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Gac Med Mex. 2016;152:582-6

Donor/recipient age index (DoRAIn) as an independent predictor of long-term living-donor renal graft function

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Abstract

Problem: *The effect of donor/recipient age disparity on living-donor renal graft function is controversial. The objective of this study is to find new clinical predictors of renal graft function and evaluate the effect of donor/recipient age disparity in our series.* **Methods:** *A retrospective review of our institutional renal transplantation database was performed. We calculated the glomerular filtration rate of our patients with the Chronic Kidney Disease Epidemiology Collaboration formula. Our receptors were categorized using a cut-off of 60 ml/min calculated glomerular filtration rate. An index called "Donor/Recipient Age Index" was created based on the interaction between donor/recipient ages. Univariable and multivariable regression analysis were performed. The Mantel-Cox model was used for statistical analysis.* **Results:** *A total of 220 donor/recipient pairs were selected from January 2005 to August 2013. Only 186 pairs completed the one-year follow-up. The mean age of the donors was 35.3 ± 10.4 years and 31.6 ± 11.7 years for the recipients. The Donor/Recipient Age Index significantly predicted a glomerular filtration rate < 60 ml/min at one-year follow-up in univariable (p = 0.02) and multivariable (p = 0.033) regression models.* **Conclusion:** *We propose the Donor/Recipient Age Index as a significant predictor of long-term graft function.* (Gac Med Mex. 2016;152:582-6)

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KEY WORDS: *Glomerular filtration rate. Living donor. Prognosis. Renal. Transplantation.*

Resumen

Problema: *El efecto en la disparidad de edad entre donador/receptor renal es controversial. El objetivo de este estudio es hallar nuevos predictores clínicos para la función del injerto renal y evaluar el efecto de la disparidad de edad entre donador/receptor renal en nuestra población.* **Métodos:** *Se realizó una revisión retrospectiva en la base de datos institucional de los postrasplantados renales. Se calculó el índice de filtrado glomerular (GFR) con la fórmula CKD-EPI. Los receptores fueron segmentados en función del GFR de 60 ml/min. El índice de edad donador/receptor (DoRAIn) evalúa la discrepancia de edad entre el donador y el receptor. Se realizó un análisis de regresión univariado y multivariado. El modelo de Mantel-Cox fue ocupado para el análisis estadístico.* **Resultados:** *Doscientas veinte parejas de donador-receptor fueron seleccionadas*

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Received for publication in modified version: 10-08-2015
Accepted for publication: 24-08-2015

de enero 2005 a agosto 2013. Únicamente 186 parejas completaron el año de seguimiento. La edad media de los donadores fue de 35.3 ± 10.4, y 31.6 ± 11.7 años para los receptores. El DoRAIn predice significativamente un GFR < 60 ml/min tras un año de seguimiento en los modelos de regresión univariado (p = 0.02) y multivariado (p = 0.033). **Conclusión:** *Proponemos el DoRAIn como un importante predictor de función a largo plazo del injerto renal.*

PALABRAS CLAVE: *Índice de filtrado glomerular. Donante vivo. Prognosis. Trasplante.*

Introduction

Since the first effective renal transplant by Dr. Joseph E. Murray in 1954[1], it has become one of the most studied and perfected procedures in modern medicine.

Due to the improvement in quality of life and reduced mortality in patients with chronic renal failure, as well as being cost-effective when compared with hemodialysis[2,3], renal transplantation has become the treatment of choice for all chronic nephropathies[4]. Despite this, early and chronic complications of renal transplantation are causing a loss of up to 34-41% of grafts during the first 10 years after transplantation[4]. Approximately 16.6% of transplanted patients will re-enter a kidney transplant list[5]. During the last 15 years the main focus has been the assessment, management, and research of immunological and non-immunological causes of acute graft rejection as they are the main risk factors for developing chronic allograft nephropathy[6]. As a result, rates of acute graft loss have decreased considerably. However, that has caused an oversight in the study of early detection clinical markers for long-term graft survival and function[7].

Materials and methods

A retrospective review of our institutional database of renal transplantation was performed. The database is prospectively maintained and authorized by our local Ethics Committee. This research complies with the Declaration of Helsinki and the Declaration of Istanbul. For analysis, only donor/recipient pairs with a complete one-year follow-up were selected. We calculated the glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula[8]. The receptors' GFR (rGFR) was calculated at one-year follow-up. Two groups were formed based on the rGFR, having 60 ml/min as a cut-off point. After analyzing the interaction between donor and receptor ages, we created an index called the "Donor/Recipient Age Index" (DoRAIn) using the following formula: (receptor age)/(donor age). A univariable and multivariable regression analysis was performed to identify potential prognostic variables for long-term graft function, specifically at one-year follow-up. In both models, the dichotomized rGFR was used as a dependent variable. The Mantel-Cox model was used for statistical analysis and statistical significance was established at $p < 0.05$. We used SPSS® v. 17.0 (IBM corp.) as an auxiliary statistical program.

Results

During this study, a total of 220 donor-recipient pairs were selected between January 2005 and August 2013. Only 186 pairs had a complete one-year follow-up and were included in analysis.

The donor group presented a higher percentage of female patients (47.3%), while the receptor group had a bigger number of male patients (55.4%). The mean age of the receptor group was 31.6 ± 11.7 years and 35.3 ± 10.4 for the donor group. All basal characteristics are listed in tables 1 and 2.

After final analysis, the mean DoRAIn obtained was 0.97 ± 0.45 for all pairs. A total of 108 pairs presented a DoRAIn < 1 (receptor younger than donor) and only 78 pairs presented a DoRAIn > 1 (receptor older than donor).

During univariable analysis, only two studied variables resulted as significantly related to the rGFR at one year: "graft dysfunction episode" during the one-year post-transplantation ($p < 0.001$) and DoRAIn ($p = 0.02$). The rest of the univariable regression analysis results are listed in table 3.

When the multivariable regression analysis was done, we found a significant statistical relationship between having a GFR < 60 ml/min at one-year post-transplantation and the receptors' gender ($p = 0.046$). Also, "a graft dysfunction episode" during the first year post-transplantation ($p < 0.001$) and DoRAIn ($p = 0.033$) resulted as significant. Table 4 shows the rest of the multivariable regression analysis.

Discussion

A previous retrospective study analyzed a cohort of renal grafts at 1, 5, 10, 15, and 18 years and determined

Table 1. Baseline characteristics of the sample

		Donor n (%)	Recipient n (%)
n		186 (100)	186 (100)
Gender	Male	88 (47.3)	103 (55.4)
	Female	98 (52.7)	83 (44.6)
Age (years)*		35.3 ± 10.4	31.6 ± 11.7
BMI (kg/m^2)*		25.0 ± 2.6	23.1± 3.6

*Average ± standard deviation.
BMI: body mass index.

Table 2. Relevant peri-operatory and follow-up variables

Variable	Description	
Induction pretransplant	None	25
	Thymoglobulin	15
	Daclizumab	78
	Basiliximab	68
Warm ischemia	3.3 ± 2.2 minutes	
Dialysis pretransplant	None	10
	Peritoneal	85
	Hemodialysis	69
	Unknown	22
Haplotypes	None	71
	One	96
	Two	19
PRA I	7.3 ± 16.8	
PRA II	4.9 ± 14.7	
1-year graft dysfunction	No	123
	Yes	63

PRA: panel reactive antibody.

that overall graft survival was 97.1, 92.3, 86.2, 77.6, and 60.3%, respectively. Therefore, there must be factors that affect graft function and survival over time. Donors and recipients have been studied to find those factors that could be treated during the life of a renal graft to improve its life expectancy.

Among the factors that proved to be predictors of graft function are body mass index (BMI) and the donor kidney volume[10-12]. The relationship between BMI and long-term failure of grafts follows a U pattern, where the most extreme values comprise those patients that have an elevated risk of graft failure[13]. Furthermore, one similar study found that obese patients (BMI > 30 kg/m^2) were related to delayed graft function, acute rejection, and graft loss[14].

Evaluating our results, the gender of the receptors presented a significant association with the prognosis of the GFR at one-year post-transplantation. Some studies suggest that grafts from male donors tend to have a better function in the long term than the kidneys donated by female patients[15,16]. It has been proved that receptors of female donor grafts present a lower survival rate at 1 and 10 years of follow-up[17]. Additionally, these receptors have a higher incidence of complications and require more hospitalizations[18]. Male characteristics that might explain these results are a higher GFR related to a larger kidney mass and larger number of glomeruli[19].

In addition to demographic and clinical factors, the measurements of serum markers, such as KIM-I,

Table 3. Results from the univariate regression analysis

GFR at 1 year	Variable	HR	95% confidence interval	p
< 60 ml/min	Pre-transplant induction	1.60	0.57-4.52	0.38
	Warm ischemia	1.06	0.92-1.22	0.41
	Pre-transplant dialysis	1.05	0.58-1.89	0.87
	Haplotypes	0.68	0.40-1.14	0.14
	PRA I	0.99	0.97-1.01	0.51
	PRA II	1.01	0.99-1.03	0.21
	1-year graft dysfunction Dichotomous (yes vs. no)	5.57	2.91-10.63	< 0.001
	Donor BMI	1.02	0.90-1.15	0.79
	Donor gender	1.57	0.82-3.03	0.18
	Recipient gender	1.28	0.67-2.44	0.46
	Recipient BMI	0.98	0.89-1.07	0.58
	DoRAIn (Continuous)	0.36	0.15-0.84	0.02

GFR: glomerular filtration rate; HR: hazard ratio; PRA: panel reactive antibody; BMI: body mass index; DoRAIn: Donor-Recipient Age Index.

Table 4. Results from the multivariate regression analysis

GFR at 1 year	Variable	Types of variable	p	HR	95% confidence interval	
					Minor interval	Minor interval
< 60 ml/min	Pre-transplant induction	Dichotomous (yes vs. no)	0.773	0.79	0.17	3.73
	Warm ischemia	Continuous (seconds)	0.919	0.99	0.82	1.19
	Pre-transplant dialysis	Categorical (HD/PD/none)	0.159	0.57	0.26	1.25
	Haplotypes	Categorical (0/1/2)	0.112	0.51	0.22	1.17
	PRA I	Discrete (percentage)	0.321	0.98	0.95	1.02
	PRA II	Discrete (percentage)	0.063	1.03	0.99	1.06
	1-year graft dysfunction	Dichotomous (yes vs. no)	0.000	7.64	3.17	18.42
	Donor BMI	Continuous (kg/m^2)	0.544	0.95	0.79	1.13
	Donor gender	Dichotomous (M vs. F)	0.668	1.22	0.49	2.98
	Recipient gender	Dichotomous (M vs. F)	0.046	2.57	1.02	6.49
	Recipient BMI	Continuous (kg/m^2)	0.572	1.04	0.92	1.17
	DoRAIn	Continuous	0.033	0.22	0.05	0.88

GFR: glomerular filtration rate; HR: hazard ratio; PRA: panel reactive antibody; BMI: body mass index; DoRAIn: Donor-Recipient Age Index; HD: hemodialysis; PD: peritoneal dialysis; M: male; F: female.

NAGL, NAG, or H-FABP, have been proposed as potential predictors of graft function and survival[20,21].

One of the first factors studied was the age of donors. Older ages of the donors impact future function of the grafts[10,22,23]. Likewise, receptors of grafts from donors younger than 65 years have better results in GFR and a higher survival rate at five years post-transplantation[23]. Moreover, donors older than 50 years present an elevated risk of increased creatinine levels after transplantation[24]. A small functional mass, increased interstitial fibrosis, and glomerular sclerosis are factors more frequently found in older donors that might explain the diminished long-term survival of the grafts[25].

The relationship between donor and receptor ages has been a subject of study during recent years. It has been proved that receptors from similar age donors tend to have a better graft prognosis[22] and differences of less than 20 years between the age of the donor and the recipient are related to lower creatinine levels at follow-up[18]. However, a novel study did not find a clear association between donor-receptor ages and graft survival[13,14].

Our research team proposes a novel index created to express the interaction between the age of the donor and the receptor. Additionally, we propose that this index, named DoRAIn, is a significant predictor of long-term graft function. After univariable and multivariable regression analysis, we found a significant correlation between DoRAIn and the risk of having a GFR < 60 ml/min at one-year follow-up after transplantation (HR: 0.21; p = 0.033).

Probably, this index may have a better discriminative capacity since it describes the interaction between donor/receptor ages in an objective and quantitative manner as an independent variable.

In conclusion, we propose that the calculation of DoRAIn is a simple index that could be used to find donor/recipient couples at risk of diminished graft function after transplantation. It is an easy method that can be calculated by all physicians. Further external validation should be pursued.

Our study has some limitations. Our sample size is still relatively small compared to other series. The immunosuppressive therapy was not analyzed because all patients usually receive a three-medication basic scheme in our institution; however it may pose a potential bias because doses and compliance were not included. The study population belongs only to our institute, so it would be advisable to extend the sample to other centers. A prospective analysis would improve results. The next goal is to validate this parameter with a longer follow-up and a wider multi-institutional sample.

References

1. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. J Am Med Assoc. 1956;160:277.
2. Landreneau K, Lee K, Landreneau MD. Quality of life in patients undergoing hemodialysis and renal transplantation: a meta-analytic review. Nephrol Nurs J. 2010;37:37-44.
3. Barnieh L, Gill JS, Klarenbach S, Manns BJ. The cost-effectiveness of using payment to increase living donor kidneys for transplantation. Clin J Am Soc Nephrol. 2013;8:2165-73.
4. McArthur C, Geddes CC, Baxter GM. Early Measurement of Pulsatility and Resistive Indexes: correlation with long term renal transplant. Radiology. 2011;259:278-85.
5. Haririan A, Nogueira JM, Zandi-Nejad K, et al. The independent association between serum uric acid and graft outcomes after kidney transplantation. Transplantation. 2010;89:573-9.
6. Meier-Kriesche HU, Ojo AO, Hanson JA, et al. Increased impact of acute rejection on chronic allograft failure in recent era. Transplantation. 2000;70:1098-100.
7. Tantravahi J, Womer KL, Kaplan B. Why hasn't eliminating acute rejection improved graft survival? Annu Rev Med. 2007;58:369-85.
8. Levery AS, Steverns LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Inter Med. 2009;150:604-12.
9. Saatchi M, Poorolajal J, Amirzagar MA, Mahjub H, Esmailnasab N. Long-term survival rate of kidney graft and associated prognostic factors: a retrospective cohort study, 1994-2011. Ann Transplant. 2013; 18:153-60.
10. Brenner BM, Milford EL. Nephron underdosing: A programmed cause of chronic renal allograft failure. Am J Kidney Dis. 1993;21:98-104.
11. Saxena AB, Busque S, Arjane P, Myers BD, Tan JC. Preoperative renal volumes as a predictor of graft function in living donor transplantation. Am J Kidney Dis. 2004;44:877-85.
12. Eschwege P, Trifa M, Randrianjohany A, et al. Effects of donor and recipient weight differences on serum creatinine levels in renal transplantation. Transplant Proc. 1995;27:2456-8.
13. Meier-Kriesche HU, Arndorfer Ja, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. Transplantation. 2002;73:70-4.
14. Pham PT, Danovitch GM, Pham PC. Kidney transplantation in the obese transplant candidates: to transplant or not to transplant? Semin Dial. 2013;26:568-77.
15. Kouli F, Morrell CH, Ratner LE, Kraus ES. Impact of donor/recipient traits independent of rejection on long-term renal function. Am J Kidney Dis. 2001;37:356-65.
16. Muller V, Szabo A, Viklicky O, Gaul I, Portl S, Philipp T, et al. Sex hormones and gender related differences: their influence on chronic renal allograft rejection. Kidney Int. 1999;55:2011-20.
17. Zeier M, Dohler B, Opelz G, Ritz E. The effect of donor gender on graft survival. J Am Soc Nephrol. 2002;13:2570-6.
18. Dharnidharka VR, Agodoa LY, Abbott KC. Risk factors for hospitalization for bacterial or viral infection in renal transplant recipients—an analysis of USRDS data. Am J Transplant. 2007;7:653-61.
19. Tan GC, Kim JP, Chertow GM, Grumet FC, Desai M. Donor-Recipient sex mismatch in kidney transplantation. Gend Med. 2012;9:335-47.
20. Nauta FL, Bakker SJ, van Oeveren W, et al. Albuminuria, proteinuria, and novel urine biomarkers as predictors of long-term allograft outcomes in kidney transplant recipients. Am J Kidney Dis. 2011;57:733-43.
21. Choi HM, Park KT, Lee JW, et al. Urine neutrophil gelatinase-associated lipocalin predicts graft outcome up to 1 year after kidney transplantation. Transplant Proc. 2013;45:122-8.
22. Molnar MZ, Streja E, Kovesky CP, et al. Age and the associations of living donor and expanded criteria donor kidneys with kidney transplant outcomes. Am J kidney Dis. 2012;59:841-8.
23. Øien CM, Reisaeter AV, Leivestad T, Dekker FW, Line PD, Os I. Living donor kidney transplantation: the effects of donor age and gender on short and long term outcomes. Transplantation. 2007;83:600-6.
24. Chen GD, Gu JL, Zhang XD, Qiu J, Wang CX, Chen LZ. Donor factors predictive for poor outcomes of living donor kidney transplantation. Transplant Proc. 2013;45:1445-8.
25. Tan JC, Busque S, Workeneh B, et al. Effects of aging on glomerular function and number in living kidney donors. Kidney Int. 2010;78: 686-92.