Determinants of decreased glomerular filtration rate estimated with cystatin C in kidney transplant recipients

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Abstract

Introduction and Objectives. Cystatin C could be used as a reliable alternative marker to creatinine in estimating glomerular filtration rate (GFR), even in kidney transplant recipients. The aim of our study was to evaluate the clinical and biological determinants of glomerular filtration rate estimated with cystatin C (CysC) in kidney transplant recipients, at 3 months after kidney transplantation.

Materials and Methods. We performed a prospective observational study on 44 consecutive kidney transplant patients, followed for 3 months after kidney transplantation. Cystatin C was measured by latex enhanced immunoturbidimetric assay (EuroLyser).

Results. Thirty patients (68.2%) out of 44 had an estimated GFRCysC less than 60 ml/min/1.73m2. Patients with estimated GFRCysC < 60 ml/min/1.73m2 tended to be older (33.4 ± 11 vs 40.6 ± 12 years, p = 0.06), were more frequently males (35.7% vs 80%, p = 0.004) and presented significantly decreased levels of pretransplant total cholesterol (208± 32.7mg/dl vs 175.8 ± 54.6 mg/dl, p= 0.04). By multivariate binary logistic regression, recipient male gender (OR: 5.59; 95% CI: 1.06-29.53; p= 0.04) and pretransplant total cholesterol levels (OR: 0.97; 95% CI: 0.95-0.99; p= 0.02) were independently associated with estimated GFRCysC < 60 ml/min/1.73m2 at 3 months after transplantation and recipient age had a near-significant trend (OR: 1.08; 95% CI: 0.98-1.18; p= 0.07).

Conclusions. In conclusion, we found that recipient male gender and pretransplant total cholesterol levels were independent determinants of glomerular filtration rate estimated with cystatin C in kidney transplant recipients, at 3 months after kidney transplantation

Key-words: serum cystatin C, estimated GFRCysC, recipient gender, body mass index, total cholesterol, kidney transplant.

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Introduction And Objectives

Cystatin C is a 13-KD protein produced at a constant rate in all nucleated cells.[1] It's freely filtered by the kidney, not secreted and also independent of gender and muscle mass.[2] Serum levels of cystatin C could be influenced by obesity, diabetes, smoking and dyslipidemia.[3] Existing data showed that serum cystatin C is a reliable alternative marker to creatinine in estimating glomerular filtration rate (GFR) in patients with chronic kidney disease (CKD), even in kidney transplant recipients.[4],[5],[6] Moreover, it can be used as a marker of acute kidney injury, inflammation and cardiovascular morbidity and mortality.[7],[8] In kidney transplantation, cystatin C is a marker of long term graft outcome and mortality. Also, cystatin C tends to be superior to serum creatinine in evaluating early stages of CKD in kidney recipients, which is critical to early detection of acute rejection[9],[10]

The aim of our study was to evaluate the clinical and biological determinants of glomerular filtration rate estimated with cystatin C in kidney transplant recipients, at 3 months after kidney transplantation.

Materials And Methods

Study population

We performed a prospective observational study on 44 consecutive kidney transplant patients from Fundeni Clinical Institute, Department of Uronephrology and Renal Transplantation, between June 2017 and November 2017. Patients were followed for 3 months after transplantation.

Measurements

Recipient and donor data were collected prior and after transplantation. Graft kidney function was evaluated with cystatin C and was estimated with Cystatin C formula. For cystatin C evaluation, we obtained blood sample tests, which were centrifuged at 5000 rpm for 15 minutes and the serum was analyzed on a latex enhanced immunoturbidimetric assay (EuroLyser). The parameters of interest were classified as demographic, comorbidities, biological, graft and ischemia time characteristics.

Statistical analysis

Categorical variables were reported as percentages, continuous parametric variables as mean ± SD and those continuous non-parametric as median + interquartile range. To identify the determinants, first of all, we divided our study population according to GFR estimated with cystatin C in two subgroups: < and ≥ 60 ml/min/1.73m2. Variable comparison between the two subgroup was made with chi-square test for categorical variables, t student test for continuous normally distributed variables and Mann-Whitney U for those abnormally distributed. Variables with a p value < 0.20 were included in binary logistic regression analysis. To obtain a multivariate model, we used Backward Stepwise selection. Statistical data was analyzed using IBM SPSS Software 20 (Chicago, Illinois). Statistical significance was considered as a p value < 0.05.

Results

General data

In Table 1 are described the features of the study population. Mean age of recipients at the moment of kidney transplantation was 38.3±12.1 years. Twenty-five (65.9%) out of 44 recipients were males. The most frequent primary cause of CKD was glomerulonephritis (47.7%). The primary modality of renal function substitution was hemodialysis (77.3%) and the median pretransplant dialysis time was 10 months (IQR : 3 - 23.3). Mean BMI was 24.8±3.5 and 23 out of 44 (52.3%) had a BMI ≥ 25 kg/m2. Thirty-three (75%) patients were hypertensive, 4.5% had diabetes and 31.8% were current or past smokers. From a biological point of view, pretransplant median values of glucose levels and triglycerides were in normal range. Also we identified normal values of pretransplant total cholesterol and haemoglobin levels. Median estimated glomerular filtration rate evaluated with cystatin C formula was 52 ml/min/1.73m2 (IQR: 31.5-66). The predominant donor type in our group was deceased donor (52.3%). Regarding donor graft details, we found a mean graft weight of 187.7±46.8 grams and a mean graft length of 10.9±0.9 centimeters. Also, we found a cold ischemia time of 375 minutes (IQR: 101.5 – 1000.56) and median hot ischemia time of 30.5 minutes (IQR: 28.2-35).

Table 1. Characteristics of the study population.

Variable	Overall (N=44)
Recipient age (Mean, Years)	38.3 ± 12.1
Recipient gender (%) Female Male	 15 (34.1%) 29 (65.9%)
Residence (%) Urban	 25 (56.8%)
Pretransplant recipient weight (Mean, Kg)	74.9 ±12.9
Pretransplant BMI (Mean, Kg/m2) ≥25 Kg/m2 (%)	24.8 ± 3.5 23 (52.3%)

Hypertension (%)	33 (75%)
Diabetes mellitus (%)	2 (4.5%)
Current/past smoker (%)	14 (31.8%)
Hemodialysis (%)	34 (77.3%)
Peritoneal Dialysis (%)	4 (9.1%)
Preemptive transplant (%)	6 (13.6%)
Pretransplant dialysis duration (Median, Months)	10 (3 – 23.3)
Primary disease for CKD (%) Glomerulonephritis Diabetic Nephropathy ADPKD Obstructive Nephropathy Infectious Nephropathy Unknown disease	 21 (47.7%) 2 (4.5%) 7 (15.9%) 7 (15.9%) 2 (4.5%) 5 (11.4%)
Pretransplant glucose level (Median, mg/dl)	83.1 (75 – 91.7)
Pretransplant triglycerides level (Median, mg/dl)	148.5 (110.2 – 221.1)
Pretranplant total cholesterol level (Mean, mg/dl)	186 ± 5.6
Pretransplant haemoglobin level (Mean, g/dl)	11.6 ±1.4
Cystatin C at 3 months post-transplant	1.5 (1.3-2.04)
eGFRCysC (Median, ml/min/1.73m^2) at 3 month post-transplant	52 (31.5 – 66)
Graft weight (Mean, grams)	187.7 ± 46.8
Graft length (Mean, cm)	10.9 ± 0.9
CIT (Median, mins)	375 (101.5- 1056)
WIT (Median, mins)	30.5 (28.2 - 35)
Cadaveric donor type (%)	23 (52.3%)
Hospital length of stay (Median, days)	28 (20 – 34.5)

BMI – body mass index; CKD – chronic kidney disease; ADPKD – autosomal dominant polycystic kidney disease; eGFRCysC – estimated glomerular filtration rate by cystatin C; CIT – cold ischemia time; WIT – warm ischemia time.

Subgroup comparison

In Table 2 we pointed out the differences between patients with estimated GFRCysC < and ≥ 60 ml/min/1.73m2.Thirty patients (68.2%) out of 44 had an estimated GFRCysC less than 60 ml/min/1.73m2. We found that patients with estimated GFRCysC < 60 ml/min/1.73m2 tended to be older (33.4±11 vs 40.6± 12 years, p= 0.06), were more frequently males (35.7% vs 80%, p=0.004) and had an increased pretransplant weight, but with no significant difference between BMI. Also, patients from this subgroup were less hypertensive and less frequently current or past smokers, but not at a significant level. Regarding the biological parameters, they presented significantly decreased levels of pretransplant total cholesterol (208± 32.7mg/dl vs 175.8 ± 54.6 mg/dl, p= 0.04) and lower but non-significant pretransplant levels of glucose, triglycerides and haemoglobin. There were no significant differences in cold ischemia time, warm ischemia time, graft weight, graft length and hospital length of stay between the 2 subgroups. The only variables with statistical significance at subgroup comparison were recipient male gender and pretransplant total cholesterol level.

Determinants of glomerular filtration rate

We performed an univariate and multivariate analysis to identify the determinants associated with eGFRCysC < 60 ml/min/1.73m2 at 3 months post-transplant (Table 3). By univariate analysis, we found that recipient age and pretransplant total cholesterol levels showed a trend of association and recipient male gender was significantly associated with eGFRCysC < 60 ml/min/1.73m2 at 3 months post-transplant (OR: 7.2; 95% CI: 1.75-29.56; p=0.006). In multivariate binary logistic regression, recipient male gender and pretransplant total cholesterol levels were independent determinants for eGFRCysC < 60 ml/min/1.73m2 at 3 months after transplantation and recipient age had a near-significant trend. Among these determinants, recipient male gender increased the risk for eGFRCysC <60 ml/min/1.73m2 5.59-times and pretransplant total cholesterol levels could be considered a protective factor for renal dysfunction (OR: 0.97; 95% CI: 0.95-0.99; p= 0.02). For a decrease in value of pretransplant cholesterol level of 10mg/dl, there would be a 9.7% decrease in chance for renal dysfunction.

Table 2. Comparison of subgroup analysis

Variable	eGFRCysC at 3 months post-transplant ≥ 60 ml/ min/1.73m^2 (n=14)	eGFRCysC at 3 months post-transplant < 60 ml/ min/1.73m^2 (n=30)	P value
Recipient age (years)	33.4±11	40.6±12	0.06
Recipient male gender (%)	35.7%	80%	0.004
Pretransplant recipient weight (kg)	70.5±12.6	76.9±12.7	0.13
Pretransplant recipient BMI (mean, Kg/m^2) ≥25 Kg/m2 (%)	24.5±3 57.1%	24.9±3.7 50%	0.67 0.65
Hypertension (%)	50%	46.7%	0.83
Current/past smoker (%)	42.9%	26.7%	0.28
Hemodialysis (%)	71.4%	80%	0.53
Pretransplant dialysis duration (months)	9.5(0-15.7)	6(1.7-26.7)	0.63
Primary disease for CKD (Glomerulonephritis %)	50%	50.3%	0.83
Pretransplant glucose level (mg/dl)	81.1(75-91.2)	83.2(75-95.7)	0.65
Pretransplant triglycerides level (mg/dl)	132.9(100-216.2)	150(117-231.5)	0.54
Pretransplant total cholesterol level (mg/dl)	208±32.7	175.8±54.6	0.04
Pretransplant haemoglobin level (g/dl)	11.5±1.6	11.7±1.3	0.69
Graft weight (g)	182.9±54.9	189.9±43.5	0.64
Graft length (cm)	10.8±0.9	11±0.9	0.52
CIT (minutes)	143.5(87-645.5)	470(105-1005)	0.13
WIT(minutes)	32.5(28-35)	30(28.7-35)	0.72
Cadaveric donor type (%)	42.9%	56.7%	0.39
Hospital length of stay(days)	23(18.5-39.2)	28.5(20.7-33.5)	0.36

BMI – body mass index; CKD – chronic kidney disease; eGFRCysC – estimated glomerular filtration rate by cystatin C; CIT – cold ischemia time; WIT – warm ischemia time

Table 3. Binary logistic regression analysis to identify the determinants associated with eGFRCysC at 3 months post-transplant < 60 ml/min/1.73m^2

	Univariate analysis			**Multivariate analysis**		
Variables	OR	95% CI	P value	OR	95% CI	P value
Recipient age	1.05	0.99-1.11	0.07	1.08	0.98-1.18	0.07
Recipient male gender	7.2	1.75-29.56	0.006	5.59	1.06-29.53	0.04
Pretransplant recipient weight	1.04	0.98-1.10	0.13	-	-	-
Pretransplant total cholesterol level	0.98	0.96-1	0.05	0.97	0.95-0.99	0.02
CIT	1.01	1-1.03	0.14	-	-	-

OR-odds ratio; CI- confidence interval; CIT- cold ischemia time

Discussions

Knowing the lack of evidence regarding cystatin C in kidney transplantation, we wanted to evaluate the clinical and biological determinants of glomerular filtration rate estimated with cystatin C in our transplant center. Previous studies showed that cystatin C could be a good alternative marker to serum creatinine in evaluating native kidney and graft function. In our study, recipient male gender and pretransplant levels of total cholesterol were associated with an eGFRCysC < 60 ml/min/1.73m2 at 3 months after kidney transplant. Groesbeck et al. reported that males had higher serum cystatin C values than females and gender accounted for approximately 14.8% of the variability in serum cystatin C levels.[11] Another study conducted by Knight et al showed that male gender is an independent determinant for cystatin C levels and glomerular filtration rate.[12] In our study group, male gender was predominant (69.5%) and was 80% present in the eGFR < 60 ml/min/1.73m2 subgroup. Moreover, cystatin C was significantly higher in males from the the eGFRCysC < 60 ml/min/1.73m2 subgroup in the univariate analysis (1.8 vs 1.4 mg/dl, CI 95%, p<0.001- analysis not shown in the text). This could explain the increased risk of renal dysfunction given by male gender in our analysis. The positive correlation between total cholesterol levels and serum cystatin C was previously shown in studies and also, the negative impact of hypercholesterolemia on glomerular filtration rate independent from cystatin C.[13],[14] According to our results, pretransplant total cholesterol levels were negatively and non-significantly correlated with cystatin C and eGFR CysC (r= -0.08, p= 0.60 and r= -0.15, p= 0.13). Patients with eGFR CysC < 60 ml/min/1.73m2 had a significantly lower level of pretransplant total cholesterol (208± 32.7mg/dl vs 175.8 ± 54.6 mg/dl, p= 0.04) and after multivariate binary logistic regression, this variable remained a protective factor for the decrease of glomerular filtration rate (a decrease of 10mg/dl reduced the probability of glomerular filtration decline below 60 ml/min/1.73m2 by 9.7%). The strengths of our study were the prospective design and multivariate adjusted model. There were also a few limitation, like a small study group and single center experience.

Conclusions

In conclusion, we found that recipient male gender and pretransplant total cholesterol levels were independent determinants of glomerular filtration rate estimated with cystatin C in kidney transplant recipients, at 3 months after kidney transplantation.

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