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The association of brain-dead donors' serum/urine NGAL with renal transplant function

Farzanehsadat Minoo[1,2], Somayeh Narimani[1], Mitra Mahdavi-Mazdeh[1], Azam Alamdari[1,2*]

Abstract

Introduction: Accurate diagnostic techniques are necessary for the function assessment of deceased donor (DD) kidneys. Lipocalin-2, or neutrophil gelatinase-associated lipocalin (NGAL) is a novel biomarker of kidney injury that can be suitable in this concern.

Objectives: This study assessed the association between DDs' serum and urine lipocalin-2 levels and graft function.

Patients and Methods: A prospective cohort study was conducted on 85 kidney transplant recipients in eight recipient hospitals who received kidneys from 44 consecutive brain-dead donors who were referred to the Iranian Tissue Bank in 2011. The serum and urine NGAL levels of donors were measured at the time of admission and before organ recovery. Recipients were followed for one year for operative and early outcome.

Results: The NGAL median level in donors' sera whose kidneys experienced delayed graft function (DGF) in recipients was 350 ng/mL at admission and 290 ng/mL prior to organ retrieval. These figures corresponded to 340 ng/mL and 215 ng/mL in recipients with early graft function (EGF), respectively ($P=0.048$). In the case of donors' urinary level of NGAL, the median was 32 ng/mL and 40 ng/mL in those whose recipients experienced DGF versus 27.5 ng/mL and 20 ng/mL in those whose recipients felt in EGF group ($P=0.031$). In this regard, the area under the curve (AUC) of ROC analysis was 0.63 (CI= 0.509 to 0.755); However, it could not predict DGF according to logistic regression analysis.

Conclusion: It seems that DGF is associated with increased pre-retrieval levels of sNGAL and uNGAL in brain-dead donors; nevertheless, studies with more representative samples can show more considerable statistical significance and probable predictive value.

Keywords: Deceased donor, Neutrophil gelatinase-associated lipocalin, Delayed graft function, Kidney graft function, End-stage renal disease

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Introduction

Kidney transplantation increases longevity and improves quality of life in patients suffering from end-stage renal disease (ESRD). Yet, kidney allograft demand grows progressively and far exceeds the available supply. Different approaches such as kidney transplantation from expanded criteria donors (ECDs) have been taken to resolve this discrepancy partly (1-3). Evidence has shown that brain death significantly affects the donor's organ quality and is a major risk factor for the outcome of kidney transplantation. Brain death activates immunity faster, and during this process the inflammatory mediators, representing tissue injury, are up-regulated which may lead to graft dysfunction. Moreover, this antigen-independent reaction may predispose the graft to additional ischemia-reperfusion injury such as delayed graft function (DGF) and accelerated host alloresponse and as a consequence graft loss compared with those from living sources (4-7). According to the definition suggested by Halloran and coworkers, DGF is diagnosed when one of these situations exists; oliguria less than one liter in 24 hours for more than two consecutive days, serum creatinine level >500 μmol/L during first week of transplantation or requirement to dialysis during one week after transplantation. This clinical condition prolongs the length of hospitalization and increases the cost, morbidity and mortality (8,9). Accordingly, the success of transplantation can be influenced by donor's characteristic and thus early detection of deceased donor (DD) kidney injury and then appropriate care for optimal organ preservation may improve the outcome of renal graft (10).

Current laboratory tests, including serum creatinine, do not have enough accuracy for early detection of acute kidney injury. Lipocalin-2, or human neutrophil gelatinase-associated lipocalin (NGAL) is a one of the new biomarkers of acute renal injury that is comparable with troponin in myocardial infarction and rises in two hours after kidney injury. It is a member of the lipocalin protein family which was first discovered in specific neutrophil granules. Then its expression was found in other tissues such as tubular kidney cells, particularly after injury and

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[1]Nephrology Research Center, Tehran University of Medical Sciences, Tehran, Iran. [2]Center of Excellence in Nephrology, Tehran, Iran.
***Corresponding Author:** Azam Alamdari, Email: a-alamdari@sina.tums.ac.ir, azamalamdari@yahoo.com

Implication for health policy/practice/research/ medical education

Kidney grafts from brain death donors with higher pre-retrieval serum neutrophil gelatinase-associated lipocalin are more sensitive to ischemia–reperfusion induced injury.

activation of the inflammatory cascade (11-14). In a study of 91 deceased-donor kidney transplant patients by Hall et al, detected that urine NGAL (uNGAL) and IL-8 could predict DGF or 3-month graft function (15). Kusaka and coworkers found that the median serum NGAL (sNGAL) in normal samples was 53±30 ng/mL but rose significantly about 963±33 ng/mL in patients with ESRD. Furthermore, it was shown that sNGAL level decreased markedly after transplantation from living donors (LDs) except in two DGF cases whose serum level was over 400 ng/mL. Serum NGAL levels even declined in patients receiving kidney transplants from donors after cardiac death before recovery of urine output and decreasing of serum creatinine level and so allowed to predict DGF and need for dialysis in these groups sooner (16).

Therefore, NGAL can be used as an accurate simple laboratory test to predict acute renal injury in DDs immediately. It could be a tool to assess the suitability of graft for transplantation. Despite studies on the predictive value of sNGAL or uNGAL level and other new biological markers in kidney transplant recipients, there are just a few studies that have evaluated the outcome of kidneys from DDs.

Objectives

Given the potential predictive role of sNGAL or uNGAL level as a sensitive biomarker, this study was designed to assess the capability of this marker in the sera of brain-dead donors to predict the outcome of graft function after transplantation.

Materials and Methods

Participants and study design

A cohort of 85 kidney transplant recipients from eight renal transplant centers in Tehran, Iran, was followed prospectively for one year. They received kidneys from 44 consecutive brain-dead donors who were harvested in the Organ Procurement Unit of the Iranian Tissue Bank and Research Center, affiliated to Tehran University of Medical Sciences, in 2011. The serum and urine levels of donors' NGAL were measured at the time of admission and just prior to organ recovery. The inclusion criteria for donors were based on national protocols.

Methods

The levels of sNGAL and uNGAL of donors were measured using collected samples at the time of admission and before organ retrieval. The samples were firstly frozen at -20 °C and all 176 samples (44 donors, each 4 samples) were tested simultaneously by a single operator using one kind of kit. Serum NGAL was measured by a commercially available enzyme-linked immunosorbent assay (ELISA) Technique and uNGAL was determined by the ARCHITECT (R) method. The peri-operative and follow-up data of the recipients were recorded for further analysis.

Statistical analysis

The distribution of numerical variables was assessed for normality using Kolmogrov-Smirnov test. Descriptive statistics was conducted to define baseline characteristics. Due to non-normal distribution of s/u NGAL levels, Mann Whitney U test or Kruskal-Wallis tests were conducted, once applicable. Based on the data, parametric Pearson's or non-parametric Spearman's correlation coefficients were considered. Logistic regression was used to examine the association between s/u NGAL level and DGF. In case of any significant correlation in one-sample hypothesis tests, receiver operating characteristic (ROC) curve and multivariate logistic regression tests were used to assess their predictive values concerning DGF. Unadjusted survival probabilities were estimated using Kaplan-Meier method. A Log-Rank test was used to compare survival probabilities in different subgroups of recipients (recipients with/without DGF, recipients of kidneys from donors with normal or increased levels of NGAL). Two-sided *P* value less than 0.05 was considered statistically significant. A statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software (IBM SPSS Statistics, version 19. SPSS Inc. Chicago, USA).

Results

Donors

There were 44 brain-dead donors with a mean age of 29.8 ±14.9 years. The male-to-female ratio was 1.6. The most common causes of brain death were traffic accidents (28; 63.6%) and cerebral vascular events (10; 22.7%). Mean serum creatinine (±SD) was 1.16 (±0.44) mg/dL at the time of admission and 1.07 (±0.39) mg/dL prior to organ recovery. Mean (±SD) time between brain death announcement and organ retrieval was 12.6 ± 5.5 hours (Table 1). There was no association between sNGAL or uNGAL level and gender. There was a correlation between sNGAL or uNGAL and age (older versus younger than 30 years old) (sNGAL: r = 0.36; $P = 0.001$, uNGAL: r = 0.47; $P \leq 0.001$). The level of uNGAL correlated with a history of hypertension in donors (r: 0.6; $P = 0.023$). Moreover, sNGAL and uNGAL levels showed significant differences between donor groups with various brain death causes based on the Kruskal-Wallis test ($P = 0.005$ in sNGAL, $P = 0.002$ in uNGAL). Urine NGAL showed significant difference in ECDs compared to standard criteria donors ($P = 0.023$) while sNGAL did not show any difference by Mann-Whitney U test.

Table 1. The baseline characteristics of 44 deceased donors

Characteristics	
Age (mean ± SD) years	29.8 ± 14.9
Gender (n, %)	
Male/female	27 /17(1.59)
Cause of brain death (n, %)	
Traffic accident	28 (63.6%)
Head Trauma	2 (4.5%)
Suicidal hanging	1 (2.3%)
Drug intoxication	2 (4.6%)
Cerebral vascular events	10 (22.7%)
Post- CPR	1 (2.3%)
Time to harvesting (h) (mean ± SD)	12.6 ± 5.5
Serum Creatinine (mg/dL) (mean ± SD)	
At admission	1.16 ± 0.44
Before organ retrieval	1.07 ± 0.39
sNGAL (ng/mL) (median) (range)	
At admission	340 (90-910)
Before organ recovery	240 (70-1910)
uNGAL (ng/mL) (median) (range)	
At admission	30 (5-1390)
Before organ recovery	20 (5-715)

Abbreviations: CPR, Cardiopulmonary resuscitation; sNGAL, Serum neutrophil gelatinase-associated lipocalin; uNGAL, Urinary neutrophil gelatinase-associated lipocalin.

Recipients

The mean age of 85 kidney transplant recipients at the time of transplantation was 40.1 ±13.1 years. The most common cause of ESRD was unknown etiologies (41; 48.2%). Seven recipients (8.2%) received renal allograft for the second time.

The mean serum creatinine level of recipients was 2.7 ±2.4 mg/dL at the end of the first week and 1.8 ±1.7 mg/dL at the end of first year of transplantation. Overall, one-year mortality rate was 9 (10.6%), including two operative mortalities (2.4%) in addition to seven (8.2%) after that. DGF occurred in 31 recipients (31/83: 37.3%) and eight patients (8/83: 9.6%) experienced graft loss in the first year. Nineteen patients (22.9%) needed dialysis treatment (Table 2).

Bivariate and multivariate analyses

There was no correlation between DGF and other variables such as donor and recipient age and gender, organ retrieval time and duration, cold ischemic time, cause of brain death, donor's serum creatinine and creatinine clearance, cause of ESRD and dialysis length before transplantation. Median of sNGAL and uNGAL level of donors, whose kidneys showed DGF after transplantation were higher than those without DGF after transplantation. Median of sNGAL was 350 ng/mL at the time of admission to ICU and 290 ng/mL at pre-retrieval time in donors of recipients with DGF, while median of sNGAL level at the time of admission and pre-retrieval was 340 ng/mL and 215 ng/mL in donors, whose kidneys showed early function after transplantation respectively. The median of uNGAL was 32 ng/mL at admission and 40 ng/mL before organ recovery in donors, whose kidneys showed DGF after transplantation but it was 27.5 ng/mL and 20 ng/mL respectively in those whose kidneys showed early function after transplantation. Despite these findings, only pre-retrieval sNGAL was significantly higher in donors of DGF recipients based on the Mann-Whitney U test ($P=0.048$, median: 290 ng/mL). Based on a paired analysis on about 40 donors whose both kidneys were conducted for transplantation, early graft function (EGF) of both transplanted kidneys was seen in 17 cases (42.5%), DGF of one transplanted kidney in 16 cases (40%), and DGF in both grafts in 7 cases (17.5%). The median of pre-retrieval sNGAL was higher in donors whose both donated kidneys experienced DGF versus (pre-retrieval sNGAL in both EGF: 210 ng/mL, in one graft DGF: 230 ng/mL, in both graft DGF: 340 ng/mL) but there were no significant differences in sNGAL at admission and uNGAL between these three groups (Table 3). In ROC curve analysis, the

Table 2. The baseline characteristics of 85 recipients

Characteristics	
Age (mean±SD) years	40.1±13.1
Gender (n %)	
Male/female	53 /32(=1.65
Underlying renal disease	
Glomerulonephritis	7 (8.2%)
Diabetes	9 (10.6%)
Hypertension	7 (8.2%)
Polycystic kidney disease	4 (4.7%)
Congenital diseases	6 (7.1%)
Infection or kidney stones.	6 (7.1%)
Vasculitis	5 (5.9%)
Unknown	41 (48.2%)
First versus re-transplant	
First-time transplant	78 (91.8%)
Re-transplantation	7 (8.2%)
The duration of dialysis before transplantation(year) (mean±SD)	2.1 ± 2.1
Serum creatinine (mg/dL) (mean±SD)	
End of the first week	2.7 ± 2.4
One year after transplantation	1.8 ± 1.7
GFR (mL/min) (mean±SD)	
End of the first week	48.8 ± 25.2
One year after transplantation	62.9 ± 23.2
Graft loss in the first year (n, %)	8 (9.6%)
Mortality in the first year (n, %)	9 (10.6%)

Abbreviations: GFR, Glomerular filtration rate.

Table 3. Median NGAL levels(ng/mL) in pair kidney analysis of donors based on graft function after transplantation

Graft function	sNGAL at admission	Pre-recovery sNGAL	uNGAL at admission	Pre-recovery uNGAL
Both EGF	340	210	25	13
One DGF	330	230	40	95
Both DGF	410	340	31	30

Abbreviations: sNGAL, Serum neutrophil gelatinase-associated lipocalin; uNGAL, Urinary neutrophil gelatinase-associated lipocalin; DGF, Delayed graft function; EGF, Early graft function.

area under the curve (AUC) of pre-retrieval sNGAL for DGF was 0.63 (95% CI: 0.5- 0.7) and at median of sNGAL (240), its sensitivity and specifity was 64.5% and 61% to 65%, respectively (Figure 1). In multivariate regression analysis, donors' sNGAL and uNGALlevels were not able to predict DGF occurrence in their recipients. Moreover, we did not find any significant difference between donors' sNGAL or uNGAL and various stages of chronic kidney disease in recipients during one year with Kruskal- Wallis test. There was no association between graft loss and death with increased level of donors' sNGAL or uNGAL.

Discussion

Predictive tools are designed to divide donors into "standard" or "expanded criteria". Some of these tools are donor serum or urine biomarkers but the role and predictive value of them in evaluating of graft suitability have been undetermined until now (17). Based on The Organ Procurement and Transplantation Network (OPTN) definition in 2002, ECD kidneys are from a DD ≥ 60 years old, or a 50 to 56 years old donor with at least two of these criteria: history of hypertension, serum creatinine >1.5 mg/dL (133 mmol/L), or cerebrovascular cause of death; however, kidney grafts from donors after circulatory death is a different entity (18,19). Thus, the serum creatinine is now conducted as a most acceptable universal biomarker for assessing DDs' kidneys but it is somehow unreliable in diagnosis of acute renal injury, especially in unstable patients (11).

In this study, we showed that preoperative sNGAL had significant difference in donors whose recipients experienced DGF compared to with those without DGF.

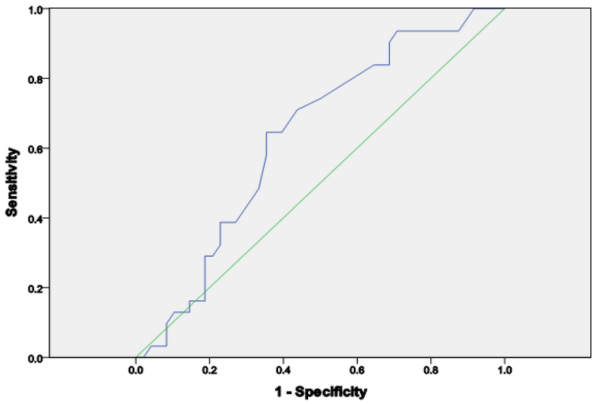

Figure 1. ROC curve of preoperative donors' serum NGAL for DGF.

In addition, median of preoperative sNGAL was higher in donors whose both kidneys suffered from DGF after transplantation in comparison with those whose one or none of their kidneys did not suffer. Furthermore, the AUC of pre-retrieval sNGAL for DGF was about 0.63 which may show relative value of this factor in brain death's renal injury assessment; but they could not predict DGF or various stages of kidney injury in recipients in the first year after transplantation. These results are more or less similar to the study done with Buemi et al, on 80 DDs (n=80) and 17 LDs (n=17) and their recipients. Serum NGAL in DDs was significantly higher than LDs. There were not any episodes of DGF among LD kidney recipients but 25% of DD kidney recipients experienced it. Plasma NGAL was also monitored in recipients before transplantation and then 6, 24, and 48 hours after surgery. They found that sNGAL level of recipients may be a reliable factor for prediction of DGF occurrence and graft function, but not from donors. Moreover, recipient plasma NGAL was more reliable than uNGAL (20).

Based on our study DDs uNGAL seems incompetent to predict DGF and graft outcome in their recipients and graft suitability assessment of brain death donors. Urine NGAL unsuitability and insensitivity, as an acute renal injury biomarker in recipient or critically ill patients, was reported in other studies too. Glassford et al, measured sNGAL and uNGAL (monomeric and homodimeric form of uNGAL) in 102 critically ill patients with oliguria, and/or a serum creatinine rise>25 µmol/L. Their study showed uNGAL didn not have accuracy in this ICU population to predict outcome, probably due to complex nature and source of uNGAL (21,22). Hollmen et al, had a same study about DDs NGAL level in predicting DGF, as the first study in this entity. They found uNGAL, but not sNGAL , was higher in DDs with recipients who experienced DGF. Thus, they concluded that uNGAL can be useful in evaluating deceased kidney donor; but none of uNGAL or sNGAL of DDs able to predict DGF in their recipients that was the same as our finding (23).

As mentioned above, NGAL is an acute reactant protein in neutrophils and macrophages which it's secretion induced by cytokine mediators. Brain death causes inflammatory responses and important cytokine cascades in donor that may vindicate high levels of sNGAL and uNGAL in our study (24). We measured sNGAL with ELIZA while urine NGAL was measured with ARCHITECT(R) method; therefore, the levels of these values may be incomparable.

Conclusion

Kidney grafts from brain death donors with higher pre-retrieval sNGAL are more sensitive to ischemia – reperfusion induced injury and therefore sNGAL, but not uNGAL, can be a prime candidate in evaluation of brain death donor's kidney situation for transplantation instead of creatinine especially in ECD group which have higher level of inflammatory process; however, it cannot predict DGF or one-year outcome based on our study. More multicenter studies with higher sample size, imaging or histological assessment accompanied by sNGAL study and its comparison with other biomarkers may add light to the path much more.

Limitations of the study

The most important limitation in such studies including ours is a lot of contributors that may have an effect on occurrence of DGF and serum or urinary NGAL levels. We tried to contemplate most of them but it is impossible to control all with certainty. Moreover, it is better to conduct a study as a comparative research between equal numbers of same recipients with normal and increased donor's NGAL level and follow these two groups for graft function. This study design may reduce interfering factors.

Authors' contribution

Conceptualization: Mitra Mahdavi-Mazdeh.
Data curation: Mitra Mahdavi-Mazdeh, Somayeh Narimani.
Formal analysis: Somayeh Narimani.
Investigation: Somayeh Narimani.
Methodology: Mitra Mahdavi-Mazdeh, Somayeh Narimani.
Project administration: Mitra Mahdavi-Mazdeh.
Resources: Mitra Mahdavi-Mazdeh.
Supervision: Mitra Mahdavi-Mazdeh, Azam Alamdari, Farzanehsadat Minoo.
Validation: Mitra Mahdavi-Mazdeh, Somayeh Narimani, Farzanehsadat Minoo.
Visualization: Mitra Mahdavi-Mazdeh, Somayeh Narimani, Azam Alamdari.
Writing–original draft: Mitra Mahdavi-Mazdeh, Somayeh Narimani, Azam Alamdari, Farzanehsadat Minoo.
Writing–review and editing: Mitra Mahdavi-Mazdeh, Somayeh Narimani, Azam Alamdari, Farzanehsadat Minoo.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Tehran University of Medical Sciences. In addition to obtaining official written informed consent from donors' next-of-kin for organ donation for transplantation based on national act; consent was granted by donors' relatives for this study. Detailed information of the study objective and procedures were given to the recipients and individual formal consent were obtained prior to recruitment. The study was extracted from Somayeh Narimani thesis in the department of nephrology at this university (Thesis #877). The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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