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Measurement of the value of the arterial resistance index using doppler in the function of the renal graft at medium and long term

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ABSTRACT

Objective: To evaluate the association between the value of the arterial resistance index (RI) measured by Doppler at the month after transplantation, and the loss of graft. Secondary outcomes of loss greater than or equal to 50% of renal function, death with functioning graft, biopsy findings (inflammation, hyalinosis, rejection, interstitial fibrosis - tubular atrophy, IFTA) are reported.

Methods: A cohort study of 66 patients, who underwent renal transplantation at San José Hospital of Bogotá between October 2007 and April 2011. The RI of the hilar artery was measured by Doppler ultrasound at the month post-transplant. Most patients had follow-up until the second year. We describe the cumulative incidence of renal graft loss, loss greater than or equal to 50% of the glomerular filtration rate. At the second year after transplantation, rejection, IFTA, hyalinosis and documented inflammation were reported in protocol biopsies. Association analysis was performed on the histological outcomes.

Results: only 2 cases of renal graft loss were reported, belonging to the group with normal RI (3.8%). At 3 years of follow-up, 5 patients had lost more than 50% of GFR compared to baseline, 4 occurred in patients with RI <0.8, 2 of them (3.7%) ocurred in the first year and only one patient with RI> 0.8 ocurred at 3 years. The median GFR at 3 years of follow-up in both groups is greater than 60 ml / min. In the first year of follow-up 22 (47%) patients with normal RI had IFTA, and 7 (54%) with RI> 0.8 had IFTA. Hyalinosis was reported for 23% with RI> 0.8 and 25.5% with RI <0.8.

Conclusion: the outcome of the grafts depends not only on RI, but also on factors such as cold ischemia, induction and maintenance immunosuppressive treatment, degree of incompatibility between donor and recipient.

Histopathological changes such as IFTA, inflammation, hyalinosis, were observed in both groups, suggesting that there are other factors stronger than the RI, which correlates with the occurrence of these findings.

Key Words: Renal graft, Arterial resistance index, Glomerular filtration rate.

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Valor del índice de resistencia arterial medido por Doppler en la función del injerto renal a mediano y largo plazos

RESUMEN

Objetivo: evaluar la asociación entre el valor del índice de resistencia arterial (IR) medido por doppler al mes postrasplante y la pérdida de injerto. Se reportan los desenlaces secundarios de pérdida mayor o igual al 50% de la función renal, muerte con injerto funcionante, hallazgos de la biopsia (inflamación, hialinosis, rechazo, fibrosis intersticial - atrofia tubular, IFTA, por sus siglas en inglés).

Métodos: se realizó un estudio de cohorte de 66 pacientes, que recibieron trasplante renal, del Hospital San José de Bogotá, entre octubre de 2007 y abril de 2011; se midió el IR de la arteria hilar por ecografía doppler al mes postrasplante. La mayoría de los pacientes fueron seguidos hasta el segundo año. Se describe la incidencia acumulada de pérdida del injerto renal, pérdida mayor o igual al 50% de la tasa filtración glomerular; al segundo año postrasplante se reporta el rechazo, IFTA, hialinosis e inflamación documentada en las biopsias de protocolo. Se realizó análisis de asociación en los desenlaces histológicos.

Resultados: solo se reportaron 2 casos de pérdida del injerto renal, pertenecientes al grupo con IR normal (3.8%). A los 3 años de seguimiento 5 pacientes habían perdido más del 50% de la TFG respecto a la basal, 4 ocurrieron en los pacientes con IR <0.8, 2 de ellos (3.7%) fueron al primer año y solo un paciente con IR >0.8 a los 3 años. La mediana de la TFG a los 3 años de seguimiento en ambos grupos es mayor de 60 ml/min. En el primer año de seguimiento 22 (47%) pacientes con IR normal presentaron IFTA y 7 (54%) con IR >0.8 presentaron IFTA; la hialinosis con un 23% para IR >0.8 y 25.5% para IR <0.8.

Conclusión: los desenlaces de los injertos no solo dependen del IR, hay otros factores que pueden influir como es el tiempo de isquemia fría, esquema de tratamiento inmunosupresor de inducción y mantenimiento, grado de incompatibilidades entre donante, receptor.

Cambios histopatológicos como IFTA, inflamación, hialinosis, se observaron en cualquiera de los 2 grupos, lo que sugiere que hay otros factores más fuertes que el IR, que se correlaciona con la aparición de estos hallazgos.

Palabras clave: Injerto renal, Índice de resistencia arterial, Tasa de Filtración Glomerular.

Introduction

In terms of survival and quality of life, renal transplantation is nowadays the best therapeutic option for patients with chronic renal failure1. Great advances in induction and maintenance immunosuppressive regimens with mycophenolate sodium and mofetil, calcineurinics, M-tor inhibitors, have increased survival in patients and renal grafts during the years after transplantation, from a 70% reported in the early 1990s to 90% today[1,2]. Despite this, long-term renal survival, ie, after the first year of transplantation, has not improved the same way and about 50% to 80% of renal grafts are lost within the first 10 years. But what we do not have fully understood is whether there is any method of outcomes prediction[3,4].

The most frequent cause of non-renal etiology of graft loss remains cardiovascular disease[5], followed by the development of malignant neoplasias precipitated by some of the immunosuppressive regimens[6] Other causes are renal irreversible alterations secondary to immunological processes, which can be observed in the renal biopsy, such as: IFTA and its correlation with the degree of alteration (IFTA GI alteration from 5% to 25%, IFTA GII alteration from 26% to 50 %, IFTA GIII greater than 50%)[7].

For the identification of renal graft recipients who are at risk of late loss, diagnostic strategies have been proposed that lead to therapeutic interventions. Aditionally, multiple risk factors with limited predictive values have been designed in the literature[8,9]. One of these factors is the use of RI, of the renal graft, measured by Doppler ultrasound as a predictor of late-onset dysfunction8. Literature evaluating the value of RI equal or greater than 0.8 as a risk factor for graft dysfunction has been documented with encouraging results in terms of its role in establi-

shing the prognosis of the function in the long term. However, the studies present some methodological limitations[10,11].

There are publications in which it is argued that perhaps the RI is a predictor of atherosclerotic disease or rather reflects a complex integration between peripheral resistance, distensibility and arterial pulsatibility, which are associated with other traditional cardiovascular risk factors. But not a specific marker of renal damage, therefore its clinical usefulness in the diagnosis of graft rejection or loss would be limited[12].

Research points out that the best understanding of the RI / chronic graft nephropathy ratio is through the correlation of ultrasound measurements and histological examination of renal biopsies[13,14].

Objective

The objective of this study was to evaluate the association between the value of RI measured by Doppler at the first month after transplantation and the loss of graft. Secondary outcomes, loss of 50% or more of renal function, death with functioning graft, and findings of renal biopsy are reported; inflammation, rejection, hyalinosis, and IFTA.

Methods

Patients and study design

The protocol was approved by the Research and Ethics Committee of the University Foundation of Health Sciences - San José Hospital.

It was a prospective cohort with 3-year follow-up. All consecutive cases that met the inclusion criteria were recruited: older than 18 years who underwent a kidney transplant at the Hospital San José of Bogotá and had RI measurement at first month after transplant. Patients persisting on slow function (diuresis less than 100 cc / hour or less than 30% decrease in baseline creatinine without dialysis requirement) or delayed function (post-transplant dialysis requirement, secondary to renal graft dysfunction) were excluded for more than four weeks after transplantation and the presence of mechanical complications that had not been corrected at the time of RI measurement.

Color Doppler ultrasound was performed in the hilar artery at the end of the first month after transplantation, choosing this time to ensure recovery of graft function from any type of acute injury. All procedures were performed with the Toshiba Nemio 20 equipment, using a 2-4 MHz transducer, in the radiology service. The RI was obtained from the following formula: peak systolic velocity - peak velocity at the end of diastole / systolic peak velocity. It was stratified as less than 0.8 and greater than or equal to 0.8, interpreted as normal and abnormal, respectively[5,6].

The glomerular filtration rate was calculated at the first month (baseline), the first year using the MDRD formula, with annual monitoring of the glomerular filtration rate for 3 years. By protocol of the service, from the year 2007 all the patients are taken to graft biopsy between the sixth month and the first year after transplant, unless they have some contraindication.

Statistic analysis

The analysis was carried out using the program S tata® version 10. Using descriptive statistics the quantitative variables are summarize with measures of central tendency and dispersion. Boxes and mustache charts and graphs are presented to describe the evolution of the glomerular filtration rate. Qualitative variables are presented as absolute frequencies and percentages. We report the cumulative incidence of renal graft loss, 50% loss of GFR and death. The second year after transplantation, rejection, IFTA, hyalinosis and documented inflammation were reported in protocol biopsies. Association analysis was performed on the histological outcomes.

Results

We analyze 66 cases admitted to the cohort between October 2007 and April 2011. The baseline demographic characteristics of the population according to the RI are described in Table 1.

Table 1. Demographic and clinical characteristics according to the arterial resistance index (RI)

	RI <0.8		RI ≥0.8	
	n	(%)	n	(%)
	53	(80.3)	13	(19.7)
Age (average DE *)	42.3	(13.0)	49.2	(13.0)
Min MAX		(18-65)		(26-74)
Gender, n (%)				
Male	17	(32.1)	4	(30.1)
Etiology chronic kidney disease in natives, n (%)				
arterial hypertension	14	(26.4)	4	(30.7)
Mellitus diabetes	5	(9.4)	2	(15.3)
Glomerular disease	7	(13.2)	0	0
Polycystic disease	0	0	1	(7.6)
Systemic lupus erythematosus	2	(3.7)	1	(7.6)
Interstitial nephritis	0	0	0	0
Other	5	(9.4)	1	(7.6)
Unknown	20	(37.7)	4	(30.7)
Cold ischemia, mean hours	12	(8,14)	12	(12,13)
Less than 12 hours n (%)	28	(52.8)	7	(53.8)
12- 24 hours n (%)	25	(47.2)	6	(46.2)
Type of donor n (%)				
cadaverous	47	(88.7)	13	(100)
Alive	6	(11.3)	0	
Marginal donor n (%) ‡	3	(5.6)	3	(23.1)
Miss match de HLA §, n (%)				
0	1	(1.8)	0	
1	2	(3.7)	0	
2	8	(15.9)	1	(7.6)
3	16	(30.1)	5	(38.4)
4	16	(30.1)	4	(30.7)
5	7	(13.2)	2	(15.3)
6	3	(5.6)	1	(7.6)

The woman / man ratio is 2: 1. The mean age in patients with RI less than 0.8 was 42.3 years and RI> 0.8 was 49.2 years. The proportion of patients with hypertension and diabetes mellitus as a cause of renal failure was lower among those with normal RI, 26.4% and 9.4%, respectively, compared to 30.7% and 15.3% in the population with abnormal RI. The proportion of patients with an unknown cause of chronic renal failure was higher among those with normal RI (37.7% vs. 30.7%).

The median time of cold ischemia for the entire cohort was 12 hours (RIQ 8-14). The majority of renal

grafts were from cadaveric donors, 89% for the RI group <0.8 and 100% for the RI> 0.8, with 3 marginal donors in each group.

The degree of HLA incompatibility between donor and recipient that predominated in the two groups was 3 and 4 in 60.2% for normal RI and 69.1% for abnormal RI.

The most commonly used induction regimen in the two RI groups was basiliximab in 64%. The immunosuppressive treatment based on tacrolimus, mycophenolate and corticoid was used in 41 cases (77.3%) of patients with normal RI and in 8 cases (61.5%) of patients with abnormal RI.

The majority of patients in the two groups had immediate graft function, 39 subjects (73.6%) with normal RI and 9 subjects (69.2%) with abnormal RI. Slow graft function was present in 6 patients with normal RI (11.3%) and one patient with abnormal RI (7.6%). Delayed graft function was present in 15% of patients with normal RI and in 23.1% of patients with abnormal RI. Acute tubular necrosis was the most frequent cause of delayed function in both groups.

In patients with normal RI, 3 mechanical complications were observed (5.7%) and in patients with abnormal RI, mechanical complications were observed (7.7%), all secondary to ureterovesical fistulas. It should be noted that at the time of measurement of the RI at the month after transplantation these fistulas were already corrected. We presented a case (1.9%) of vascular complication corresponding to an alteration at the level of the venous vascular anastomosis with delayed graft function and requiring warfarin indefinitely as a treatment, reason for which renal biopsy was not performed.

Two rejection events were identified in the first month after transplantation from patients with normal RI (3.8%) with adequate response to steroids and without loss of renal function.

The outcomes according to RI are represented in table 2. Death with functional graft was present in 3 cases with normal RI (5.6%), 1 secondary to septic process of abdominal origin and 2 due to cardiovascular cause. They all occurred before the end of the first year post-transplantation, whereas in patients with abnormal RI only one case (7.7%) was found secondary to a cardiovascular event; also before the first year after transplantation. Two cases of renal graft loss (3.8%) belonging to the normal RI group are reported: One corresponds to the development of nephropathy by polyoma virus. No graft loss was found in the group with abnormal RI. The loss of more than 50% of the GFR compared to the baseline one year of follow-up was present in 2 patients (3.8%) with normal RI; With a total of 5 patients at 3 years of follow-up, of which only one presented with RI> 0.8 and occurred at 3 years.

In the first year of follow-up, 22 (47%) patients with normal RI had IFTA, most of them classified as grade I-severity IFTA in 32.6%. Among patients with abnormal RI, 7 (54%) presented IFTA classified as grade I in 46.1%. After the first year of follow-up, protocol biopsies were performed, showing an increase in global IFTA: 33 patients (65%) in patients with RI <0.8 and 10 patients (77%) with RI> 0.8. In addition, a greater than 50% increase in the degree of IFTA classified as grade II was observed with respect to the first protocol biopsy for both groups, without changes in grade III IFTA.

We identified any type rejection in protocol biopsies (most subclinical features) at the first month, first year and after year. Up to the first year 13 patients (24.5%) with normal RI and 3 patients (23%) with abnormal RI had presented some type of graft rejection. But with the follow-up of the protocol biopsies in the second year, it was observed that the incidence of rejection in both groups increased to 31.4% with RI <0.8 and 38.4% to those of RI> 0.8.

In this cohort, a nearly similar percentage of hyalinosis was observed in the two groups of patients, with a 23% for RI> 0.8 and 25.5% for RI <0.8. Aditionally, 2 of the 3 patients converted to Mtor in the group ≥0.8 presented hyalinosis and 5 of the 13 patients in the RI group <0.8 presented it.

The presence of some degree of interstitial inflammation was evident in 61% of patients with RI <0.8 and in 61.5% of RI patients greater than 0.8, with greater severity of inflammation in the group of RI <0.8.

Twenty conversions were made to inhibitors of the M-tor complex, 14 with normal RI (26.4%) and 6

Table 2. Outcomes according to arterial resistance index

	IR <0.8		IR ≥0.8	
	N	53	n	13
Death with working graft n (%)	3	(5.7)	1	(7.7)
Loss of graft * n (%)	2	(3.8)	0	
Loss TFG ≥50% at 1 year n (%)	2	(3.7)	0	
Loss TFG ≥50% at 2 years n (%)	2	(3.7)	0	
	0		1	(7.7)
TFG month post-transplant MDRD†				
MDRD median (RIQ)	64	(48.3-72.3)	58	(49.8-70.6)
Mín-MAX	12.7	(138.5)	22.7	(100.1)
TFG 1 year post-transplant MDRD†				
MDRD median (RIQ)	67.8	(56.9-86.2)	64.4	(59.1-82.8)
Mín-MAX	18.7	(138.5)	32.1	(102)
TFG at 3 years post-trasplant MDRD†				
MDRD median (RIQ)	65.2	(48.9-70.7)	64.6	(60.1-71.5)
Mín- MAX	44	(118)	25	(105)
I Severity IFTA at the first year of transplantation	15	(32.6)	6	(46.1)
II	5	(10.8)	1	(7.7)
III	2	(4.35)	0	0
Severity IFTA up to 2 years of transplantation §				
I	22	(42.3)	8	(61.5)
II	11	(21.1)	2	(15.3)
III	1	(1.9)	0	
Any rejection of the renal graft at the first year	13	(24.5)	3	(23.1)
Any rejection of the renal graft at the second year §	16	(31.4)	5	(38.4)
Hyalinosis §	13	(25.5)	3	(23)
Inflammation §	31	(61)	8	(61.5)
Conversion to inhibitors of the M-tor n complex (%)	14	(26.4)	6	(46.1%)

* Two-year follow-up of 53 patients. † Median glomerular filtration rate calculated by MDRD 1 year 64 follow-up patients, at 3 years with 34 follow-up patients. ‡ BANFF Classification 2009 Mild <25% of the cortical area. Moderate 26-50% Severe> 50%. Data are available for 43 patients with normal RI and 12 patients with abnormal RI. § For 2nd year biopsies hyalinosis, inflammation, rejection are available data for 51 patients with normal RI and 13 for abnormal RI.

with abnormal RI (46.1%). Twelve of all conversions were performed during the first 6 months after transplantation. Of the patients with normal RI converted to M-tor inhibitors, 2 (3.8%) lost more than 50% of GFR at the first year. The first of them at 3 months due to a polyoma virus nephropathy that led to the loss of Graft function at 10 months after transplantation. The second patient for a humoral rejection. Of the patients with abnormal RI, none lost more than 50% of GFR at 1 year and only 1 patient

Table 3. Outcomes of patients converted to inhibitors of the M-tor complex

	IR < 0.8	IR ≥ 0.8
	n (%)	n (%)
	53	13
Number of patients converted n (%)	14 (26.4)	6 (46.1)
Loss of GFR ≥50% per year * n (%)	3(5.6%)	0
Functional graft death n (%)	0	1 (7.6%)
Loss of graft n (%)	1 (1.8%)	
Severity IFTA at the first year of transplantation †		
I	5(9.4%)	3 (23%)
II	2 (3.7%)	0
III	2 (3.7%)	1 (7.6%)
Hyalinosis	5 (9.4)	2(3.8)
Rejection of the renal graft at the first year	0	0
* Accumulated incidents. † Data available for 20 patients		

converted to M-tor inhibitor showed a 50% decrease in GFR occurring at the third year of follow-up. Hyalinosis was present in 5 patients with RI <0.8 and 2 patients with RI> 0.8. Twelve patients presented IFTA, degree of severity III, two patients all with normal RI. There were no rejections of renal grafts (Table 3).

Figures 1 and 2 show changes in the glomerular filtration rate during the first and second year, respectively. It can be observed that the median baseline glomerular filtration rate is lower in the RI group> 0.8 almost 6 ml / min and subsequently in the 2 groups it remains stable during the two years of follow-up. There does not seem to be a moment in time where there are representative changes in the rate of glomerular filtration.

The median glomerular filtration rate calculated by MDRD in the 2-year follow-up with 54 patients and at 3 years with 34 patients remains greater than 60 ml / min (Table 4).

32.4% of patients with normal RI and 25% with abnormal RI did not lose more than 30% of GFR compared to baseline at one year of follow-up. These same outcomes in the 2 groups are shown in Figure 3 At follow-up, 3 cases of polyoma virus nephropathy were present, one of them before reaching one year of transplantation and the graft function was lost. The other two had elevated serum creatinine levels but did not require renal replacement therapy.

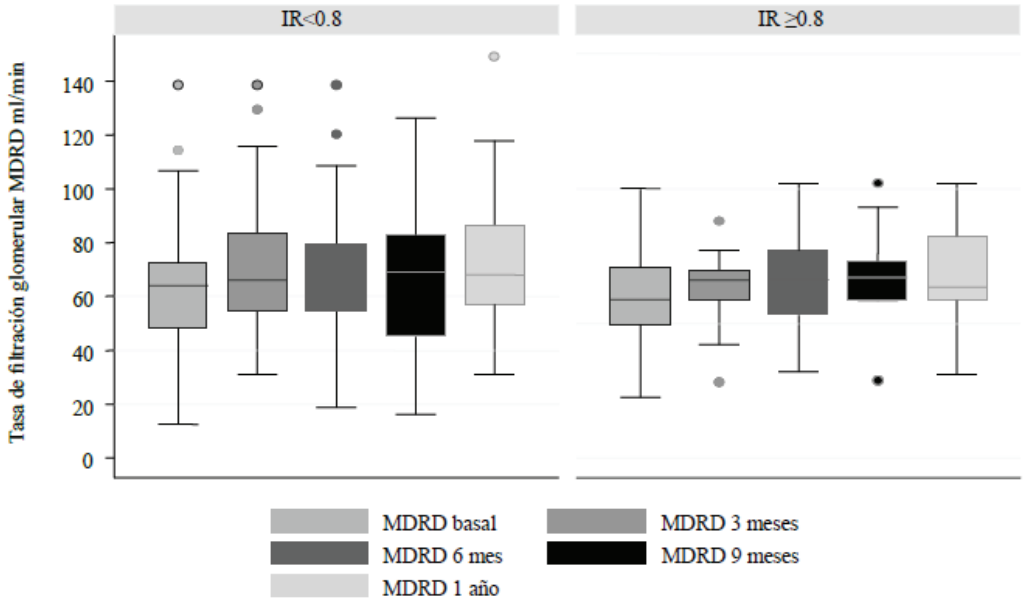
Discussion

Major advances in immunosuppression regimens have allowed a greater increase in patient and renal graft survival in the first year after transplantation; from 70% reported in the early 1990s to 90% today[1,2]. However, long-term survival has not improved in parallel and between 50% and 80% of renal grafts are lost within the first 10 years. This has led to the implementation of early diagnostic strategies in order to diagnose patients at high risk of losing the renal graft. The controversy arises to find the most timely, effective and effective tool to help us make therapeutic decisions that are of long term benefit.

There are several studies in the literature that evaluate the value of RI as a risk factor for late graft function, with encouraging results in terms of its role in establishing the prognosis of graft function in the long term. Several publications are in favor of and against the evaluation of the relationship between RI

Graph 1.

Changes in GFR, control 12 months after transplantation



Graph 2.

Changes in GFR, control 24 months after transplantation

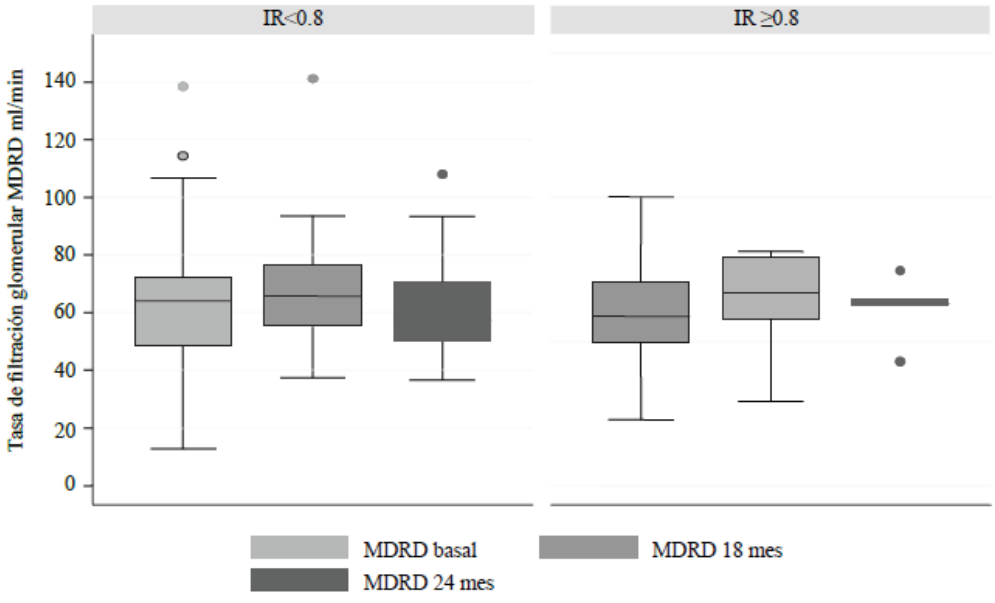


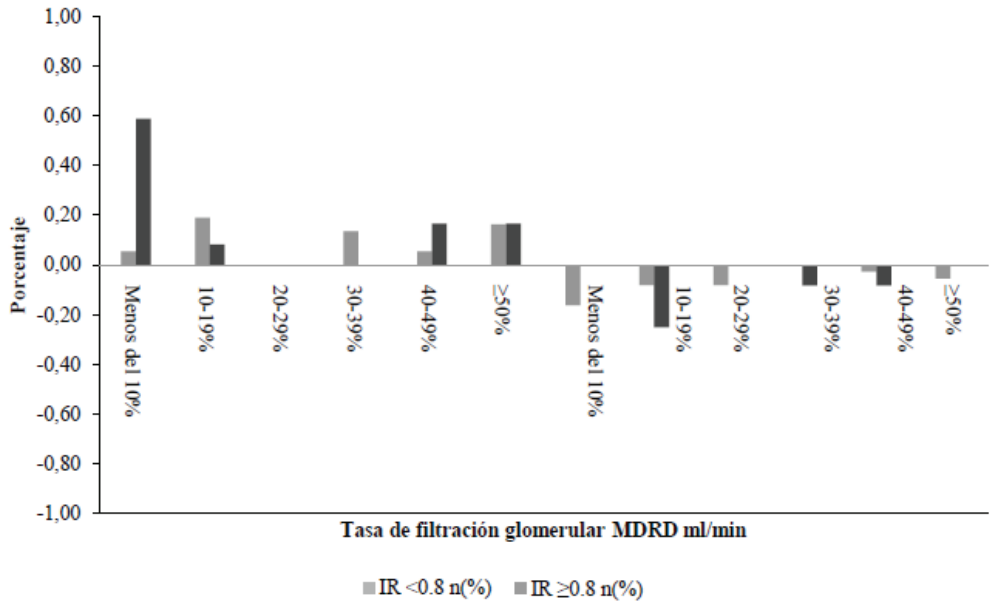
Table 4. Changes in the glomerular filtration rate (MDRD) according to resistance index

		TFG basal *	TFG 3 meses †	TFG 6 meses‡	TFG 9 meses §	TFG 12 meses‖	TFG 24 meses¶	TFG 36 meses **	TFG 48 meses††
IR <0.8	Mediana (RIQ)	64 (48.3-72.3)	66 (51.3-83.6)	67.1 (54.4-79.6)	69.2 (45.1-82.8)	67.8 (56.9-86.2)	71.3 (61.3-83.8)	65.2 (48.9-70.7)	67.8 (56.5-78.1)
IR ≥0.8	Mediana (RIQ)	58.8 (49.8-70.6)	66.1 (58.8-70)	66.3 (53.1-77)	66.9 (58.4-73)	64.4 (59.1-82.8)	68.5 (66.6-70.4)	64.6 (60.1-71.5)	67 (63.2-70.5)

* Available data for 53 patients. † Data available for 51 patients with normal RI and 13 patients with abnormal RI. ‡ Data available for 45 patients with normal RI and 13 patients with abnormal RI. § Available data for 39 patients with normal RI and 10 patients with abnormal RI. || Data are available for 45 patients with normal RI and 13 patients with abnormal RI. ¶ Data available for 43 patients with normal RI and 11 patients with abnormal RI. ** Data available for 26 patients with normal RI, and 8 with abnormal RI. †† Data are available for 9 patients with normal RI and 4 patients with abnormal RI.

Graph 3.

Percentage of patients with increase and loss of GFR, control 12 months after transplantation



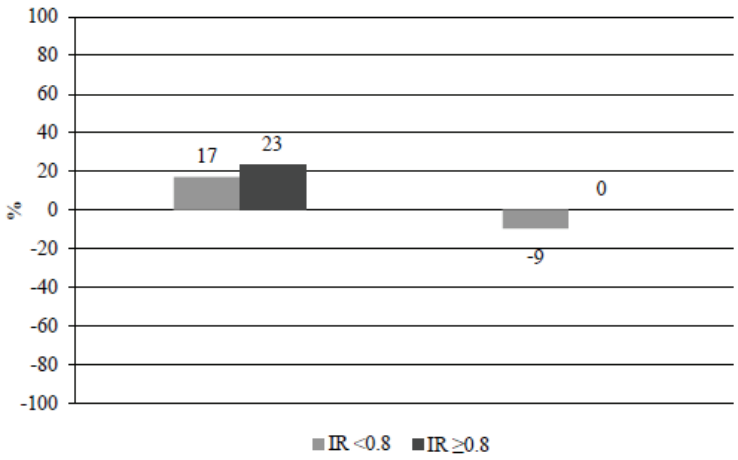
and renal graft function over time, with the aim of having a noninvasive measure that serves as a predictor of survival with clinical impa[8,9,15,16].

Radermacher performed a 36 months of follow-up with 601 transplanted patients, showing that those with RI> 0.8 had a relative risk (RR) of 9.1 (CI 6.6-12.1) for graft loss in 2.5 years[11], and concluded that RI greater than 0.8 correlate with a high risk of renal graft loss, even in the multivariate análisis. However, RI measurement was not performed at a stipulated point, only at follow-up, which may lead to erroneous conclusions of the results.

Saracino, in a retrospective study with 76 patients and follow-up period of 100 months decreases the cut-off point of the RI, with results showing that those with values greater than 0.63 had a GFR deterioration of 24% with a RR of 3.77 (CI 1.5-12) with a close correlation with the age of the donor and recipient[15].

Graph 4.

Increase of GFR more than 50% with respect to baseline, cumulative incidence.



Nezami, years later, also describes the same significant association between RI and serum creatinine levels measured at the first month post-transplant in a retrospective cohort of 273 patients. The conclusión was that the presence of stenosis in the renal artery can falsely give normalized values[13]. In spite of these studies, other authors discuss the fact that the RI can have clinical value in relation to the function of the graft in the time; Kebkowska showed no relationship to GFR at month of transplant in a prospective cohort of 41 patients, RI between 0.74-0.76[14]. Bergman, in a prospective 36-month study, evaluated 200 transplant patients finding correlation of the glomerular filtration rate with age, presence of diabetes or cardiovascular disease, and particularly with levels of ADMA (dimethyl arginine asymmetric), a uremic toxin well described as a cause of arterial hypertension in uremic patients; However, there was no association with RI[13].

Trying to establish a link between abnormal RI and GFR that explains the relationship found, very few studies have addressed the findings of renal protocol biopsies and the RI association with RI. Vallejo, in a retrospective study that included 87 patients, described that the highest RI grafts (0.85) showed a higher glomerulitis score in the pathology. Nevertheless, there was no correlation between RI and chronic graft nephropathy[18].

Kirkpantur[19] in a series of transplant patients found that an RI greater than 0.75 was associated with increased glomerular sclerosis, interstitial fibrosis and severe arteriosclerosis. The evidence in this topic is very limited, but it is expected that with the accomplishment of protocol biopsies, as part of the follow-up in transplanted patients, more progress will be identified.

The increase of RI per month is still observed in our patients with older, diabetic and hypertensive patients; this phenomenon perhaps associated to the greater presence of atherosclerosis.

The minority of the population transplanted in our center comes from a living donor and, as in the literature[20], no increase in RI was found in this group of patients, probably related to surgical factors, shorter times of cold ischemia and less HLA incompatibility in comparison with cadaveric donor graft recipients. It is known that the time of cold ischemia is a determinant factor in the survival of the grafts[21,22], such that those patients with times less than 12 hours of cold ischemia would not have to raise their RI and the graft would have better survival. In this study patients with less than 12 hours of cold ischemia elevated RI. In agreement with publications already made, the data reveal that cold ischemia alone does not determine the increase of the RI[23].

Regarding immunosuppressive medical treatment, it has been observed in some articles[24], and in this one, that the induction schemes did not clinically contribute any significant difference on RI. However, with maintenance regimens if a trend was observed in patients taking ciclosporin to elevate RI, whereas patients taking tacrolimus did not. A greater number of patients in the RI arm greater than 0.8 were converted to M-tor inhibitors, and this may be one of the explanations why the glomerular filtration rate in this group of patients started with a baseline mean Of 6ml / min lower than the RI group <0.8, is maintained in the long term.

In the studied cohort, patients once transplanted usually had immediate RI graft independent function. According to a previous study[25], patients who presented more delayed-function events revealed an abnormal RI, this is explained that since after the impact of hemodialysis vascular resistance and hemodynamics vary, thus altering the RI. Slow graft function was expected to predominate in patients with abnormal RI, or otherwise the same frequency was found in both groups. The data demonstrate that it is greater in the patients with normal RI being its main cause the acute tubular necrosis. The rate of acute tubular necrosis was similar for the 2 groups, suggesting that mechanical complications may be more valuable for slow graft function, without altering the RI, since at the moment of measurement this complication is already present is corrected. The vascular complication was presented in patients with normal RI, it was of venous characteristics such that the artery remained undamaged and therefore the RI was not affected.

As mentioned above, there are studies that support the relationship between graft survival with normal RI; however in the results of this study it was not expected that when comparing the cohort, patients with normal RI although in a small proportion would present more events of graft loss than patients with abnormal RI. When the cases of graft loss are analyzed specifically, it is observed that there was no way to show that the RI measured in time would lead to its loss. This shows that not all patients with normal RI taken at the first month post-transplant will develop favorable outcomes for the graft, likewise not all patients with abnormal RI will lose at least the first 3 years of grafting.

In contrast to the previously mentioned in the literature, the main cause of death with a functioning graft was of cardiovascular etiology and the highest percentage was observed in patients with abnormal RI[12,14], since perhaps the RI in this case is related to the main disease atherosclerotic of the patient and not a renal injury per se.

During this study it was observed that patients with RI greater than 0.8 had a lower glomerular filtration rate (6 ml / min) than those in the group with RI <0.8, which for some authors may be of vital importance[26]. At the 3-year follow-up period the glomerular filtration rate was balanced, this can be explained by the greater therapeutic intervention in this group of patients and leads to the conclusion that RI in the studied population does not determine the outcome of GFR. At 3 years of follow-up, it was observed that patients with normal RI had a loss ratio of more than 50% of GFR than those of abnormal RI, this alerts the nephrologist because it goes against what is known today, observing that patients with normal RI can severely deteriorate theRI GFR every year. This shows that RI alone is not the only intervention that can affect the GFR of the graft, there are others (time of cold ischemia, surgical complications, induction and maintenance schemes, infections, drug choice, among others, Table 4) . This statement indicates that all interventions that are performed to increase or avoid the reduction of glomerular filtration rate over time should be performed, since a patient with abnormal RI may improve his GFR significantly, including 12 months After transplantation. It should be remembered that RI is performed at the first month after transplantation, thus reflecting the status of the graft in a single moment; Perhaps if RI measurements were made along with increases in glomerular filtration rates there would be some difference. In our population it is impossible to assure that patients with abnormal RI are destined to lose the graft or to reduce glomerular filtration rates.

The median glomerular filtration rate at follow-up in the first, second, and third year was almost similar in the 2 RI groups, with an average of greater than 60ml / min. In addition, many of these patients

had early histological changes in the protocol renal biopsy, so that, as in the literature[26,27], changes in the glomerular filtration rate are not associated in the first years with the presence of histological findings of poor prognosis. More closely monitored studies are needed to see at what point in the follow-up the deterioration curve of renal function and the histological findings in protocol biopsies begin to correlate.

Graft biopsies guide the clinician toward decision making and are strongly useful in determining the prognosis of graft and chronic nephropathy. There are few publications that attempt to correlate RI with histological findings[19]. In this study, more than 80% of the population, of the 2 groups, underwent protocol biopsy and despite all the measures known to prevent chronic graft nephropathy, this remains the most frequent finding even with normal RI ; In addition other histopathological findings of poor prognosis such as IFTA, interstitial inflammation, arteriolar hyalinosis, were found with equal proportion in both groups. This shows that not all patients with normal RI will have good histological outcomes.

Histologic changes in renal graft biopsy demonstrating chronicity such as IFTA, hyalinosis, were observed in both groups.

In the literature[28] different RI cut-off points are reported with histological changes. We have tried to find the cutoff point for RI in this study population with greater sensitivity and specificity, however, given the low percentage of outcomes and the follow-up time, it was impossible to prove it.

Immunological rejection is a frequent cause of early and late kidney transplant dysfunction. There are several types of immune reaction such as acute and chronic humoral acute rejection of allograft with clinical and histological demonstrations in renal biopsies, which require the presence of anti-HLA antibodies for diagnosis. The criteria of Banff[26] are uniform biopsy application criteria for the diagnosis of renal graft rejection, which are updated periodically and constitute the basis for deciding prognosis and treatment. In this population the immunological rejection, mostly of subclinical characteristics, occurred in equal proportion in both RI groups, in the first year. In the second year protocol biopsy, the percentage in the RI group> 0.8 increased, so rejection may occur independently of RI, and its onset may be more correlated with other factors (Miss match, type of Donor, induction and maintenance treatment etc.).

Conclusion

The outcomes of the grafts are not only dependent on RI, but other factors that can influence such as cold ischemia time, induction and maintenance immunosuppressive treatment schedule, degree of donor / recipient incompatibilities, among others. The increase or loss of glomerular filtration rate does not appear to correlate with RI.

Histopathological changes such as IFTA, inflammation, hyalinosis in this studied population were observed in any of the 2 RI groups with equal proportion, suggesting that there are other stronger factors that correlate with the appearance of these histological findings.

It is necessary to take into account the limitations of the study. It's a descriptive study, with low frequency of outcomes and short follow-up, so it does not allow evidence of RI as a single causality of the outcomes.

Only the performance of a multicenter study, which allows to recruit more population with multivariate analysis in the future, will be able to determine the true impact of RI on the glomerular filtration rate of the graft in the long term.

The findings suggest that the measurement of RI at the first month after transplantation is an important tool that can guide the clinician with certain anatomical changes, but in the long run does not predict optimally outcomes that relate to graft survival.

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