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Serum cystatin C versus creatinine in the assessment of allograft function in early periods of kidney transplantation

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ABSTRACT

Introduction: Serum cystatin C is not routinely used in the evaluation of renal function and this may be due to its high cost, lack of adequate studies to approve the use of cystatin C and lack of accessibility and reliability. Many kidney transplanted patients encounter with decreased performance before creatinine rising and go toward rejection without certain actions. Certainly, the early detection of renal function reduction can prevent spiritual and physical damage among patients.

Objectives: This study was aimed to determine the predictive value of serum cystatin C and creatinine in the assessment of allograft function in the early period after kidney transplantation in Urmia city, Iran.

Patients and Methods: In this prospective study, serum creatinine, cystatin C and glomerular filtration rate (GFR) of 49 kidney transplanted patients in the 3rd, 8th and 14th day were measured and compared together. The correlation of creatinine and cystatin C was examined using Spearman's correlation. ROC curves were used to investigate sensitivity and specificity.

Results: In this study, there was a statistically significant relationship between serum levels of creatinine and serum levels of cystatin C in 3rd, 8th and 14th day. The sensitivity and specificity of cystatin C in 14th day were 76% and 91.2%, respectively and for creatinine were 72% and 75% respectively, indicating cystatin C is a more sensitive indicator compared to creatinine on the 14th day in the presence of loss of GFR below 60 mL/cc.

Conclusion: Serum cystatin C as a valuable marker can be an effective predictor marker of renal function reduction beside creatinine. Due to high cost of measuring kits of serum cystatin C, it is not possible to use this marker in all transplanted patients in the world. Therefore, we can use this marker in high-risk patients with probability of transplantation rejection.

Implication for health policy/practice/research/medical education:
Given the predictive role of serum cystatin C in kidney function, the poor financial status of patients with chronic kidney diseases and the high cost of this test, it should be considered only in high risk patients with high probability of transplantation rejection.
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Introduction

A kidney transplantation is the preferred method of treatment for the majority of patients with chronic kidney disease and it is cost-effective compared to dialysis, which allows patients to return natural life. One of the major problems in patients after renal transplantation surgery is acute rejection after surgery, which is preventable with early detection and diagnosis. The level of serum

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creatinine is one of the markers in routine measurement of renal function. However, when half of the kidney function is not impaired, it does not increase and leads to delayed diagnosis of transplanted kidney rejection. One of the proposed alternative markers instead of creatinine is serum cystatin C, which it can be more accurate based on the molecular properties in measurement of renal function. It is a protein with low molecular weight and 122 amino acids (13 kDa). It is also a leukocyte proteinase-inhibitor cysteine enzyme in all cells of the body. Due to the low molecular weight and positive charge, it passes freely cross the membrane of glomeruli and is absorbed near the tubules (1). There is no notifiable changes in the level of cystatin C during the overnight but the average value of the changes during the daylight is 13% which is higher than serum creatinine (2). An ideal marker should be an endogen substance with regular and continues production completely filtered by the glomerulus and totally be out from urine and it should not be bonded to proteins (3). Estimated glomerular filtration rate (GFR) by creatinine can be underestimated or overestimated due to influences by factors such as age, gender, muscle mass, drugs, food and tubular secretion (4). GFR is considered as the best marker of kidney function in kidney transplanted patients and it could be affected before creatinine rising, in such a way that this is one of the disadvantages of creatinine (5,6). Serum cystatin C is not routinely used in the evaluation of renal function and this may be due to its high cost, lack of adequate studies to approve the use of cystatin C and lack of accessibility and reliability. In some studies conducted on serum cystatin C, results showed its priority to creatinine, but other studies showed another results (7,8), thus now creatinine is preferred to serum cystatin C. Therefore more kidney transplanted patients before creatinine rising encounter with decreased performance and go toward rejection without certain actions. Certainly the early detection of reduction in the renal function can prevent spiritual and physical damage in these patients, as well as the cost of the complications of kidney transplantation rejection can be also reduced.

Objectives

This study was aimed to determine the predictive value of serum cystatin C and creatinine in the assessment of allograft function in the early period after kidney transplantation in Urmia city, Iran.

Patients and Methods

Study population

In this prospective study, 49 patients with end-stage renal disease (ESRD) were under kidney transplantation surgery from October 2015 to May 2016 and clinical data were recorded by questionnaire. The blood of all patients in 3rd, 8th and 14th day were measured regarding creatinine. Measurement of creatinine by Jaffe's reaction was done in a wavelength of 500 nm using BT-3000 (manufactured by Italy) and it was performed automatically with multiple controls. Then each of the above serum samples maintained in the temperature of -20°C. The level of serum cystatin C was evaluated by enzyme-linked immunosorbent assay (ELISA) using bioassay technology cystatin C kits. ELISA was done using Avernes (manufactured by USA) machine. Then Cockcroft-Gault formula was used to calculate GFR. Then the level of serum cystatin C and creatinine were compared with glomerular filtration. Critical point of glomerular filtration was determined in 60 mL/min/73.1 m^2. In our study also acute rejection was defined by consecutive increase in the level of creatinine and approved by Tc-99m DTPA (diethylene-triamine-pentaacetate) scan, if necessary. In order to assess the deeper relationship between serum levels of cystatin C with creatinine, linear regression analysis was used. Sensitivity and specificity of cystatin and creatinine in serum in the diagnosis of GFR reduction (GFR <60 mL/min/1.73 m^3) in renal transplanted recipients were determined by receiver operating characteristic (ROC) curves and compared together. In order to do matching in patients, patients who received drug regime other than cyclosporine, corticosteroids and mycophenolate mofetil as well as patients with a history of liver, lung and heart problems were excluded from the study. Patients who had surgical complication leading to nephrectomy during the study were excluded too.

Ethical issues

The research followed the tenets of the Declaration of Helsinki; written informed consent was obtained; patients were free to leave the study at any time and the research was approved by the ethical committee of Urmia University of Medical Sciences (#ir.umsu.rec.1394.432).

Statistical analysis

The data was analyzed using MedCalc statistical software version 15.8. In the descriptive analysis, the mean index and standard deviation (SD) were used. In this study, the correlation was evaluated among serum cystatin with serum creatinine, GFR, sex, age, body mass index, duration of dialysis before surgery using Spearman's coefficient. In all statistical tests, the level of 0.05 was considered significant.

Results

This study included 49 kidney transplanted patients, including 26 male (53.1%) and 23 female (46.9%). The mean age of patients was 41.18 ± 13.31 years. The mean body mass index and duration of dialysis before transplantation were 24.28 ± 4.56 kg/m^2 and 23.12 ± 20.08 months, respectively.

The causes of kidney failure in our patients were: 1) Hypertension in 24 cases (49%), 2) Diabetes in 8 cases (16.3%), 3) Glomerulonephritis in 6 cases (12.2%), 4) Infectious diseases in 4 cases (8.2%), 5) vesicoureteral

reflux (VUR) in 3 cases (6.1%), 6) Polycystic kidney disease in 2 cases (4.1%), 7) Congenital atrophy in 1 patient (2%) and 8) Systemic lupus erythematosus (SLE) in 1 case (2%).

The mean levels of serum cystatin C, creatinine and GFR in the 3rd, 8th and 14th day are shown in Table 1. In this study, there was a significant relationship between serum level of cystatin C and serum levels of creatinine in the 3rd, 8th and 14th day that is shown in Figure 1A-C.

In the 3rd, 8th and 14th day, 23 (46.9%), 19 (38.8%) and 25 (51%) patients had a GFR below than 60 cc/min, respectively. Analysis of variance (ANOVA) analysis showed that the changes were significant in serum creatinine and cystatin C level in the 3rd, 8th and 14th day. The sensitivity and specificity of serum cystatin C were 65.2% and 96.2% in the third day, respectively and 78.3% and 88.5% for creatinine, respectively (Figures 2A and 2B).

According to ROC curves plotted for the third day, serum cystatin C showed more sensitivity compared with creatinine in cases of GFR decline below than 60 cc/min (Figure 2A). Sensitivity and specificity of serum cystatin C in the 8th day were 63.2% and 100%, respectively and 84.2% and 73.3% for creatinine, respectively.

According to ROC curves plotted for the third day, serum cystatin C showed no more sensitivity compared with creatinine in cases of GFR decline below 60 cc/min (Figure 2B). Serum cystatin C in the third day was more sensitivity compared with creatinine in cases of GFR decline below than 60 cc/min. In the critical point of 3418 ng/mL, sensitivity and specificity of cystatin C were 88% and 79.2%, respectively (Figure 2C). In this study, there was no significant relationship between changes in the level of serum cystatin C and various factors such as age, gender, muscle mass index and duration of dialysis before surgery.

Early diagnosis of acute rejection is very important. Considering that the level of serum creatinine can have a slight change at the beginning of rejection or can be asymptomatic, it is considered to be necessary the replacement of more precise marker for early diagnosis. There are different studies with different results in the case of the use of cystatin C marker instead of serum creatinine in early diagnosis of rejection.

In the study of Geramizadeh et al in 2009 on 60 transplanted patients, the serum cystatin C and serum creatinine value in the first week was evaluated, in such a way that serum cystatin C changes in this week were increasing but serum creatinine changes were decreasing and there was a significant relationship between serum creatinine and serum cystatin after 7 days. In this study, it was suggested that serum cystatin C after the first week should be used as accurate predictive marker for kidney function. In the present study, although there was a significant relationship between serum creatinine and serum cystatin in the first week, it was not better predictor in renal function than creatinine and in the end of second

Table 1. The mean levels of serum cystatin C, creatinine and GFR in the 3rd, 8th and 14th day

Date	Cystatin C (ng/mL)	Creatinine (mg/dL)	GFR (ml/min)
3rd day	4722.31±2707.57	1.75±1.31	59.51±20.88
8th day	4313.67±2566.66	1.66±1.35	63.01±22.31
14th day	4390.96±2476.20	1.56±1.03	61.33±1840

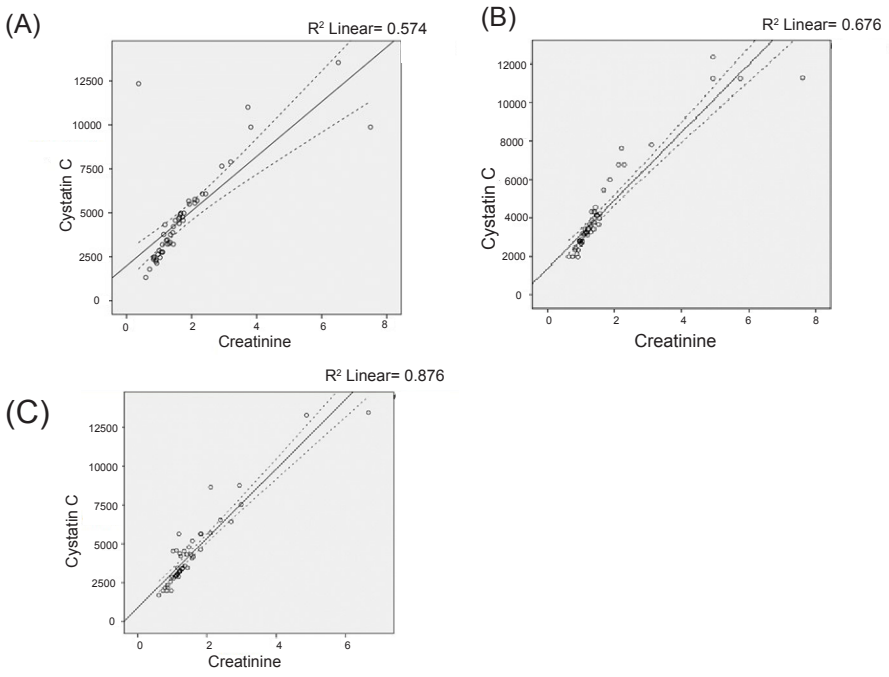

Figure 1. The correlation between serum levels of cystatin C (ng/mL) and creatinine (mg/dL) in **(A)** the 3rd day (r = 0.863, *P* < 0.001, **(B)** the 8th day (r = 0.970, *P* < 0.001), and (C) the 14th day (r = 0.892, *P* < 0.001) after kidney transplantation.

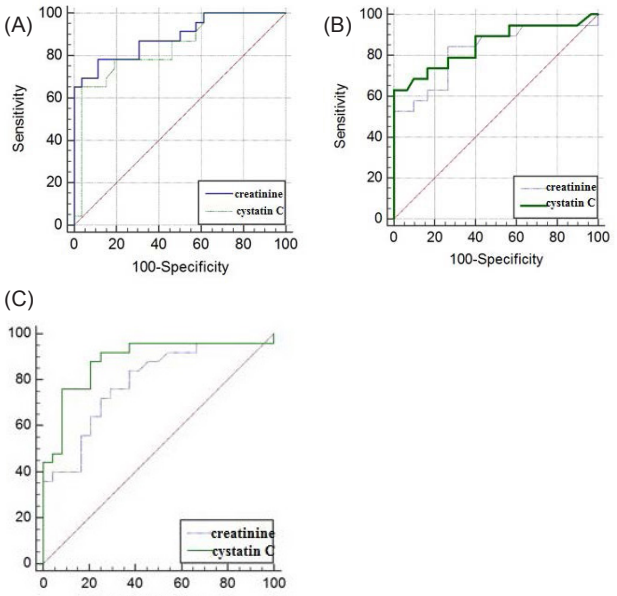

Figure 2. ROC curve, sensitivity and specificity of creatinine (dotted line) and cystatin C (solid line) in the diagnosis of reduced renal function (GFR below than 60) in **(A)** the third day ($P = 0.17$ vs. $P = 0.17$), **(B)** the 8th day ($P = 0.20$ vs. $P = 0.20$), **(C)** and the 14th day ($P = 0.01$ vs. $P = 0.01$).

week, serum cystatin C was more precise than creatinine in predicting renal function (9).

In the study of Zahran et al, patients were evaluated after relative stability and 1 month after kidney transplantation. In contrast with our study, Zahran et al revealed that the serum cystatin C was not sensitive predictor marker in renal function in comparison with creatinine (8).

In the study of Christian et al, conducted on the 117 kidney transplanted patients, the sensitivity of serum cystatin C in the prediction of renal function was more precise than serum creatinine in GFR below 60 cc/min or above 60 cc/min. The difference between this study and our study was how to measure GFR. It is also a study in patients after five months but the results of the study after two weeks were consistent with the long-term results of this study (10). In the study of Krishnamurthy et al, conducted on 30 kidney transplanted patients and 29 controls after at least six months of their kidney transplantation, it was shown that serum cystatin C in case of loss of GFR is a better marker than creatinine and the result was similar to our study in two weeks after renal transplantation (11).

In the study of Young et al, conducted on 72 patients with kidney transplantation, serum creatinine and GFR levels and cystatin C from first day to one year were calculated and compared together. In this study, cystatin C was a markers with high sensitivity and low specificity when creatinine clearance was reported below 60 cc/min. It is recommended to calculate the GFR based on cystatin C to evaluate the accurate role of cystatin C. In our study, there was a defect based on Cockcroft-Gault formula, then it is recommended that other formula be used to avoid the underestimation or overestimation of GFR in further studies (12).

In the study of Harman et al, which contained 14 different studies with different methods of GFR measuring, creatinine and serum cystatin C, it was concluded that calculated GFR based on Le Bricon formula for serum cystatin C was more accurate compared with calculated GFR based on the modification of diet in renal disease (MDRD) equation in prediction of rejection (13).

Given the comparison of our results with similar studies, it is seems that serum cystatin C can be used as an alternative marker in the evaluation of decreased renal function. It is an important issue that there were different sensitive times in case of cystatin C in studies and it is variable from the first week after kidney transplantation surgery until some months later. In our study, serum cystatin C was preferred compared with serum creatinine. On the other hand, in our study and the majority of similar studies serum cystatin C is a significant relationship between serum creatinine and serum cystatin C indicating strong correlation between these two markers. Other issues are difference between the above studies and our study regarding predictive value of cystatin C, different methods of measuring cystatin C serum, different analysis of biochemical parameters and different methods of GFR measurement. In our study, GFR was calculated with Cockcroft-Gault formula and was affected by muscular mass and creatinine values, then GFR values were nearly estimated and could affect our results. In fact, it is possible to avoid this contradiction using standard method to measure GFR.

Another issue in this study is the difference in definition of GFR critical point that cystatin C marker is more sensitive than serum creatinine at that point. In our study, GFR below than 60 cc/min was significant and results below 80 than cc/min were not significant. In some above-mentioned studies, the results were similar to our study and in some were opposite.

During the two-week of our study, only two cases of acute rejection happened in the first week after transplantation and cystatin C and creatinine changes increased proportionally in these two cases, as well as in the diagnosis of acute rejection in the first week. Additionally, in the beginning of the second week, one case of acute rejection happened that cystatin C value increased to 2876 ng/mL and the level of creatinine was 0.99 mg/dL.

Conclusion

Serum cystatin C as a valuable marker can be used as an early predictor marker for reduction in kidney function. Due to the high cost of the measuring kits, it is not possible to use this marker in all transplanted patients, therefore this marker can be used in high-risk patients with high probability of transplantation rejection. On the other hand, in order to assess more accurate the role of serum cystatin C, studies with large population of renal transplantation in long duration are needed. In addition, standardization

of GFR criteria and biochemical measurement of serum cystatin C and creatinine are required for accurate estimation of the results of the studies. Thus, with regard to the effect of immunosuppressive drugs on cystatin C that is used after renal transplantation surgery, the role of these drugs should be included in the results of the study.

Limitations of the study

This study was conducted on a limited proportion of patients. Thus larger studies are suggested.

Authors' contribution

ATA, MMF and MMR conducted the research. RV, MA and SA collected the data. RV and MHA analyzed the data. RHS and SAK prepared the primary draft. RV, MA and MMR edited the final draft. All authors signed the manuscript.

Conflicts of interest

The authors declared that there was no conflict of interest in this study.

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