was obtained with C-G formula at all three time points. The estimated allograft GFR did not correlate with directly measured GFR of donated kidney. Donor age well correlated with the graft function at 12 months. Allografts from standard criteria donors-SCD (<60 years) had better function than allografts form expanded criteria donors-ECD (>60 years). The highest GFR was estimated with C-G equation (106.08±39.26 ml/min), while GFR estimated with Nankivell was 86.86±15.30 ml/min, and with MDRD 79.67±20.28 ml/min, presenting patients in stage 2 of chronic kidney disease. Duration of hemodialysis treatment under 24 months showed better graft function estimated by C-G at 12 months (102.23±38.86 ml/min), compared to that above 24 months of HD (77.84±18.11 ml/min). Different type of calcineurin inhibitors did not influence on the graft function at any time point.

Conclusion. Creatinine-based formulas for estimation of the graft function did not correlate with directly measured function of the donated kidney with radiolabeled isotopes, nor between each other. Hence, the monitoring of the graft function should be done by a single formula in the posttransplantation period. Expectedly, a better graft function was observed in young donors (standard criteria) and in patients with shorter hemodialysis treatment.

Keywords: glomerular filtration rate, creatinine-based formulas, kidney transplantation

Introduction

Living donor kidney transplantation (LDKT) or cadaver transplantation is superior compared to keeping the patient on a dialysis treatment, and it represents a modality of choice for treatment of an end-stage kidney disease [1,2]. Superiority of a living donor transplantation compared to that from a deceased donor is visible though the shorter time of cold ischemia of the graft, better HLA matching, choice of a quality kidney and electivity during the surgery itself. At the same time, performing transplantation at the right time, that is to say the preemptive transplantation or shorter dialysis treatment is a precondition for long-term survival of both, the graft and the recipient. The patients who are kidney transplant

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candidates are well informed and aware of these advantages, and at the same time they represent a motive for kidney donation among closer and distant family members and spouses. Living donor transplantation is accompanied with very low short-term or long-term risk for the kidney donors themselves [3].

The assessment of the kidney function is the basic component when evaluating the potential kidney donors. Glomerular filtration rate (GFR) assessed through inulin clearance still remains to be the gold standard in the assessment of kidney function. At the same time, the other exogenous markers for direct measurement of GFR as the radiolabeled isotopes (^{99m}Tc DTPA or ^{125}I Iodthalamate) and non radioactive contrast agents (Iodthalamate or Iohexol) are considered to be the gold standard in the direct determination of GFR [4,5].

Transplantologists have dedicated much of their time and have made efforts to improve the renal transplant function. A lot of therapeutic interventions were developped in the last decades in order to improve or at least to preserve the graft function expressed through GFR [6]. The primary or secondary aim of many clinical studies, which include renal transplant patients, is the function of the graft [7]. The observations were conducted in terms of association between the levels of the graft function assessed with the serum concentration of creatinine or, the estimated GFR based on the serum creatinine formulas, and the survival of the graft [8].

The paradigm: The Higher GFR, the longer graft survival, remains to be a motto in the field of transplantation, especially in finding out new less nephrotoxic medications. Indeed, the process of survival of the transplantted kidney itself and the better function of the graft leads to longer survival of the kidney recipient [9,10].

The renal transplant patients by default are prone to develop chronic kidney disease (CKD) and related complications caused by the condition itself.

The recommendations of KDIGO (Kidney Disease: Improving Global Outcomes) include usage of mathematicall formulas based on creatinine, which are intended for routine clinical practice in the care of renal transplants patients [11].

The reduced graft function at a certain point of transplantation, especially after the first year is associated with a faster loss of graft as well as with a higher mortality of the renal transplant recipients [12].

The aim of our study was to compare the graft function through formulas based on creatinine as an estimated GFR with the basic function of the donated kidney determined with radioisotopes at 3, 6 and 12 months after transplantation. In addition, to determine the factors which directly influence on the improvement/worsening of the graft function during 12 months after transplantation.

Material and methods

Patients

A total number of 55 adult patients with LDKT from our transplant centre were included in the study. The transplantation was performed during the period from 2011 to 2014. The inclusion criteria were: first transplantation of one organ-kidney, use of living donor related or not related, emotionally related (spouses) donor; graft with a stable function during a 12-month-period after transplantation.

Methods

The data which are related to donor-sex, age of the donor, type of donation (related or not related donor).

Data which refer to the patient: sex, age, length of hemodialysis treatment prior to transplantation, basic disease, type of immunosuppressive therapy.

Clinical and biochemical variables, serum creatinine, serum urea, protein status, proteinuria 24 hours, body weight and height were analyzed at 3, 6 and 12 months after transplantation.

According to the immunosuppressive protocol, patients were divided into two groups-either on calcineurin inhibitor Cyclosporine or Tacrolimus.

The estimated GFR was calculated with three formulas.

1. **Cockcroft–Gault formula:**
$$[(140\text{-age}_{(\text{years})})\text{xweight}_{(\text{kg})}/(0.814\text{serum creatinine}_{(\mu\text{mol/l})}] \text{ (x0.85, for females).}$$

2. **Nankivell equation:**
$$6.7/(\text{serum creatinine}_{(\text{mmol/l})}+0.25\text{xweight}_{(\text{kg})}\text{-0.5 x urea(mmo/L)-100/height}_{(\text{m})}^{2}+35\text{(25 for females)}$$

3. **MDRD study equation:**
$$170\times(\text{serum creatinine}_{(\text{mg/dl})})^{-0.999}\times(\text{age}_{(\text{years})})^{-0.176} \times (0.762 \text{ if patient is female})\times(1.18 \text{ if patient is black})\times(\text{serum urea nitrogen concentration}_{(\text{mg/dl})})^{-0.170}\times(\text{serum albumin concentration}_{(\text{g/dl})})^{0.318}.$$

Statistical analysis was conducted by pair analysis and comparison of repetitive measurements with ANOVA. Further stratification of patients was conducted according to the improvement or worsening/stabilizing of the graft function and determination of the factors which influence them, with the multiple logistic regression analysis. P level <0.05 was considered significant.

Results

Characteristics of donors and recipients are listed in Table 1.

Table 1. Characteristics of donors and recipients

Age of recipient (years)	30.7±9.6
Age of donor (years)	55.48±9.41
Hemodialysis experience (months)	27.8±22.8
Creatinine (μcmol/L)	
3 months	116.9±58.9
6 months	114.1±57.4
12 months	109.5±41.7
Urea (mmo/l)	
3 months	6.9±2.6
6 months	6.9±2.5
12 months	6.9±1.9
Albumen (g/L)	
3 months	44±0,34
6 months	45±0.4
12 months	45±0.30
Scan of a donated kidney (^{99m}TcDTPA)	47.61±5,72

The mean age of the donors was 55.48±9.41. Out of these, 40 (78.4%) were related, and 11 (21.5%) donors were non-related, but emotionally related. From the performed radioisotope ^{99m} Tc DTPA kidney scans, the separated GFR of the donated kidney was analyzed. Prior to transplantation the mean value of the directly assessed GFR of donated kidney was 47.61±5.72 ml/min.

Characteristics of the recipients

The mean age of the recipients was 30.7± 9.6 years.
Forty-five (45) patients were included in a chronic hemodialysis program prior to actual transplantation and only one patient underwent peritoneal dialysis as a modality treatment of terminal kidney failure. A preemptive transplantation was conducted in five patients.
The average duration of hemodialysis treatment was 27.8±22.8 months. The average duration of peritoneal dialysis treatment was 24 months.
Based on the underlying disease patients were divided into four basic groups: chronic glomerulonephritis, polycystic kidney disease, diabetic nephropathy and non-differentiated CKD.

Biochemical variables

The mean value of s. creatinine at 3 months after transplantation was 116.9±58.9, at 6 months 114.1±57.4 and at 12 months 109.5±41.7 μcmol/L. The mean value of s. urea at three months was 6.9±2.6, at 6 months 6.8±2.5, and at 12 months 6.9±1.9 mmo/L.

Assessment of GFR with mathematical formulas (Cockcroft-Gault, MDRD 6 variables, Nankivell)

The monitoring of the GFR in graft recipients in the posttransplantation period was conducted with the three formulas at 3, 6 and 12 months after transplantation.
The results obtained with these estimated GFR values with the 3 formulas are given in Table 2.

Table 2. GFR at 3, 6 and 12 months

GFR (formulas)	ml/min
MDRD (6 variable)	71.26±23.75
3 months	71.26±23.75
6 months	73.87±24.74
12 months	72.65±22.6
Cockcroft-Gault (C-G)	
3 months	91.10±34.22
6 months	92.78±41.35
12 months	94.25±36.42
Nankivell	
3 months	80.04±18.39
6 months	80.44±19.91
12 months	81.78±17.89

The mean value of the calculated GFR with Cockroft - Gault at 3 months was 91.10±34.22 ml/min. At 6 months after transplantation, it was 92.78±41.35, and at 12 months 94.25± 36.42 ml/min.
The mean value of the calculated GFR with MDRD formula at 3 months after transplantation was 71.27±23.75 ml/min. At 6 months after transplantation it was 73.87±24.74, and at 12 months after transplantation 72.65±22.6 ml/min.
The mean value of the calculated GFR with Nankivell formula 3 months after transplantation was 80.04±18.39, and 6 months after transplantation 80.44±19.91 ml/min. At 12 months the mean value of GFR was 81.78±17.89 ml/min.
The results obtained showed that the largest number of patients at 12 months after transplantation were in the stage 2 of kidney failure.
The correlation of the directly assessed GFR of the donated kidney prior to transplantation with the estimated GFR with the three formulas at the three time points after transplantation is presented in Table 3.

Table 3. Correlation between the estimated GFR by formulas with the baseline GFR of the donated kidney

	Spearman	**p-level**
MRDR 3m& GFR graft	-0.005	0.973
MDRD 6m& GFR graft	-0.006	0.967
MDRD 12m& GFR graft	-0.060	0.705
C-G 3m& GFR graft	-0.042	0.781
C-G6m& GFR graft	0.108	0.484
C-G12m& GFR graft	0.006	0.964
Nankivell 3m	-0.036	0.811
Nankivell 6m	0.137	0.372
Nankivell 12 m	-0.043	0.778

Furthermore, we analyzed factors which may have had a direct influence on the function of the transplanted kidney.
According to the age of the donors, the patients were divided into two groups: donors with standard criteria - SCD (up to 60 years of age) and donors over the age of 60 (expanded criteria donors - ECD).
Of the total number of donors, 30 (58.8%) were under the age of 60, and 21 (41.1%) were over 60 years old.
In addition, the graft function was compared according to the age of the donors (<60 vs. >60 years or SCD vs. ECD).

Table 4. Comparison of estimated GFR with the age of donors

	Donor (≤60 years old) Mean ± SD	Donor (≥60 years old) Mean ± SD	p
MRDR 3m	75.03 ± 22.76	65.73 ± 17.58	0.188
MDRD 6m	79.91 ± 24.23	65.28± 17.08	0.058
MDRD 12m	**79.67 ± 20.28**	**60.72± 15.61**	**0.005**
C-G 3m	100.01± 37.53	80.38 ± 18.79	0.057
C-G 6m	103.23 ± 46.71	79.64 ± 18.86	0.068
C-G12m	**106.08 ±39.26**	**78.95 ± 18.87**	**0.012**
Nankivell3m	82.88 ±16.38	78.73 ± 14.98	0.406
Nankivell6m	84.62 ±16.73	77.34 ± 14.92	0.164
Nankivell12m	**86.86 ±15.30**	**76.76 ± 15.07**	**0.038**

Statistically significant difference was obtained for the estimated GFR with MDRD formula at 12 months in the group of allografts from ECD (older than 60), which was lower (60.72±15.61 ml/min), compared to the group of allografts from SCD (younger than 60) and it was 79.67±20.28 ml/min (p= 0.005) (Figure 1). Furthermore, statistically significant differences were found for the estimated GFR with C-G formula in patients from SCD 106±08 ml/min versus those from ECD 78.95±18.87 ml/min (p=0.012) (Figure 2). The results obtained with the Nankivell formula were 86.86±15.30 ml/min for the SCD group vs. 76.76±15.07 ml/min for the ECD (p=0.38) (Figure 3).

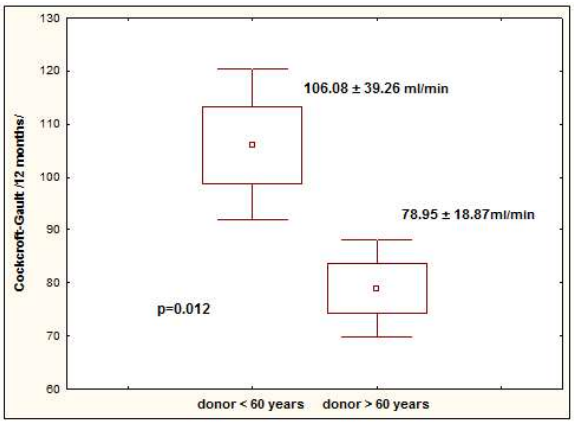

Fig. 2. Cockcroft-Gault at 12 months and donor age

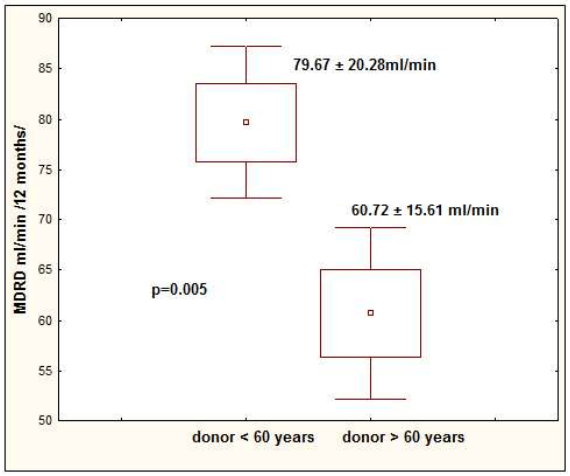

Fig. 1. MDRD at 12 months and donor age

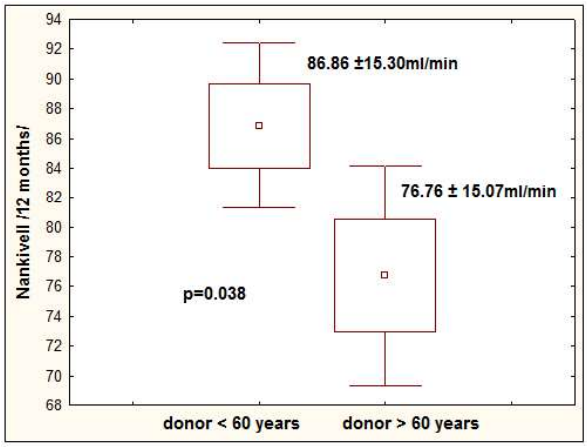

Fig. 3. Nankivell at 12 months and donor age

Table 5. Comparison of the estimated GFR compared to the duration of HD (<24 and >24 months)

	HD less than 24 months ± SD	HD over 24 months ± SD	p
MRDR 3m	75.45±24.58	64.38±15.93	0.159
MDRD 6m	80.46±25.71	64.99±13.23	0.057
MDRD 12m	77.52±23.04	64.77±13.92	0.084
C-G3m	96.89±36.37	78.70±21.09	0.111
C-G6m	100.69±45.82	78.27±19.14	0.110
C-G 12m	**102.23±38.86**	**77.84±18.11**	**0.043**
Nankivell 3m	82.80±16.81	75.61±14.23	0.196
Nankivell 6m	84.44±17.44	75.30±11.91	0.103
Nankivell 12m	**85.80**±16.09	**75.34**±13.59	**0.052**

The influence of the duration of hemodialysis treatment (more and less than 24 months) compared to the graft function estimated with the three formulas at 3 time points is given in Table 5.

A significantly higher estimated GFR was obtained with the C-G formula at 12 months after transplantation in patients undergoing hemodialysis treatment shorter than 24 months (102.23 ml/min±38.86 ml/min; p= 0.043), and it was at the borderline of significance with Nankivell formula at 12 months after transplantation (85.80±16.09 ml/min; p= 0.052).

Table 6. Comparison of the type of calcineurin inhibitor (Cyclosporine/Tacrolimus) compared to the estimated GFR with three formulas

	Cyclosporine	Tacrolimus	P
MRDR 3m	70.57± 23.13	72.03±24.98	0.84
MDRD 6m	71.47±26.92	76.62±22.33	0.50
MDRD 12m	70.21±24.61	75.30±20.41	0.46
C-G3m	93.07±40.45	88.94±26.88	0.68
C-G6m	93.43±52.84	92.09±25.58	0.91
C-G12m	93.90±44.57	94.62±25.82	0.94
Nankivell 3m	78.38±19.00	81.84±17.95	0.52
Nankivell 6m	77.39±20.76	83.63±16.47	0.26
Nankivell 12m	78.80±18.69	85.03±16.79	0.23

The comparison of the estimated GFR with the three formulas related to the two groups of recipients treated with different calcineurin inhibitor (Cyclosporin or Tacrolimus) showed no statistical difference at any time point.

Discussion

Our study evaluated the association of the directly determined GFR of the donated kidney with the estimated GFR of the graft during the first year. Three mathematical formulas based on creatinine were used. These formulas have been extensively used in the clinical practice. According to the consulted studies, these formulas are with the best predictive performances or have been used for the longest period of time [13].

The Cockcroft-Gault (C-G) formula was initially presented in 1976. A study results were based on the 24 hours creatinine excretion/kg (creatinine clearance) in 236 adult patients, mostly men at the age of 18-92. Because most of them were men, a correction was made with the coefficient of 0.85 for women. A small number of studies have presented its application in transplant patients [14].

Nankivell formula is the only one which is derived from the group of transplant patients, as compared to the direct measurement of GFR of plasma clearance of ^{99m}TcDTPA. Thus, it was expected to be the most suitable for application in the transplant patients [15]. Nevertheless, this formula was integrated into methods of many clinical trials long time before the first studies trying to confirm the initial promising data were reported [13].

Levy *et al*. derived another predictive formula from a group of patients comprising 1628 subjects included in Modification of diet with renal diseases (MDRD) study, and derived clearance of ^{125}I Iothalamate. This study presented a new standard in the GFR prediction, and many studies which have been successively conducted confirmed this fact [16].

Our study evaluated the direct correlation of separate GFR of donated kidney with the estimated GFR of the graft with the three formulas. A direct correlation of the given time points was not registered. The superiority of the directly measured GFR with clearance of isotopes compared to the estimated GFR with formulas remains to be a topic for discussion and research. The awareness of the limits while conducting the methods for determining the GFR is important in the clinical application of the measurements and the need to understand their potential limits [17].

Our results demonstrated a slight decrease and stabilization of serum creatinine between the third and the twelfth month. This kind of stabilization of the graft function at 12 months has been confirmed in the literature. This trend is considered to be a result of the stable period between three to six months after transplantation with already determined concentrations of immunosuppressive therapy and lower level of acute rejections [12].

One of the important factors for long-term survival of the transplanted kidney is the quality of the transplanted kidney itself.

The literature data show better survival of kidneys received from living donors compared to kidneys from a cadaver. It may be partially explained with the careful pretransplantation evaluation, non-existing of the preagonal and agonal state which is present in cadaveric transplantations and short time of cold ischemia of the graft [18]. The kidneys received from donors of standard criteria (younger than 60 years) have a better function compared to the kidneys received from donors with extended features [19,20]. In our study the GFR values estimated with the three formulas in the group of allografts received from SCD were higher and statistically significantly different compared to the level of the estimated GFR of the grafts received from ECD (over 60 years of age).The highest estimated GFR was obtained with the C-G formula. These results were somewhat expected having in mind the already known fact that this formula overestimates GFR. The formula itself incorporates the body weight, but it does not express the muscle mass as a determinant for production of creatinine, but there are other factors which change the body weight, such as obesity, presence of edemas, the influence of long-term use of steroid therapy, etc. Although in the formula itself there is a correction related to sex, the creatinine itself is not exclusively filtrated through glomerulus and tubular excretion of creatinine remains to be an important factor [13,21,22].

From the other analyses, reduced estimated GFR was received for the recipients with hemodialysis duration longer than 24 months at 12 months after transplanttation compared to the patients who were with shorter hemodialysis treatment. In our study, there was a statistically significant difference between the two groups using the C-G formula. In the beginning of the 2000s Meier-Kriesche *et al.* showed that longer hemodialysis treatment induces shorter survival of the transplant kidney [23]. Long-term cardiovascular complications in the transplantation period are the second important factor for the graft survival. It is well known that patients with terminal kidney failure are at a higher risk of cardiovascular diseases and patients in chronic program of hemodialysis have 10 to 20 times higher risk of cardiovascular morbidity compared to the general population [24,25].

With reference to the used immunosuppressive therapy, standard protocols included calcineurin inhibitors for our research population. The comparison conducted between the two groups of patients who used Cyclosporine and Tacrolimus respectively in terms of the estimated GFR in the three time periods after transplantation did not show statistical difference. Both medications are in the same immunosuppression group (calcineurin inhibitors-CNI) and have the same immunosuppressive mechanism and both medications express nephrotoxicity. Certain studies show more rapid lowering of GFR in patients treated with Cyclosporine compared to Tacrolimus, in the long-term follow-up of the graft function [26]. Another study, which treated patients with Cyclosporine and Tacrolimus, registered a lower rate of acute rejections proved with biopsy at six months in the Tacrolimus group, but at 12 months there was no statistical difference. On the other hand, two and three year follow-up of patients showed lower rate of graft loss, lower serum creatinine and lower mortality in the Tacrolimus group. At the same time, the long term observation of the group treated with Tacrolimus showed usage of protocols with immunosuppressive monotherapy and less registered cardiovascular events [27,28].

Our study included only kidney transplant recipients from living donors, who were followed for 12 months, with short time of cold ischemia of the graft, good pretransplantation preparation and evaluation and with regards to the posttransplantation protocol with recommended lower levels of serum concentrations of immunosuppressive therapy. These parameters may reduce the nephrotoxicity of the calcineurin inhibitors.

The obtained difference in the GFR value with the different formulas and the decision which of them is most appropriate is a motive for another clinical study.

So far, there have been no comparisons with direct measurement of GFR with isotopes in transplant patients, which would probably confirm the value of the used formulas.

A question has been raised: which of the widely used formulas is a reference method for prediction of GFR in transplant patients. The analyses which have already been conducted pose the question whether it is time to create a new formula. We would like to point out several observations from studies which have been already conducted as also being a limitation of our study.

Most of these formulas are derived from the general population and do not include factors which refer exclusively to the transplant patients, and thus, it may have an impact on their predictive value. For instance, the number of acute rejections, or the cumulative steroid dosage which was received by recipients that could influence on the muscle mass should be probably incorporated in the mathematical formulas. The nephron mass itself transplanted to the recipient has never been taken into consideration in the mathematical formulas, and it directly influences the GFR after transplantation. Hence, the formula which is directly derived from the cohort of the transplant patients includes variables which are relevant only for the recipient. Relevant to the fact that the renal mass is in correlation with the body size itself, maybe it should raise an issue to create a formula which would include the donors' features [13].The studies so far do not give a conclusion which of the formulas would be superior for usage in transplant patients.

Conclusion

Formulas for assessment of the graft function based on creatinine were not in correlation with the assessed function of the donated kidney determined through radioisotopic measurement, nor were they in correlation with each other. Therefore, there is a need of monitoring of the transplanted kidney function through uniquely selected formula. In terms of the factors of influence, the better function of the graft was obtained in those from younger donors (SCD) and in patients with shorter dialysis treatment.

Conflict of interest statement. None declared.

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