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Evaluation and short-term impact of functional renal reserve in extended-criteria kidney donors vs. healthy donors: A single-center observational study.

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Abstract

Introduction: Given the growing demand for organs, the use of extended-criteria donors requires precise methods to assess their safety after nephrectomy. This study evaluated functional renal reserve (FRR) in healthy donors and extended-criteria donors and compared the oral protein load test with changes in the intraparenchymal renal resistance index (VIRRI) using Doppler ultrasound. This study analyzes whether VIRRI, a noninvasive technique based on vascular autoregulation in response to abdominal pressure, can replace complex methods for predicting renal compensatory capacity.

Materials and methods: A prospective observational study was conducted at two transplant centers with 32 adult donors (eGFR >80 ml/min/1.73 m²). The functional renal reserve (FRR) was compared via two methods: an oral protein load (1.2 g/kg) with creatinine clearance and the intraparenchymal renal resistive index variation (IRRI) test via Doppler ultrasound under abdominal mechanical stress. Statistical analysis included Student's t tests, Pearson correlation tests, and Mann-Whitney U tests, with significance set at $p < 0.05$ and 95% confidence intervals.

Results: Thirty-two participants were included (27 with extended criteria; 5 healthy). The extended-criteria donors were older, heavier, and had higher BMIs, glucose levels, and LDL cholesterol levels ($P < 0.05$). Although the baseline eGFRs were similar between the groups (109 ml/min), the functional renal reserve was significantly lower in the extended criterion group (39.3 ± 33.7 vs. 87.2 ± 71 ml/min; $P < 0.05$). No statistically significant correlation was found between the protein load measurement and the VIRRI test ($R^2 = 0.054$).

Conclusions: Donors with extended criteria exhibit a significantly reduced need for renal replacement therapy (RRT), despite having a normal baseline estimated glomerular filtration rate (eGFR). Aging and metabolic alterations erode renal compensatory capacity, a finding that conventional static assessments fail to detect. The lack of correlation between the evaluated methods highlights the need for dynamic protocols. Integrating RRT into donor selection optimizes risk stratification, ensuring greater graft viability and longevity in kidney transplantation.

Keywords: Criteria donors extended, functional renal reserve, glomerular filtration rate, variation in the intraparenchymal renal resistance index.

Introduction

Kidney transplantation today faces a growing demand for organs, which has driven the use of extended criteria donors [1]. These individuals, characterized by mild metabolic disorders such as obesity, dyslipidemia, or advanced age, have adequate baseline renal function but are not without long-term risk. Although the absolute increase in the risk of end-stage renal disease (ESRD) after donation is small, the loss of nephron mass imposes a significant physiological burden on the remaining kidney.

Following nephrectomy, the solitary kidney undergoes functional adaptation, increasing its glomerular filtration rate (GFR) to 60–70% of the predonation value, driven by increased renal blood flow. However, this compensatory mechanism involves adaptive hyperfiltration, which can lead to glomerular hypertension and progressive nephrosclerosis [2].

The current concern is that marginal donors, particularly older adults and obese individuals, may have limited adaptive response capacity, raising questions about the safety of generalizing the results of previous studies to these subpopulations. Given this uncertainty, there is a critical need to improve risk stratification. In this context, estimating functional renal reserve (FRR) has emerged as a key tool for assessing the true compensatory capacity of the kidney and for more accurately predicting the risk of progression to chronic kidney disease [3].

The correlation between variations in the intraparenchymal renal resistance index (VIRRI) and functional renal reserve in healthy subjects could have important clinical implications. Preventing acute and/or long-term decline in renal function is essential in specific situations in which healthy subjects are at greater risk of developing renal dysfunction, such as during kidney donation [4, 5].

In this critical scenario, a negative VIRRI test can obviate costly, complex, and troublesome tests to assess renal functional reserve [6, 7]. Evaluation of the renal microvasculature has identified Doppler ultrasound as a crucial tool for indirectly measuring vascular bed stiffness and remodeling. The use of the Pourcelot resistive index (RI) and the pulsatility index enables detection of changes attributable to factors such as age, diabetes, or interstitial damage. These indices, with normal adult values of 0.70 and 1.20, respectively, serve as sensitive markers of tissue resistance and arterial impedance in response to alterations in hydrostatic pressure or capillary damage. In this context, the variation in the intraparenchymal renal resistance index (VIRRI) is presented as a noninvasive innovation for assessing renal functional reserve. The test involves increasing abdominal pressure by applying a controlled weight equivalent to 10% of body mass, thereby compressing the vasculature and activating the kidney's autoregulatory mechanisms. In healthy individuals, a physiological response is indicated by a decrease in the resistive index of at least 0.05, indicating renal reserve greater than 15 ml/min. The clinical significance of the VIRRI test is notable, especially given its high sensitivity and negative predictive value (100%), which allows for the reliable exclusion of functional reserve deficiencies. In critical scenarios, such as evaluating living donors for nephrectomy, the implementation of VIRRI provides an inexpensive,

quick, and reproducible alternative that could replace more costly and cumbersome methods, ensuring proactive protection against long-term renal impairment. The objective of this study was to assess functional renal reserve in potential kidney donors with extended criteria and in healthy donors via a method that measures variations in the intraparenchymal renal resistive index and an oral protein load test.

Materials and methods

Studio design

This was an observational, cross-sectional study. The data source is prospective.

Scenary

This study was conducted in two living donor transplant units: the “Salvador Zubirán National Institute of Nutrition and Medical Sciences” and the “Dr. Eduardo Liceaga” General Hospital of Mexico. The study period was from March 1, 2021, to December 31, 2022.

Participants

Records of adult patients over 18 years old enrolled in the kidney donation protocol with a glomerular filtration rate (GFR) calculated by the CKD-EPI equation greater than 80 ml/min/1.73 m² were included. Patients were excluded if they were a) on chronic treatments that could alter renal blood flow and/or GFR (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or diuretics); b) using nonsteroidal anti-inflammatory drugs (NSAIDs) within the 2 days prior to testing; or c) showing ultrasound evidence of renal morphological abnormalities or renal artery stenosis. Patients who were lost to follow-up or had incomplete data were also excluded.

Variables

The sociodemographic variables included age, sex, ethnicity, and obesity or overweight status. The laboratory variables consisted of hypercholesterolemia, HDL cholesterol, LDL cholesterol, hypertriglyceridemia, hyperuricemia, and serum creatinine. The intraparenchymal renal resistive index and functional renal reserve were measured.

Data sources/measurements

The source was direct. All the subjects were fed a standard protein diet and fasted for at least 12 hours prior to the test. They received initial hydration with 1000 ml of water, followed by hydration at 300 ml/h for 2 hours. Renal function was measured via an oral protein loading test (1.2 g of protein/kg of body weight) with whey protein isolate. Urinary creatinine (uCr) and serum creatinine (sCr) were measured via an enzymatic method (Unicel DxC 600). Creatinine clearance (CrCl) was calculated and corrected for body surface area (BSA) as follows: $CrCl = uCr \text{ (mg/dL)} / sCr \text{ (mg/dL)} * \text{urine volume (mL)} / \text{time (minutes)} * 1.73 / BSA \text{ (m}^2\text{)}$. The creatinine clearance time used

was 120 minutes. A 2-hour CrCl value was assessed after protein loading. The difference between the highest CrCl obtained after protein loading and the baseline value was defined as the RRF. $RRF = CrCl \text{ max} - \text{baseline eGFR}$.

Evaluation of functional renal reserve via renal Doppler ultrasound with the intraparenchymal renal resistive index variation (VIRRI) test:

The functional renal reserve was estimated via renal Doppler ultrasound (UDUS) following the protocol previously validated by Samoni et al. (27,28). The renal resistive index (RRI) was measured by a physician from the Radiology and Imaging Department via a multifrequency convex probe and appropriate machine settings. Because a difference was observed between automated and manual RRI measurements, we decided to use manual RRI calculations in all cases, in accordance with our standard clinical practice. The RRIs were calculated via the following formula: $RRI = [(peak \text{ systolic velocity} - \text{end-diastolic velocity}) / peak \text{ systolic velocity}]$, where peak systolic and end-diastolic velocities were measured on the same waveform. The RRIs were calculated for three interlobular arteries (superior, middle, and inferior) of each kidney. The average value for each kidney was then recorded, followed by the average for both kidneys. All renal artery glomerular filtration rates (RAGs) in the interlobular arteries, rather than the interlobar or segmental arteries, were measured to assess the vasculature near the glomerulus. The VIRRI test was performed on all the subjects in the supine position after they had rested for at least 5 minutes. A saline bag containing 10% of the subject's actual body weight was applied to the abdominal wall. We recorded the RAG in the middle interlobular artery at 1-minute intervals for 10 minutes of mechanical abdominal stress to assess changes in RAG associated with compression of the renal arteries and veins and the consequent reduction in blood flow. The lowest RAG achieved during abdominal mechanical stress was used as the baseline. The VIRRI was defined as the percentage difference between the baseline and stress RAG scores.

Biases

The surveys were administered in a standardized manner by the principal investigator via a preestablished guide approved in the research protocol. The information was independently reviewed by two researchers and recorded in duplicate. Only records with complete agreement were included.

Study size

The sample was probabilistic, with an effect size of 0.9 (Cohen's d), a one-tailed alpha of 0.05, and 80% power, yielding two groups of 16 patients each. GPower 3.1 was used to calculate the sample size.

Quantitative variables

The results for ordinal variables are presented as frequencies and percentages. The results for the scale variables are presented as averages. Scale variables were not converted into quantitative variables.

Statistical analysis

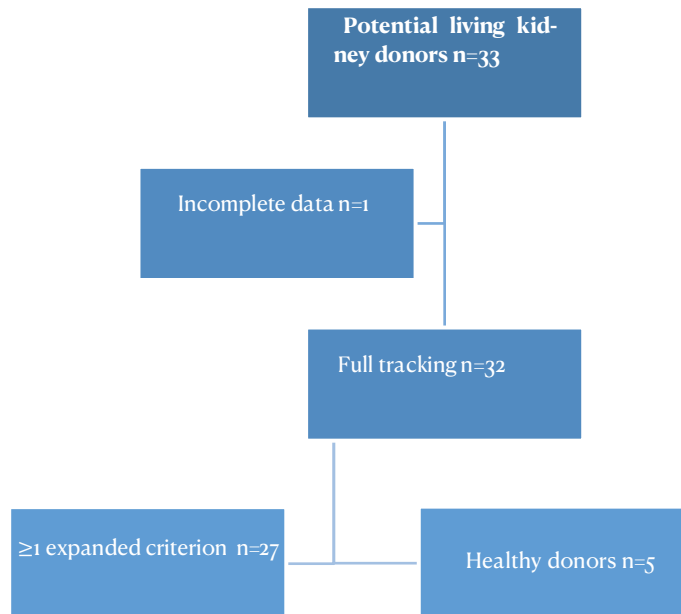
Descriptive statistics were performed using means, standard deviations, medians, and ranges for quantitative variables, depending on their distribution and normality. For qualitative variables, absolute and relative frequencies were estimated. Student's t test, Fisher's exact test, the chi-square test, or the Mann-Whitney U test were used to compare variables. Pearson's and/or Spearman's correlation coefficients were calculated to determine the associations between variables. The results were considered statistically significant for p-values < 0.05, with 95% confidence intervals.

Results

Participants

Thirty-two patients were enrolled in the study, accounting for 100% of the sample ([Figure 1](#)). A total of 27 patients met the extended inclusion criteria, and 5 were healthy.

Figure 1. Participant flowchart.



Characteristics of the study population

Among the potential donors included, the mean age was 43 years; 53% were women. Table 1 presents the general clinical characteristics of the donors. The extended donor group was 16 years older, weighed 16.5 kg more than the healthy donor group, and had a higher body mass index (BMI) of 22.7–27.1 kg/m². There were no differences between the groups in the other descriptive values.

Table 1. General characteristics of the study group.

	Healthy Subjects n=5	Criteria extended n=27	<i>p</i>
Sex (Male/Female)	0/5	15/12	< 0.05.
Age (years)	31 (27-32)	47(22-70)	< 0.05.
Weight (kg)	58 (56- 59.4)	74.5 (51-94)	< 0.05.
Size (cm)	159(152-167)	163 (150-178)	< 0.05.
BMI (kg/m ²)	22.7 (21.3- 24.4)	27.1 (21.9- 32.1)	< 0.05.
ASC (m ²)	1.5 (1.4- 1.6)	1.7 (1.4- 2.09)	< 0.05.
PAS (mmHg)	107 (100-131)	110 (100-131)	0.8
PAD (mmHg)	80 (65-93)	70 (60-89)	0.3
Frequency cardiac (mmHg)	77 (61-85)	63 (53-95)	0.2
Cholesterol total (mg/dl)	156 ± 22.7	177 ± 36	0.1
Triglycerides (mg/dl)	88.2 ± 37.5	159 ± 92	0.1
LDL (mg/dl)	86 ± 14	109 ± 32.5	< 0.05.
HDL (mg/dl)	54 ± 9.7	43 ± 9.2	< 0.05.
Acid Uric (mg/dl)	4.3 ± 1.1	5.2 ± 1.08	0.8
Glucose (mg/dl)	87 ± 2.3	94 ± 9.6	< 0.05.
Density Urinary	1017 ± 12	1018 ± 5.8	0.7
Ph Urinary	5.8 ± 0.6	5.5 ± 0.5	0.3

*Data presented in medians and ranges. kg: kilogram, cm: centimeter, m2: square meter, mmHg: millimeters

of mercury.

A Student's t test with 95% CI was performed. BSA: Body surface area. SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Functional reserve

Renal reserve function was assessed via the oral protein load test. The estimated glomerular filtration rate (eGFR) via the CKD-EPI 2021 formula was 109.8 mL/min/1.73 m². The mean functional renal reserve was 46.8 ± 43.9 mL/min/1.73 m² (Table 2).

Table 2. Test evaluation of functional renal reserve using the oral protein load test.

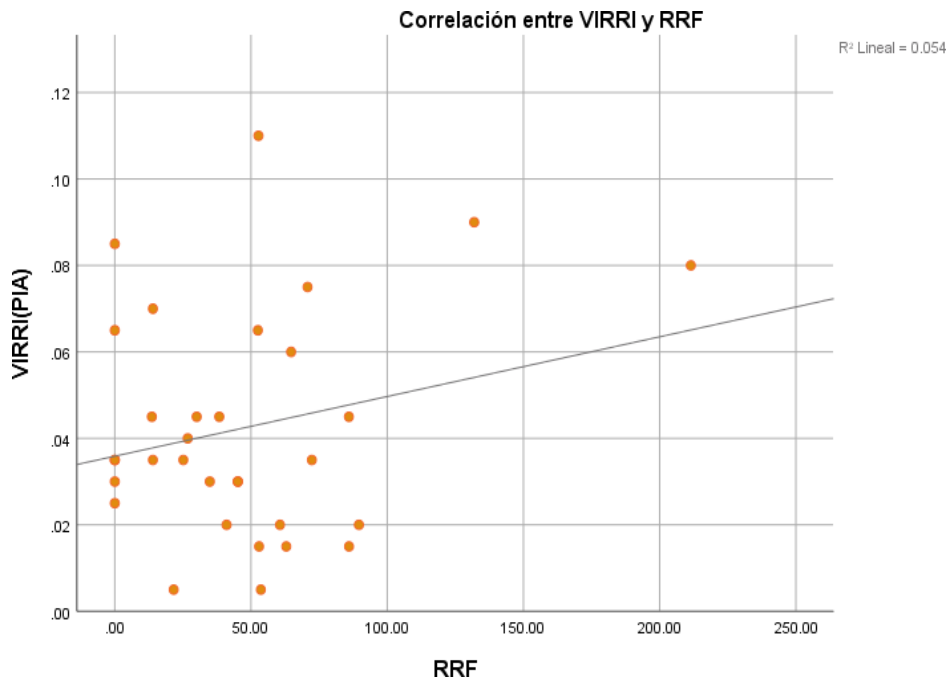
	Healthy n=5	Extended criteria n=27	p
TFGe CKD- EPI 2021(ml/min/1.73)	109 ± 14.9	109 ± 10	0.9
Creatinine baseline serum (mg/dl)	0.7 ± 0.11	0.7 ± 0.13	0.7
Creatinine basal urinary (mg/dl)	15.6 ± 14.7	30.7 ± 19.8	0.08
Volume basal urinary (ml/min)	6.7 ± 3.8	4.7 ± 2.4	0.3
Booking renal functional (ml/min/1.73)	87.2 ± 71	39.3 ± 33.7	< 0.05

Student's t test with 95% CI was performed .

Correlation between functional reserve measured by the two methods

The correlation between the two methods for measuring renal functional reserve was not statistically significant (R²=0.054) (Figure 2).

Figure 2. Correlation between the VIRRI and RRF.



Discussion

This study analyzed 32 participants (27 with extended criteria and 5 healthy individuals) and revealed that donors with extended criteria presented significantly different metabolic and physical profiles, characterized by being, on average, 16 years older, having a greater weight (74.5 kg), a higher BMI (27.1 kg/m²), and higher glucose and LDL levels than healthy individuals. Although both groups started with a similar estimated glomerular filtration rate (109 ml/min/1.73 m²), the most critical clinical finding was the marked reduction in functional renal reserve in the extended criteria group (39.3 ± 33.7 vs. 87.2 ± 71 ml/min/1.73 m² in healthy individuals), demonstrating a reduced capacity for physiological response to protein stress. Finally, the study revealed no statistically significant correlation between the two methods used to measure this reserve ($R^2 = 0.054$), suggesting that the current assessment tools may not be interchangeable.

These results suggest that conventional assessment of renal function via the estimated glomerular filtration rate (eGFR) is insufficient for early identification of functional decline in extended-criteria donors, as their physiological adaptive capacity is compromised despite normal baseline values. The observed disparity in functional renal reserve (FRR) indicates that factors such as advanced age, overweight, and metabolic abnormalities (elevated glucose and LDL) act as silent determinants that diminish compensatory hyperfiltration capacity. Furthermore, the lack of correlation between the analyzed measurement methods raises a critical question about the validity of current tools, suggesting that the lack of standardization in renal stress tests could lead to an overestimation of graft viability. Consequently, more rigorous protein stress tests need to be integrated to ensure donor selection that minimizes the risk of posttransplant renal failure.

From a clinical perspective, the practical applications of this study focus on refining donor selection protocols and on personalized recipient management. The marked decrease in functional renal reserve in subjects with extended criteria suggests that the oral protein-loading test should be incorporated as a standard diagnostic tool to assess the true quality of the graft beyond simple serum creatinine. This information would allow transplant teams to implement early nephroprotective strategies, more precisely adjusting the doses of nephrotoxic immunosuppressants in recipients receiving organs with limited reserve. Likewise, the identification of modifiable metabolic factors in donors underscores the importance of predonation optimization programs to mitigate the impact of overweight and dyslipidemia. Ultimately, adopting these more sensitive functional assessment criteria could reduce the incidence of delayed graft function and improve the long-term survival of the transplanted organ.

The findings of this study are consistent with previous scientific evidence that functional renal reserve (FRR) is a more sensitive marker than the creatinine level or estimated glomerular filtration rate (eGFR) for detecting silent renal impairment. Similar to the findings reported by Mueller and Luyckx [8], our results confirm that an apparently normal eGFR can coexist with a significantly reduced FRR, especially in donors with metabolic risk factors. Furthermore, the low

correlation observed across the different measurement methods reinforces the warning by Mancianti N et al. [9] regarding the lack of standardization of renal stress tests, underscoring that FRR assessed by protein load identifies a component of "functional nephron mass" that static estimation formulas fail to capture.

Despite these significant findings, this study has important limitations that must be considered when interpreting the data. The most notable limitation is the small sample size of the control group (n=5), which limits the statistical power to make more robust, generalizable comparisons. Furthermore, the cross-sectional design of the study prevents the establishment of a definitive causal relationship between altered metabolic parameters and long-term loss of renal reserve, limiting its ability to show an association at a single point in time. There is also potential bias stemming from the heterogeneity of the extended criteria group, in which the coexistence of multiple factors (age, obesity, and dyslipidemia) makes it difficult to isolate the individual impact of each variable on renal function. Finally, the lack of posttransplant follow-up in recipients limits this study's ability to determine whether the decrease in functional renal reserve, as measured by protein load, actually translates into lower graft survival or a greater incidence of delayed function in clinical practice.

Based on these findings, several lines of research are emerging to refine donor evaluation and improve transplant outcomes. A key priority is the development of prospective longitudinal studies correlating predonation functional renal reserve (FRR) with graft survival at 5 and 10 years. This will allow the establishment of numerical FRR thresholds that accurately predict the risk of chronic kidney failure in recipients. Likewise, it is imperative to standardize renal stress protocols by comparing oral protein loading with pharmacological stimuli to determine which technique offers greater clinical reproducibility. Another promising avenue is translational research to determine whether urinary biomarkers of early tubular damage are differentially elevated during stress testing in extended-criteria donors. Finally, interest in evaluating pretransplant metabolic conditioning interventions to determine whether optimizing the donor's BMI and lipid profile can partially restore functional reserve before organ retrieval is increasing.

Conclusion

In conclusion, this study demonstrated that extended-criteria donors have a significantly lower functional renal reserve (FRR) compared to healthy donors, despite maintaining an apparently preserved estimated glomerular filtration rate (eGFR). This indicates that factors such as aging, increased body mass index, and metabolic changes like dyslipidemia impair renal compensatory capacity, which are not detected in standard clinical assessments. The lack of correlation between measurement methods and the notable difference in response to protein stress underscores the urgent need to transition from a static to a dynamic, functional assessment model. Therefore, including FRR in the donor selection process could enhance risk assessment for recipients and serve as a crucial tool to optimize the use of extended criteria grafts, ultimately promoting better organ viability and longevity in the complex field of kidney transplantation.

Abbreviations

CKD: chronic kidney disease.

ERCT: end-stage renal disease.

TFG: glomerular filtration rate.

RRF: functional renal reserve.

TFGe: estimated glomerular filtration rate.

VIRRI: Intraparenchymal Renal Resistance Index variation. IRR: Intraparenchymal renal resistive index.

uCr: Urinary creatinine.

sCr: Serum creatinine.

CrCl: creatinine clearance.

PIA: Intra-abdominal pressure

Supplementary information

The supplementary materials have not been included.

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Authors' contributions

Jesús Daniel Lima Lucero: Conceptualization, data curation, research, visualization, original draft writing.

Lucía Monserrat Pérez Navarro: conceptualization, data curation, research, visualization and writing of the original draft.

Rafael Valdez Ortiz: Conceptualization, formal analysis, methodology, project management, resources, software, supervision, validation, writing–review and editing.

All the authors read and approved the final version of the manuscript.

Financing

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Availability of data or materials

Not applicable.

Statements

Ethics committee approval and consent to participate

The protocol was submitted to and approved by the ethics committee of the Salvador Zubirán National Institute of Nutrition, and written informed consent was obtained from each participant (INNSZ ref.4177, HGM CI/030/22).

Consent for publication

This does not apply when specific patient images, radiographs, or photographs are not published.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Use of generative AI

The authors declare that they used generative AI responsibly, without replacing their critical thinking, experience, and judgment. The AI was used under supervision and control to develop the discussion section. The use of the AI tool maintains the privacy and confidentiality of data and contributions, including published and unpublished manuscripts, as well as any personally identifiable information. The journal's policies, which permit the use of generative AI only in the introduction and discussion sections, have been followed.

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The accuracy, integrity, and impartiality of all AI-generated results were carefully reviewed and verified to ensure that the manuscript reflects an authentic and original contribution.

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