



## Changes in donor and recipient

A. I. Sánchez Fructuoso

Nephrology Department. Hospital Clínico S. Carlos. Madrid.

The incidence and prevalence of elderly patients with ESRD has increased considerably in industrial countries<sup>1</sup>, such that over 51% of hemodialysis cases in the USA in the year 2000 were  $\geq 65$  years of age. Spanish registry data also confirms a significant increase in the incidence of ESRD as age progresses, and incidence is 10 times more frequent in the 65-75 year old age group than in young patients 15-44 years of age<sup>2</sup>. Among possible treatment regimens for treating these patients, transplantation is the most desirable since it offers greater longevity, a better quality of life and lower economic costs compared to dialysis<sup>3</sup>. However the discrepancy between the number of potential recipients and available organs has grown progressively in the last 15 years in most countries<sup>4,5</sup>. Even in Spain, a country that managed to decrease the renal transplant waiting list in the last decade, a trend for increasing said waiting list has been observed in recent years with stabilization in the number of transplants performed<sup>6</sup>. Therefore, creative strategies are needed to solve this discrepancy. One possible solution is to use elderly organ donors, a measure which has clearly started in this country. The mean age of donors in Spain has thus increased in the last decade in almost 15 years, going from 34.5 years of age in 1992 to 50.7 years of age in 2004<sup>6</sup>. Today 37.9% of the donors in Spain are over the age of 60, whereas in 1992 only 10% of the donors were over the age of 60. In addition, almost 60% die of cerebral hemorrhage and only 15% of craniocerebral trauma<sup>6</sup> and it cannot be forgotten that subjects who die of cardiovascular pathology probably have a renal vascular condition as well. Data from the United States also shows a donor age increase, though not quite as remarkable, which has gone from 4.4% of donors  $\geq 65$  in 1994 to 9.7% in 2004<sup>7</sup>.

These elderly patients, who clearly are not the best option for young recipients, may be acceptable for elderly subjects. Furthermore, in these patients a

short transplant waiting list time is crucial because the death rate while waiting is clearly higher<sup>8</sup>, and it is known that subjects  $\geq 60$  years of age receive the transplant from an expanded donor (this being understood as a donor over the age of 55 with a history of more than 10 years with high blood pressure or diabetes) show better survival than wait-listed transplant patients on dialysis of the same age<sup>8</sup>. However, though the benefit of this transplant is clear, lower graft survival is also clear if compared to the survival from younger donors. In a study of USRDS data on 32557 transplants performed between the years 1996 and 2000, Woo et al.<sup>9</sup> found that the improvement in projected mean life obtained in renal grafts from donors  $< 55$  years of age did not occur in transplants from donors  $\geq 55$  years of age, who also showed worse and more unstable renal function. In a multivariate analysis of the factors that may affect the course of the transplant, these authors found that the factor that may improve results in recipients receiving transplants from elderly donors is cold ischemia of less than 24 hours; therefore, the attempt to apply this measure should be made systematically. In fact, different programs have been designed in which strict rules are applied when adjudicating organs for the purpose of obtaining the best possible results. The Eurotransplant Senior Program, for example, came about in this sense in which kidneys from donors  $\geq 65$  years of age are transplanted in recipients  $\geq 65$  years of age and in which kidneys from elderly donors are transplanted in local recipients and in which in order to reduce ischemia time and in order to reduce the risk of rejection, they are used only in subjects who are waiting for their first transplant and who also have a preformed antibody rate of less than 5% and HLA typing is not necessary (in order to reduce cold ischemia time). Thus in this program, organ assignment is based on age, ABO compatibility and negative cross-match. With these premises, Fabrizii et al.<sup>10</sup> described a similar long-term patient and graft survival in recipients  $\geq 65$  years of age in those patients who receive a graft from the Senior Program in relation to those receiving the graft from a young donor. These results are probably a result of the shorter waiting list and cold ischemia time. The attempt must further be made to act as much as possible on the other factors causing

**Correspondence:** Dra. Ana Sánchez Fructuosos  
Servicio de Nefrología  
Hospital Clínico  
Madrid  
E-mail: asanchez.hcsc@salud.madrid.org

lower survival of these organs: lower nephron mass (transplant in small recipients), senescence (use elderly recipients), greater sensitivity to ischemia-reperfusion damage (reduce cold ischemia), higher incidence of initial graft function delay and acute rejection<sup>11-13</sup>. In relation to the latter two, it must be taken into account that today, with such significant advances in immunosuppression, acute rejection has lost the importance it had years ago, while the advances in other fields such as obtaining and managing donors and conservation have been scarce, which may make the impact of the donor's characteristics on graft survival increasingly greater. A very careful elderly donor management during the cerebral death process is therefore important in order to correct any events that may favor the development of tubular necrosis and inflammation stimulation. Once the transplant is performed it is important to customize immunosuppression, using calcineurin inhibitor-free initial regimens in cases in which initial function delay is anticipated or exists, using other immunosuppressive drugs as support.

Different centers have started up elderly donor double transplant programs in an attempt to increase the number of transplants performed, showing acceptable results<sup>14,15</sup>. Good results are also obtained when they are transplanted together with pediatric donors of less than 3 years of age, the use of which had virtually been abandoned due to the poor results obtained when transplanted alone<sup>16</sup>. The greatest problem these grafts may show is surgical, with a greater risk of arterial or venous thrombosis which is why their use in recipients with significant arteriosclerosis problems is not recommended. It has also been reported that this type of transplants show better renal function, less hyperfiltration and a lower incidence of chronic nephropathy<sup>16,17</sup> so they would therefore be particularly indicated in young recipients. The non-heart-beating donor is another viable solution for reducing the renal transplant wait list. Their number has progressively increased in Spain from 35 donors in 1995 to 71 in 2004<sup>6</sup> and also in the United States (57 donors in 1994 and 271 in 2003)<sup>18</sup>. The asystole donation program in the Clinical Hospital of Madrid has led to a very significant increase in the number of transplants performed<sup>19</sup> and to such a drastic reduction of the wait list that it has led to the development of a pre-dialysis transplant program. Graft survival is similar to that obtained with young donors in cerebral death and greater than that of renal transplants from elderly donors (author's data).

On the other hand, although it is obvious that the elderly subject with ESRD benefits from the transplant, their survival is clearly lower than that of the

young recipient<sup>20-22</sup>. In order to improve the results in this population it is essential to act on all those negative factors secondary to modification, and a good evaluation is necessary before being included on the list, which among other objectives is focused on resolving most treatable problems. There is very little published evidence on survival in the elderly recipient when the recipient has been carefully evaluated and all possible associated pathologies have been corrected before the transplant. Most published studies have little information on the existence of other associated pathologies that may influence graft loss or mortality. Although elderly patient survival is logically limited by the old age itself, it is also influenced by other co-morbid factors<sup>23,24</sup>. In fact, graft loss in elderly patients is mainly related to patient mortality, essentially due to a cardiovascular or infectious cause, or tumors<sup>24,25,26,27</sup>. For this reason it is essential to know and control these factors when renal transplant results in elder recipients are studied or when they are compared to young recipients.

The following factors have been identified within the predictive factors of death in the elderly patient: tobacco consumption at the time of the transplant<sup>28</sup>, higher body mass index<sup>28,29,30</sup> and time on the wait list<sup>8,28</sup>. Acting on these factors and resolving, as much as possible, pre-transplant associated pathologies together with customized immunosuppressive therapy is essential for improving results in these patients.

## REFERENCES

1. US, Renal Data System, USRDS. Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institute of Health. National Institute of Diabetes And Digestive and Kidney Diseases, Bethesda, MD, 12: 174, 2003.
2. Ceballos M, López-Revuelta K, Saracho R, García Lopez F, Castro P, Gutiérrez JA, Martín-Martínez E, Alonso R, Bernabéu R, Lorenzo V, Arias M, Sierra T, Estébanez C, Lara M, Cleries M, Vela E, García-Blasco MJ, Zurriaga O, Vázquez C, Sánchez-Casajus A, Rodado R, Ripoll J, Asín JL, Magaz A: Informe de diálisis y trasplante correspondiente al año 2002 de la Sociedad Española de Nefrología y Registros Autonómicos. *Nefrología* 25: 121-129, 2005.
3. Winkelmayer WC, Weinstein MC, Mittleman MA, Glynn RJ, Pliskin JS: Health economic evaluations: the special case of end-stage renal disease treatment. *Med Decis Making* 22: 417-430, 2002.
4. Hariharan S, McBride MA, Bennett LE, Cohen EP: Risk factors for renal allograft survival from older cadaver donors. *Transplantation* 64: 1748-1754, 1997.
5. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D: Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 342: 605-612, 2000.
6. Valentín M, Miranda B, De la Rosa G, Martín-Escobar E, Garrido G, Matesanz R: Donación y trasplante renal en España durante 2004. *Nefrología* 25: 350-360, 2005.

7. United Network of Organ Sharing: disponible en <http://www.optn.org/latestData/rptData.asp>
8. Ojo AO, Hanson JA, Meier-Kriesche H, Okechukwu CN, Wolfe RA, Leichtman AB, Agodoa LY, Kaplan B, Port FK: Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 12: 589-597, 2001.
9. Woo YM, Gill JS, Johnson N, Pereira BJ, Hariharan S: The advanced age deceased kidney donor: current outcomes and future opportunities. *Kidney Int* 67: 2407-2414, 2005.
10. Fabrizii V, Kovarik J, Bodingbauer M, Kramar R, Horl WH, Winkelmayer WC: Long-Term Patient and Graft Survival in the Eurotransplant Senior Program: a Single-Center Experience. *Transplantation* 80: 582-589, 2005.
11. Sánchez-Fructuoso AI, Prats D, Marqués M, Pérez-Contín MJ, Fernández-Pérez C, Contreras E, Blanco J, Barrientos A: Does renal mass exert an independent effect on the determinants of antigen-dependent injury? *Transplantation* 71: 381-386, 2001.
12. Moreso F, Seron D, Gil-Vernet S, Riera L, Fulladosa X, Ramos R, Alsina J, Grinyo JM: Donor age and delayed graft function as predictors of renal allograft survival in rejection-free patients. *Nephrol Dial Transplant* 14: 9301-9935, 1999.
13. Terasaki PI, Gjertson DW, Cecka JM, Takemoto S: Fit and match hypothesis for kidney transplantation. *Transplantation* 62: 4411-4445, 1996.
14. Bunnapradist S, Gritsch HA, Peng A, Jordan SC, Cho YW: Dual kidneys from marginal adult donors as a source for cadaveric renal transplantation in the United States. *J Am Soc Nephrol* 14: 1031-1036, 2003.
15. Andrés A, Herrero JC, González E, Morales E, Morales JM, Díaz R, Polo G, Leiva O, Rodicio JL, Praga M: Long-term results of renal transplantation in elderly cadaver donor recipients 65 years old or older. *Transplant Proc* 34: 356-357, 2002.
16. Sánchez-Fructuoso AI, Prats D, Pérez-Contín MJ, Marqués M, Torrente J, Conesa J, Grimalt J, Del Río F, Núñez JR, Barrientos A: Increasing the donor pool using en bloc pediatric kidneys for transplant. *Transplantation* 76: 1180-1184, 2003.
17. Sánchez-Fructuoso AI, Prats D, Marqués M, Pérez-Contín MJ, Fernández-Pérez C, Contreras E, Blanco J, Barrientos A: Does renal mass exert an independent effect on the determinants of antigen-dependent injury? *Transplantation* 71: 381-386, 2001.
18. Delmonico F, Sheehy E, Marks WH, Baliga P, McGowan JJ, Magee JC: Organ donation and utilization in the United States, 2004. *Am J Transplant* 5(Part 2): 862-873, 2005.
19. Sánchez-Fructuoso A, Prats D, Naranjo P, Torrente J, Pérez-Contín MJ, Fernández-Pérez C, Álvarez J, A. Barrientos Guzmán: Renal transplantation from non-heart-beating donors: a single center experience. *J Am Soc Nephrol* 11: 350-358, 2000.
20. Roodnat JJ, Zietse R, Mulder PG, Rischen-Vos J, Van Gelder T, IJzermans JN, Weimar W: The vanishing importance of age in renal transplantation. *Transplantation* 67: 576-580, 1999.
21. Meier-Kriesche HU, Ojo AO, Cibrik DM, Hanson JA, Leichtman AB, Magee JC, Port FK, Kaplan B: Relationship of recipient age and development of chronic allograft failure. *Transplantation* 70: 306-310, 2000.
22. Tesi RJ, Elkhannas EA, Davies EA, Henry ML, Ferguson RM: Renal transplantation in older people. *Lancet* 343: 461-464, 1994.
23. Doyle SE, Matas AJ, Gillingham K, Rosenberg ME: Predicting clinical outcome in the elderly renal transplant recipient. *Kidney Int* 57: 2144-2150, 2000.
24. Kappes U, Schanz G, Gerhardt U, Matzkies F, Suwelack B, Hohage H: Influence of age on the prognosis of renal transplant recipients. *Am J Nephrol* 21: 259-263, 2001.
25. Howard RJ, Patton PR, Reed AI, Hemming AW, Van der Werf WJ, Pfaff WW, Srinivas TR, Scornik JC: The changing causes of graft loss and death after kidney transplantation. *Transplantation* 73: 1923-1928, 2002.
26. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK: Long-term survival in renal transplant recipients with graft function. *Kidney Int* 57: 307-313, 2000.
27. Roodnat JJ, Zietse R, Mulder PG, Rischen-Vos J, Van Gelder T, IJzermans JN, Weimar W: The vanishing importance of age in renal transplantation. *Transplantation* 67: 576-580, 1999.
28. Cardinal H, Hebert MJ, Rahme E, Houde I, Baran D, Masse M, Boucher A, Le Lorier J: Elderly Recipients Transplant Group. Modifiable factors predicting patient survival in elderly kidney transplant recipients. *Kidney Int* 68: 345-351, 2005.
29. Meier-Kriesche HU, Vaghela M, Thambuganipalle R, Friedman G, Jacobs M, Kaplan B: The effect of body mass index on long-term renal allograft survival. *Transplantation* 68: 1294-1297, 1999.
30. 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* 73: 701-774, 2002.