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Monitoring of Renal Allograft Function with Different Equations: What are the Differences?

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Abstract

Introduction. Monitoring of graft function by creatinine concentrations in serum and calculated glomerular filtration rate (GFR) is recommended after kidney transplantation. KDIGO recommendations on the treatment of transplant patients advocate usage of one of the existing mathematical equations based on serum creatinine. We compared clinical application of three equations based on serum creatinine in monitoring the function of transplanted kidney.

Methods. A total number of 55 adult patients who received their first renal allograft from living donors at our transplant center in between 2011-2014 were included into the study. Renal allograft GFR was estimated by the Cockroft-Gault, Nankivell and MDRD formula, and correlated with clinical parameters of donors and recipients.

Results. The mean age of recipients was 35.7±9.5 (range 16-58), and the mean age of donors was 55.5±9.0 (34-77) years. Out of this group of 55 transplant patients, 50(90.91%) were on hemodialysis (HD) prior to transplantation. HD treatment was shorter than 24 months in 37(74%) transplant patients. The calculated GFR with MDRD equation showed the highest mean value at 6 and 12 months (68.46±21.5; 68.39±24.6, respectively) and the lowest at 48 months (42.79±12.9). According to the Cockroft&Gault equation GFR was the highest at 12 months (88.91±24.9) and the lowest at 48 months (66.53±18.1 ml/min). The highest mean level (80.53±17.7) of the calculated GFR with the Nankivell equation was obtained at 12 months and the lowest (67.81±16.7 ml/min) at 48 months. The values of Pearson's correlation coefficient between the calculated GFR and the MDRD at 2 years after transplantation according to donor's age of r=-0.3224, correlation between GFR and the Cockfroft & Gault at 6 and 12 months and donor's age (r=-0.2735 and r=-0.2818), and correlation between GFR and the Nankivell at 2 years and donor's age of r=-0.2681, suggested a conclusion that calculated GFR was lower in recipients who had an older donors.

Conclusion. Our analysis showed difference in the calculated GFR with different equations at the same time points. Using one mathematical equation during the total post-transplantation period would be a recommended method in order to eliminate the discrepancy in determining the stage of kidney failure.

Key words: renal transplantation, glomerular filtration rate, estimation, Cockroft-Gault, Nankivell, MDRD, outcome

Introduction

The increased number of patients with chronic kidney disease (CKD) is one of the challenges encountered by nephrologists worldwide. CKD is a global public health problem that affects 5-10% of the population in western countries, with economic implications on health funds. Decrease in glomerular filtration rate (GFR) lower than 60 ml/min has also been emphasized [1,2]. Patients with kidney diseases are at higher risk of death, especially from cardiovascular events as well as at higher risk of progressive exacerbation of the kidney function leading to development of end-stage renal disease (ESRD), frequent hospitalizations and poor quality of life [3]. Treatment modalities of ESRD include dialysis (peritoneal and hemodialysis) and kidney transplantation. Increasing prevalence of ESRD on one hand, and stagnant or declined organ donation on the other hand prolong waiting time for kidney transplantation. Thus, the age of potential transplant recipients and comorbidities of patients as a result of dialysis treatment seem to be increasing over time [4]. Many factors have impact on the function of transplanted kidney. Some of them are modifiable and thus are of particular importance [5].

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Monitoring of graft function by creatinine concentrations in serum and calculated GFR is recommended after transplantation. KDIGO recommendations on the treatment of transplant patients advocate usage of one of the existing mathematical equations based on serum creatinine [6].

We compared clinical application of three equations based on serum creatinine in monitoring the function of transplanted kidney.

Material and methods

A total number of 55 adult patients who received their first renal allograft from the living donor at our transplant center in between 2011 to 2014 were included into the study. Donor data included sex, age of the donor, type of donation (related or unrelated donor), and data that refer to the patient were sex, age, length of hemodialysis (HD) treatment prior to transplantation, primary kidney disease, type of immunosuppressive therapy. Clinical and biochemical variables, serum creatinine, serum urea, protein status, 24 hours proteinuria, body weight and height were analyzed at 3, 6, 12, 24, 36 and 48 months after transplantation.

The estimated GFR was calculated with three equations.

1. Cockcroft–Gault equation

$$[(140\text{-age}_{(years)}) \times \text{weight}_{(kg)}/(0.814\text{serum creatinine}_{(\mu mol/l)}](x0.85, \text{for females}).$$

2. Nankivell equation

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

3. MDRD study equation:

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

Results

The mean age of recipients was 35.7±9.5 (range 16-58), and the mean age of donors was 55.5±9.0 (34-77) years. Out of this group of 55 transplant patients, 50 (90.91%) were on HD prior to transplantation, while pre-emptive transplantation was performed in 5 patients. HD treatment was shorter than 24 months in 37 (74%) transplant patients.

Table 1. Serum creatinine levels

Creatinine		Descriptive Statistics	
µmol/L	N	mean±SD	min - max
3 months	55	116.47±55.6	70-421
6 months	55	114.69±53.9	56-451
12 months	55	109.71±39.7	65-320
24 months	55	124.51±57.3	55-470
36 months	52	124.31±35.3	58-240
48 months	51	137.35±43.4	59-290

Table 1 presents the mean values, minimal and maximal levels of serum creatinine at 3, 6, 12, 24, 36 and 48 months after transplantation; gradual increase in the level was registered by the 48th month.

Table 2. Estimated GFR (glomerular filtration rate) based on three equations, MDRD (Modification of Diet in Renal Diseases), Cockroft-Gault and Nankivell

MDRD		Descriptive Statistics	
	N	mean ± SD	min - max
3 months	55	67.82±23.1	10.86-133.67
6 months	55	68.39±24.6	10.13-164.69
12 months	55	68.46±21.5	14.96-143.08
24 months	55	49.97±14.6	7.5-98.68
36 months	52	47.21±12.7	19.13-92.33
48 months	51	42.79±12.9	18.18-89.61
Cockroft-Gault			
3 months	55	86.41±149.9	17.29-149.96
6 months	55	86.62±24.1	16.14-161.5
12 months	55	88.91±24.9	22.75-145.79
24 months	55	76.23±21.2	14.52-115.0
36 months	52	72.52±18.8	25.27-111.15
48 months	51	66.53±18.1	27.15-104.0
Nankivell			
3 months	55	78.58±18.1	16.36-114.4
6 months	55	78.93±18.5	14.31-128.68
12 months	55	80.53±17.7	22.73-117.67
24 months	55	73.82±18.4	12.2-18.45
36 months	52	72.11±16.1	28.55-124.6
48 months	51	67.81±16.7	23.75-122.9

We used these values for estimation of allograft function by three equations (Table 2).

The calculated GFR with the MDRD equation showed the highest mean value at 6 and 12 months (68.46±21.5; 68.39±24.6, respectively) and the lowest at 48 months (42.79±12.9 ml/min). According to the Cockroft & Gault equation GFR was the highest at 12 months (88.91±24.9) and the lowest at 48 months (66.53±18.1 ml/min). The highest mean level (80.53±17.7) of the calculated GFR with the Nankivell equation was obtained at 12 months and the lowest (67.81±16.7 ml/min) at 48 months.

A negative correlation was registered between GFR calculated with the MDRD and HD treatment during the total follow-up. However, the correlation was statistically significant only at the end of the follow-up, 48 months post-transplantation (R=-0.316; p=0.03). GFR calculated with the Cockroft & Gault and Nankivell equations showed a negative statistically insignificant correlation with HD treatment duration.

The values of Pearson's coefficient on the correlation between the calculated GFR and the MDRD at 2 years after transplantation according to donor's age of r=-0.3224, correlation between GFR and the Cockfroft & Gault at 6 and 12 months and donor's age of r=-0.2735 and r=-0.2818, correlation between GFR and the Nankivell at 2 years and donor's age of r=-0.2681, suggest a conclusion that calculated GFR was lower in recipients who

had older donors.
The results obtained showed that grafts from younger donors had a better function analyzed with the MDRD equation during the total analyzed period after transplantation, but a statistically significant difference was confirmed at 24 months after transplantation (p=0.033). The function of the graft calculated with the Cockroft &Gault equation was better in those obtained from younger donors in all analyzed time points, but a statistically significant difference was confirmed at 6 (p=0.029), at 12(p=0.011), and at 24 months (p=0.028) after transplantation. Higher levels of GFR calculated with the Nankivell equation were registered for the graft from younger donors in the completely analyzed period, but the mean GFR levels between grafts obtained from donors younger than 60 years and grafts from donors aged 60 years and over did not reach statistical significance (Student t-test).
The function of the graft analyzed with the Cockroft-Gault equation was better in the groups with glomerulopathies as a primary disease compared to the group with other kidney diseases, being statistically different at 24, 36 and 48 months after transplantation ($p<0.05$).

Discussion

We have analyzed the function of the graft by using three mathematical equations based on serum creatinine concentration and factors of influence during the first 48 months after transplantation.
KDIGO recommendations for kidney transplant recipients advocate estimation of GFR during post-transplantation follow-up by determination of serum creatinine level. None of the equations demonstrated their superiority. Our study compared GFR calculated with three equations, Cockroft-Gault and Nankivell.
Cockroft-Gault is the oldest equation, most frequently applied in the clinical practice, but insufficiently analyzed for its precision and accuracy in transplant recipients [7]. Nankivell equation was constructed especially for transplant patients [8]. Levy *et al*. constructed a predictive equation from a group of 1628 patients included in the Modification of Diet in Renal Diseases (MDRD). This equation has been incorporated in majority of studies including transplant patients [9].
In our study the highest levels of calculated GFR were obtained with the Cockroft-Gault equation. Conducted studies have shown that this equation overestimate GFR. The unique component that is being changed is serum creatinine, which in the post-transplantation period depends on the improved nutritional status and corticosteroid therapy. The lowest GFR levels were obtained with the MDRD equation, that includes other biochemical variables such as serum albumin, urea, as well as other categorical variables. However, the best results for precision and specificity regarding the directly determined GFR were obtained with the MDRD equation [17].
Regarding the factors of influence, we analyzed the graft function in patients with different HD treatment duration before transplantation. We registered a negative correlation during the total follow-up between GFR calculated with the MDRD equation and HD length of treatment. The level of GFR rate with the MDRD equation decreased with the increase of HD duration. The correlation was statistically significant solely at the end of the follow-up, i.e. at 48 months post-transplantation. Using the other two equations, we also observed a negative correlation but without statistical difference.
Studies have demonstrated negative association between length of HD and post-transplantation outcome regarding survival of the graft and recipients. American Renal Data System shows advantage not only of the preemptive transplantation on graft survival, but the period of HD treatment may be also a risk factor for graft loss and mortality of recipients both for living and deceased donor transplantation [10]. This analysis has revealed that HD treatment for 6-12 months has a 37% long-term impact on graft loss in comparison with preemptive transplantation regardless the duration of the underlying disease (diabetes, glomerular diseases). Another analysis has shown that the length of HD treatment has an impact on the graft loss only in transplant patients from living donors [11]. Studies have supported the acceptance of even marginal donors if the waiting time for transplantation was very long. In the study where kidneys from the same donor were transplanted to recipients with different HD treatment duration, less than 6 months and longer than 24 months, it was shown that the long-term ten-year graft survival was statistically significant by 63% vs. 29% respectively for the mentioned groups [12].
In our study dialysis vintage longer than 24 months resulted in poorer graft function. Complications associated with HD treatment include traditional risk factors such as older age, dyslipidemia, DM, left-ventricular hypertrophy, as well as non-traditional risk factors such as albuminuria, anemia, impaired metabolism of calcium and phosphorus, malnutrition and oxidative stress, that lead to development of cardiovascular diseases. These complications are a result of the poorer function of the transplanted kidney in this group of patients.
Regarding the age of donors as a factor influencing the graft function, our analysis done with the Pearson's coefficient of linear correlation on the association of the calculated GFR with the MDRD equation at 2 years, Cockcroft & Gault equation at 6 and 12 months, and with Nankivell equation at 2 years suggested that the calculated GFR was lower in kidney recipients who had older donors.
The function of the graft analyzed with the three equations regarding the age of the donors showed a higher GFR at all time points in younger donors, with statistical difference when using the MDRD equation at 24

months post-transplantation (p=0.033), with the Cockcroft &Gault equation at 6 months (p=0.029), at 12 months (p=0.011), and at 24 months (p=0.028), and with the Nankivell equation being at borderline at 24 months (p=0.051).

Analyses about the transplantation outcome have shown that the quality of donated kidney has a leading role in the function and long-term survival of the graft. On the other hand, long waiting lists for transplantation, aging of potential kidney recipients and more rapid deterioration of the health condition during hemodialysis stimulate donation of organs from individuals older than 60 years [13]. The number of glomeruli and mean glomerular volume are in negative correlation with age after the sixth decade of life. The number of sclerotic glomeruli after the age of 60 is 30-50% as result of glomerulosclerosis, microvascular lesions and total loss of nephrons. The number of functional nephrons is smaller in grafts from older donors than from younger donors [14,15]. The systematic analysis on the transplantation outcome that included function of the graft and survival of the recipients in the period 1980-2008 showed that kidney recipients from donors older than 60 years had a poorer 5-year outcome regarding graft function and survival of the recipients than those from younger donors [16].

In some countries, as shown in the Norwegian registry, 16% of living donors are older than 60 years, and 7.7% are over the age of 65, whereas in Canada 6% of donors are older than 60 years [18,19]. The American RDS shows no upper age limits regarding acceptance of donors [20].

The results obtained in the recent analysis of United Network for Organ Sharing (UNOS) database from 1994 to 2012 that made comparison of living donors >60 years, living donors <60 years, showed equal graft survival and overall survival in older donors compared to SCD (standard criteria donor), better than ECD (expanded criteria donor), but worse than grafts obtained from younger living donors [21-23]. In comparison with other studies, our study has shown a poorer function of grafts from older donors in the early period post-transplantation, at 6 months and 2 years, with statistical difference during total follow-up of 48 months. However, the function of grafts from older donors is satisfactory and by the end of the analysis supports donation of organs from expanded criteria donors, especially in conditions of insufficiently developed cadaveric transplantation.

Our patients were divided in two groups regarding the graft function and the underlying, baseline disease. The first group included patients with glomerulonephritis and diabetic nephropathy as basic disease, and the second group included patients with obstructive nephropathy, polycystic kidney disease and undifferentiated diseases. Higher GFR levels were registered in the first group with the three used equations at all time points, and the statistical difference was observed with the C&G equation at 24, 36 and 48 months. Glomerular diseases as a cause for development of end-stage kidney disease account for 30-50% of transplant population. These patients are at risk of recurrence of the underlying disease and graft loss. The new immunosuppressive medications influence the rate of acute rejection as well as reduce the chronic allograft nephropathy [24]. The study of Briganti *et al*. comprising a total of 1505 patients with performed biopsy of the native and transplanted kidney demonstrated that recurrent GN as a cause of graft loss is on the third place of all defined causes. The risk of graft loss in the first year was 0.6% and at 10 years 8.4% [25]. Diabetes as the underlying disease can eventually develop recurrence of diabetic nephropathy, but to a different clinical degree. Eighty to hundred percent of patients with DM as an underlying disease develop histological changes within diabetic nephropathy. The time of onset of DN in the graft is 6 years after transplantation. On the other hand, the incidence for development of DN as a cause for graft loss has been insufficiently clinically examined and is considered to be rare [26].

Of note, our results have shown better function of the grafts in patients with diagnosed glomerular diseases and diabetic nephropathy versus those with undifferentiated diseases. This might be a result of the optimal doses of immunosuppressive medications, which consequently lead to a smaller number of episodes of acute rejection and decrease in calcineurin toxicity, in the period of 4 years follow up after transplantation. In order to make comparison with world trends that show poorer functioning of the graft in a long-term follow-up up to 10 years, further analyses are required. Absence of the correct etiological diagnosis pre-transplantation imposes the need of performing kidney biopsies so as to predict the post-transplantation course and to determine the most optimal immunosuppressive therapy.

Conclusion

Our analysis has shown difference in the calculated GFR with different equations at the same time points. Using a single mathematical equation during the total post-transplantation period would be a recommended method in order to eliminate the discrepancy in determining the stage of graft failure.

With regard to the factors of influence, longer HD treatment and expanded criteria donors have a negative impact on the graft function. Matching of adult groups and etiological assessment of the causes of end-stage renal disease aimed at optimization of immunosuppressive therapy are recommended with respect to the transplantation procedure outcome.

Conflict of interest statement. None declared.

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