Assessment of Renal Function Using Cystatin C and Creatinine in Saudi Patients after Transplantation

Jeraiby M
Department of Biochemistry, Faculty of Medicine, Jazan University, Jizan, Saudi Arabia

Abstract

Background: Rapid and accurate assessment of kidney function in patients after transplantation is of utmost importance. The aim of this study was to compare the relationships of serum creatinine and serum cystatin C with an estimated glomerular filtration rate (eGFR) in kidney transplants Saudi patients after a certain period of transplantation. Materials and Methods: In this prospective study, 127 patients were categorized into three groups based on their length of survival after kidney transplantation; <1 year, from 1 to 5 years, and above 5 years after transplantation. Results of cystatin C and creatinine levels were compared by eGFR derived from estimation equation chronic kidney disease epidemiology collaboration. Results: In the three assessed periods, the mean (standard deviation) cystatin C level was 1.72 (0.57), 1.59 (0.64), and 1.82 (0.82), respectively, being highest after 5 years of transplantation, normal in 9.40%, and elevated in 90.60% of the participants, while creatinine level, decreased from 1.57 (0.53) to 1.52 (0.64) in 1–5 years, then it became the highest at 1.75 (0.69) in more than 5 years. The mean was normal in 21.30% and elevated in 78.70% of the patients. Both serum creatinine and cystatin C levels were negatively correlated with posttransplantation time in kidney transplant patients. Conclusion: The cystatin C level was statistically significantly higher after 5 years of transplantation. It is a better parameter to rule out renal dysfunction after transplantation.

Keywords: Creatinine, cystatin C, estimated glomerular filtration rate, renal transplantation

Résumé

Une évaluation rapide et précise de la fonction rénale chez les patients après une transplantation est de la plus importance. Le but de cette étude était de comparer les relations de la créatinine et de la cystatine C sérique avec un taux de filtration glomérulaire estimé (DFG) chez des patients saoudiens transplantés rénaux après une certaine période de transplantation. Matériel et méthodes: Dans cette étude prospective, 127 patients ont été classés en trois groupes en fonction de leur durée de survie après une transplantation rénale; <1 an, de 1 à 5 ans et plus de 5 ans après la transplantation. Les résultats des taux de cystatine C et de créatinine ont été comparés par le DFG dérivé de l’équation d’estimation de la collaboration épidémiologique sur les maladies rénales chroniques. Résultats: Au cours des trois périodes évaluées, le taux moyen (écart-type) de cystatine C était de 1,72 (0,57), 1,59 (0,64) et 1,82 (0,82), respectivement, étant le plus élevé après 5 ans de transplantation, normal dans 9,40% et élevé chez 90,60% des participants, tandis que le niveau de créatinine est passé de 1,57 (0,53) à 1,52 (0,64) en 1 à 5 ans, puis il est devenu le plus élevé à 1,75 (0,69) en plus de 5 ans. La moyenne était normale chez 21,30% et élevée chez 78,70% des patients. Les taux sériques de créatinine et de cystatine C étaient corrélés négativement avec le temps post-transplantation chez les patients transplantés rénaux.

Introduction

Renal transplantation is the treatment of choice for end-stage renal disease for the majority of patients with chronic kidney disease (CKD). It can help to restore patient’s quality of life and reduces morbidity and mortality rates when compared to patients undergoing dialysis. However, several complications can occur after transplantation and may result in impaired renal function. Rapid and accurate assessment of kidney function in patients after transplantation is of utmost importance. The aim of this study was to compare the relationships of serum creatinine and serum cystatin C with an estimated glomerular filtration rate (eGFR) in kidney transplants Saudi patients after a certain period of transplantation.

Materials and Methods: In this prospective study, 127 patients were categorized into three groups based on their length of survival after kidney transplantation; <1 year, from 1 to 5 years, and above 5 years after transplantation. Results of cystatin C and creatinine levels were compared by eGFR derived from estimation equation chronic kidney disease epidemiology collaboration.

Results: In the three assessed periods, the mean (standard deviation) cystatin C level was 1.72 (0.57), 1.59 (0.64), and 1.82 (0.82), respectively, being highest after 5 years of transplantation, normal in 9.40%, and elevated in 90.60% of the participants, while creatinine level, decreased from 1.57 (0.53) to 1.52 (0.64) in 1–5 years, then it became the highest at 1.75 (0.69) in more than 5 years. The mean was normal in 21.30% and elevated in 78.70% of the patients. Both serum creatinine and cystatin C levels were negatively correlated with posttransplantation time in kidney transplant patients.

Conclusion: The cystatin C level was statistically significantly higher after 5 years of transplantation. It is a better parameter to rule out renal dysfunction after transplantation.
function. Rapid and accurate assessment of kidney function in patients after transplantation is of utmost importance. The glomerular filtration rate (GFR) is the best index for monitoring graft function. Serum creatinine and serum cystatin C are common markers for the estimation of GFR.[2] However, serum creatinine is known to be influenced by some factors such as age, gender, and muscle mass. Serum cystatin C was suggested as an alternative molecule in estimating GFR due to its favorable properties.[3] It is less affected by gender, age, and muscle mass than serum creatinine.[4-5] Accordingly, some studies have reported that serum cystatin C is more sensitive in determining mild reductions in renal function than serum creatinine.[6-7] The CKD epidemiology collaboration (EPI) equation (CKD) is the recommended equation for GFR calculation as it has shown to be the most accurate, according to the kidney disease: improving global outcomes 2012 (KDIGO).[8] To the best of our knowledge, there has been no previous study in kidney transplant Saudi patients that compared the relationships of serum creatinine and serum cystatin C with estimated glomerular filtration rate (eGFR) in kidney transplant patients after a certain period of transplantation. This study aims to breach this knowledge gap in Saudi patients who had kidney transplant.

MATERIALS AND METHODS

The study was performed at Prince Muhammad Bin Nasser Hospital of Gizan, Saudi Arabia, on blood samples collected at the outpatient clinic from patients who had undergone kidney transplant. The patients were further categorized into three groups based on their length of survival after kidney transplantation; <1 year, from 1 to 5 years, and above 5 years after transplantation. Serum creatinine assay was performed by Cobas C 111 (Roche Diagnostics, Basel, Switzerland) with enzymatic based method using IDMS-traceable standardization. The reference interval in our laboratory is 0.7–1.2 mg/dL for men and 0.5–1.0 mg/dl for women and serum cystatin C assay was performed according to the manufacturer’s instructions by nephelometric immunoassay using BN ProSpec analyzer (Siemens Healthcare Diagnostics), with reference interval 0.62–1.1 mg/L (Standardization IFCC). eGFR was determined using CKD EPI 2009 creatinine-based formula (mL/min/1.73 m²) and eGFR (CKD-EPI) 2012 cystatin C equation (mL/min/1.73 m²). The weight (in kilograms) was measured during the initial patient assessment.

Data were analyzed using IBM Statistical Package for the Social Sciences (IBM SPSS version 22; IBM Corp., New York, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentages. The t-test and one-way ANOVA were used for continuous variables with normal distribution. Kruskal–Wallis test was used for continuous variables without normal distribution. Shapiro–Wilk test was used to assess the normality of the data. Pearson correlation coefficient was used to assess the relation between cystatin C, creatinine, and eGFR. \( P < 0.05 \) was considered statistically significant.

Ethical considerations were followed in agreement with the Declaration of Helsinki throughout this study and it was approved by the Research Committee Jazan University/IRC Jazan, Kingdom of Saudi Arabia.

RESULTS

The total number of the current study participants was 127, 63 (49.6%) males and 64 (50.4%) females, with a mean (SD) age of 58.39 (13.10) years. In the three assessed time periods; <1 year after transplantation, 1–5 years after transplantation, and more than 5 years after transplantation, the mean cystatin C level was 1.72 (0.57), 1.59 (0.64), and 1.82 (0.82), respectively, being highest after 5 years of transplantation. In regard to creatinine level, similar results were obtained, since it decreased from 1.57 (0.53) in <1 year to 1.52 (0.64) in 1–5 years, then it increased to the highest level at 1.75 (0.69) in patients who survived beyond 5 years after transplantation. For the eGFR creatinine, the mean level decreased gradually from 52.83 (21.37) to 52.50 (18.88) and 44.57 (18.34), respectively, while eGFR cystatin C, the mean increased from 43.50 (17.19) to 49.39 (19.74) in 1–5 years then it decreased to 42.59 (21.00) in more than 5 years.

Tests of normality were done and the results showed that all variables were not normally distributed with the exception of the eGFR. There was no statistically significant difference between males and females in the current study in any of the following: age, cystatin C level, creatinine, or eGFR, where all \( P > 0.05 \) were considered. Similarly, nonsignificant results were obtained when we compared between group with <1 year after transplantation and the group of 1–5 years after transplantation, group of <1 year after transplantation, and the group with more than 5 years after transplantation and between group of 1 and 5 years after transplant and the group with more than 5 years after transplantation.

Figure 1 shows the correlation coefficients and linear regressions between cystatin C, creatinine, and eGFR in the all groups of patients studied. Cystatin C level showed a highly significant \( (P < 0.0001) \) strong positive \( (r = 0.762) \) correlation with creatinine level [Figure 1a], and a highly significant \( (P < 0.0001) \) moderately negative \( (r = -0.676) \) correlation with eGFR [Figure 1b]. For the creatinine level, it was strongly positively correlated with cystatin C, but showed

Discussion: Le taux de cystatine C était significativement plus élevé après 5 ans de transplantation. C’est un meilleur paramètre pour exclure un dysfonctionnement rénal après une transplantation.

Mots-clés: Créatinine, cystatine C, Débit de filtration glomérulaire, transplantation rénale
a moderate negative correlation with eGFR creatinine and eGFR cystatin C [Figure 1c and d], where $r$ was 0.762, $-0.669$, and $-0.644$, respectively, with a high significant $P < 0.0001$ in both cases.

The relationship between cystatin C and creatinine for patients with the duration of transplantation < 1 year was strong positive $r = 0.763$ [Figure 2a], and its correlation with eGFR creatinine and eGFR cystatin C was strong negative [Figure 2b and d] at $-0.735$ and $-0.933$, respectively. Creatinine level showed positive ($r = 0.763$) and negative ($r = -0.825$) correlation with cystatin C and eGFR [Figure 2c and d], respectively. $P < 0.0001$ in all cases.

There were strong negative correlations between each of cystatin C and creatinine level with eGFR creatinine and eGFR cystatin C for patients with a duration of transplantation from 1 year to 5 years [Figure 3]. Similarly, the eGFR creatinine and eGFR cystatin C showed a strong negative correlation with both cystatin C and creatinine [Figure 3a-d]. On the other hand, there was a positive correlation between cystatin C and creatinine level [Figure 3b].

In patients with the duration of transplantation beyond 5 years, the correlation between cystatin C and creatinine was moderately uphill ($r = 0.693$), while eGFR creatinine was moderately downhill ($r = -0.582$) and strong downhill with eGFR cystatin C ($r = -0.799$) with $P < 0.0001$ [Figure 4a and b]. The correlation between serum creatinine with cystatin C was moderately uphill at $r = 0.693$ and $P < 0.0001$, while with eGFR creatinine was weakly downhill at $r = -0.370$ and moderate downhill with eGFR cystatin C ($r = -0.613$), $P = 0.024$ [Figure 4c and d] and $P = 0.024$.

**DISCUSSION**

Follow-up of kidney function after renal transplantation is essential. Measuring GFR quickly is critical for estimating renal function in the renal transplant recipient. Endogenous markers are of interest due to their speed and simplicity, and they have been anticipated as alternate markers for assessing renal function in renal transplant recipients. At present, serum creatinine, serum cystatin C, and GFR are the parameters being used to diagnose, evaluate prognosis, and monitor the response to treatment. In an agreement with the current study findings, Hermida et al. found that the serum creatinine and cystatin C concentrations were negatively correlated with the posttransplantation time in the kidney transplant patients. The previous studies on CKD patients showed an inverse association of both serum creatinine and cystatin C concentrations were negatively correlated with the posttransplantation time in the kidney transplant patients. In a recent published study that aimed to evaluate the efficacy of serum cystatin C as a marker of renal dysfunction among...
different CKD and postrenal transplant patients, the findings showed that serum cystatin C is negatively correlated with measured GFR in all groups.\[19]\] In this study, we found that serum cystatin C is a better parameter than serum creatinine to diagnose renal dysfunction. The previous studies conducted on renal transplant patients concluded that serum cystatin C is a better parameter than serum creatinine in assessing renal function in renal transplant recipient and a better correlation between serum cystatin C and GFR.\[11,20,21]\] Masson \textit{et al.} in their systematic study on postrenal transplant patients showed that cystatin C estimated equations were superior to creatinine-based eGFR equations.\[22]\] Nevertheless, the performance of the eGFR cystatin C did not have a significant effect compared with eGFR creatinine and eGFR creatinine-cystatin C formulae.\[22]\]

**CONCLUSION**

Serum cystatin C level was statistically significantly higher after 5 years of transplantation. It is also better than serum creatinine as a laboratory parameter in the diagnosis of renal dysfunction after kidney transplantation.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000;342:605-12.
2. McMahon GM, Waikar SS. Biomarkers in nephrology: Core Curriculum 2013. Am J Kidney Dis 2013;62:165-78.
3. Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. Scand J Clin Lab Invest 1985;45:97-101.
4. Finney H, Newman DJ, Price CP. Adult reference ranges for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem 2000;37 Pt 1:49-59.
5. Vinge E, Lindergård B, Nilsson-Ehle P, Grubb A. Relationships among serum cystatin C, serum creatinine, lean tissue mass and glomerular filtration rate in healthy adults. Scand J Clin Lab Invest 1999;59:587-92.
6. Villa P, Jiménez M, Soriano MC, Manzanares J, Cassanos P. Serum cystatin C concentration as a marker of acute renal dysfunction in critically ill patients. Crit Care 2005;9:R139-43.
7. Pucci L, Triscornia S, Lucchesi D, Fotino C, Pellegrini G, Pardini E, \textit{et al.} Cystatin C and estimates of renal function: Searching for a better measure of kidney function in diabetic patients. Clin Chem 2007;53:480-8.
8. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HL, \textit{et al.} A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
9. Li FK, Ho SK, Yip TP, Tse KC, Chan TM, Lai KN. Cystatin C assay for the detection of renal dysfunction in Chinese renal transplant recipients. Clin Chim Acta 2002;322:133-7.
10. Risch L, Blumberg A, Huber A. Rapid and accurate assessment of glomerular filtration rate in patients with renal transplants using serum cystatin C. Kidney Int 2006;70:204-10.
11. Rischo L, Blumberg A, Huber A. Rapid and accurate assessment of glomerular filtration rate in patients with renal transplants using serum cystatin C. Nephrol Dial Transplant 1999;14:1991-6.
12. Xu H, Lu Y, Teng D, Wang J, Wang L, Li Y. Assessment of glomerular filtration rate in renal transplant patients using serum cystatin C. Transplant Proc 2006;38:2006-8.
C and creatinine in kidney and liver transplant patients. Clin Chim Acta 2002;316:165-70.

14. Kumaresan R, Giri P. Is cystatin C estimation a better marker in chronic kidney disease patients? Int J Pharma and Bio Sciences 2010; 2:136-4.

15. DSa J, Shetty S, Bhandary RR, Rao AV. Association between serum cystatin C and creatinine in chronic kidney disease subjects attending a tertiary health care centre. J Clin Diagn Res 2017;11:BC09-12.

16. Ayub S, Zafar MN, Aziz T, Iqbal T, Khan S, Rizvi SA. Evaluation of renal function by cystatin C in renal transplant recipients. Exp Clin Transplant 2014;12:37-40.

17. Pöge U, Stoschus B, Stoffel-Wagner B, Gerhardt T, Klehr HU, Sauerbruch T, et al. Cystatin C as an endogenous marker of glomerular filtration rate in renal transplant patients. Kidney Blood Press Res 2003;26:55-60.

18. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. Am J Kidney Dis 2002;40:221-6.

19. Ali ND, Elkhadhab SO. Cystatin: Assessment of renal function in chronic kidney disease and postrenal transplant patients. J Egypt Soc Nephrol Trans 2019;19:57-79.

20. Krishnamurthy N, Arunugasamy K, Anand U, Anand CV, Aruna V, Venu G. Serum cystatin C levels in renal transplant recipients. Indian J Clin Biochem 2011;26:120-4.

21. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW. Biological variation of cystatin C: Implications for the assessment of glomerular filtration rate. Clin Chem 1998;44:1535-9.

22. Masson I, Maillard N, Tack I, Thibaudin L, Dubourg L, Delanaye P, et al. GFR estimation using standardized cystatin C in kidney transplant recipients. Am J Kidney Dis 2013;61:279-84.

23. White C, Akbari A, Hussain N, Dinh L, Filler G, Lepage N, et al. Estimating glomerular filtration rate in kidney transplantation: A comparison between serum creatinine and cystatin C-based methods. J Am Soc Nephrol 2006;16:3763-70.