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Editorial

Living-donor kidney transplant: guidelines with updated evidence

Trasplante renal de donante vivo: guia con evidencias actualizadas

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In recent years, renowned clinical practice guidelines (CPG) have been published updating recommendations to optimise the indications and the outcomes of living-donor kidney transplantation (LDKT), two of them focused exclusively on the study of living donors,[1,2] and the third[3] addressing the transplanted recipient in more detail.

These new CPG are being published simultaneously as a supplement in the *Revista de Nefrología* [Nephrology Journal]. They have been endorsed by the Sociedad Española de Nefrología (SEN) [Spanish Society of Nephrology], the Sociedad Española de Trasplante (SET) [Spanish Transplant Society] and the Organización Nacional de Trasplantes (ONT) [Spanish National Transplant Organisation] in response to both the need to update the recommendations on LDKT published in Spain in 2010[4] to include new evidence strengthening the indications for transplantation, and the obligation to focus on maximum donor protection. They include evidence that has been consolidated over the last 11 years (Table 1), a period in which 33 hospitals across Spain performed 3,666 LDKT, covering all the current modalities and producing excellent results.

The new guidelines are also an opportunity to continue reinforcing what continues to be accredited as the best therapeutic option in selected patients to treat advanced chronic kidney disease.[5] Therefore, we hope that these CPG will improve the LDKT programmes mainly in those who still base their indications on intuition more than in evidence.[6]

In parallel with the development of this CPG, there have been published recently specific recommendations to improve each of the phases of the living-kidney donation process,[7] which has been adopted by the Permanent Commission of Transplantation of the Interterritorial Council of the Spanish National Health Service.

Finally, a CPG published in Spanish will undoubtedly help to strength and tie collaborations with medical professionals in Latin America. In some countries, LDKT is either the only kidney transplant option or the most common type of transplant.

Ethics, information and coordination

Ethical issues related to autonomy and altruism, along with beneficence, non-maleficence, voluntarism or confidentiality, continue to be essential to define the living donor's motivation

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Table 1 – New contributions in living-donor kidney transplant.

Ethics, information and coordination
Autonomy and altruism, keys to accepting the living donor.
Informed consent more precise and signed in the absence of the recipient.
Management of new technologies to disclose information about the LDKT.
Living donor evaluation
Glomerular filtration rate quantification with exogenous markers.
Individual assessment in cases of albuminuria greater than 100 mg/day (ratio 100 mg/g).
Optimisation of the detection of communicable diseases (infections, neoplasms).
Risk assessment
Estimation of the risk of CKD at 15 years in potential donors (without donation).
Metabolic assessment and risk factors for CKD and CVD.
Lifetime annual medical check-ups for all donors.
Compatibility and immunosuppression
HLA class I (A, B, C) and class II (DP, DQ, DR) typing and HLA donor-specific antibodies.
Crossmatching (virtual and with T and B lymphocytes).
Triple immunosuppression except between identical twins.
Donation and LDKT surgical techniques
Kidneys with arterial anomalies or tumours, valid in certain circumstances after bench surgery.
Renal artery ligation should not be performed with a hem-o-lok clip system.
Robotic surgery as an option in selected cases.
Incompatible donor: HLA, ABO, paired/pooled donation
Better outcomes in HLAi and ABOi transplantation with anti-CD20, polyclonal immunoglobulin, apheresis techniques and triple immunosuppressive therapy.
Serial MFI or isoagglutinin (IgG and IgM) titres key to deciding the optimal time for transplantation after the conditioning.
In HLA- or ABO-incompatible donor-recipient pairs, paired/pooled donation programmes should be offered as a preference.

LDKT, living-donor kidney transplant; CKD, chronic kidney disease; CVD, cardiovascular disease; HLAi, HLA-incompatible; ABOi, ABO-incompatible.

as optimal. In addition to being a legal and ethical obligation, the informed consent document must be prepared with great precision. It must contain information on the general risks (including death) and those originated from particular circumstances found during the study of the potential donor. It would be ideal for this document to be unified and be signed by the donor in the absence of the transplant recipient. The autonomy of the potential donor has to be recognized but it does not invalidate the prudence of the professionals, so the ethical justification for rejecting a donation is valid when, following the evaluation, the donation's risk is considered too high.[8] All donors should be informed of the (very low) risk of developing kidney failure and the need of renal replacement therapy.

No solid evidences has been found to recommend new strategies to better convey information to LDKT donors and recipients. Both nephrologists and nursing staff involved in the control of advanced chronic kidney disease are the main actors in providing information on LDKT. However, the use of new technologies to spread more precise information about this treatment option and on a more massive scale (e-learning, TV health, social networks or direct interaction in mini-groups led by transplant patients) is clearly emerging as a complement to the traditional modalities of proactive information in the media.[9]

The duration of the evaluation of the living donor is variable; in some centres, it can take far too long. It is essential to speed up the studies so the transplant can be performed as soon as possible, as this will achieve better outcomes. Lengthy delays can be a disincentive for LDKT among donors and healthcare professionals and limit the chances of performing an early transplant.[10]

Evaluation of the living donor

Evaluating the living-kidney donor is complex and may not and should not be simplified. Previous medical history, analyses, investigations and referrals to other specialist areas are essential stages which require good organisation to verify the suitability of the donor from a medical point of view and a psychosocial perspective.

The measurement of glomerular filtration rate using exogenous markers has now become the most recommended method.[11] Regarding albuminuria, if it is more than 100 mg/day (ratio 100 mg/g), the decision on whether or not to accept the donation should be made on an individual basis in the absence of other comorbidities. Persistent dysmorphic microhaematuria would invalidate the donation unless it is due to reversible causes (lithiasis, infection, intense effort). A renal biopsy is recommended when underlying glomerulonephritis is suspected, ruling out donors with IgA glomerulonephritis. There is a certain agreement that donors with thin basement membrane nephropathy could be accepted as donors if they are over 40–50 years of age.

Expanding the criteria for acceptance of the living donor to include older age, low-range glomerular filtration rate, and associated metabolic alterations is a valid strategy to help the option of LDKT for as long as safety is consider the priority.

Risk assessment

In the last decade, several alerts have been raised on the long-term risks of living kidney donors regarding kidney and cardiovascular disease. While we wait for these warnings to be

carefully analysed and confirmed recommendations issued, we need to consider them when evaluating donors with a certain risk profile.[12] It should be encouraged the use of tools that help to assess the risk of chronic kidney disease in all potential donors.[13]

There are areas of uncertainty in the acceptance of donors with obesity, prediabetes or type 2 diabetes, as well as those with metabolic syndrome (25–30 %) and those who smoke (30%). In these cases, the decision has to be made on a individual basis and, the it should be reassessed after they make lifestyle changes that could reduce the risk of complications.

To reduce post-donation risks, all donors should have a lifelong annual follow-up. It should be emphasise the control of smoking, overweight, high blood pressure and sedentarism, and perform regular tests for albuminuria, serum creatinine and estimated glomerular filtration rate, confirming with exogenous markers such as iohexol in cases of reasonable doubt.

Finally, in countries where it is not already regulated, it should be implemented changes in the law which maximise the protection of the living donor from a social and labour perspective.

Compatibility and immunosuppression

In addition to determining blood groups and subtypes (for example, A2), HLA typing by molecular methods has prevailed over serological methods due to its greater sensitivity and resolution.[14] In LDKT it should be performed for class I (A, B, C) and class II (DP, DQ, DR) antigens. Anti-HLA alloantibodies may be determined using lymphocytes expressing HLA molecules on their cell surface as target cells using cytotoxicity or flow cytometry; or with "artificial" systems which present the HLA molecules on solid phase support, currently measured using Luminex® technology.[15]

Recipients with high levels of anti-HLA antibody (sensitised patients) have greater difficulty finding a matched donor and are at greater risk of antibody-mediated rejection. First, a compatibility study or virtual crossmatch will be carried out in these patients to allow initial immunological evaluation, according to the recipient's alloantibody profile, compared with the living donor's HLA antigens. In addition, it is recommended a crossmatch with T and B lymphocytes and recipient serum; this test should be confirmed a few days before transplantation. If the anti-HLA antibodies are donor-specific, desensitisation or inclusion in crossover donation programmes should be considered at the discretion of the transplant group.[16]

Induction immunosuppression in LDKT should be performed with basiliximab or thymoglobulin, depending on whether the recipients are at low or high immunological risk respectively. Maintenance immunosuppression should be supported based on triple therapy, at least for the first year, mainly in patients with high immunological risk.

Donation and transplant techniques

The preference on which kidney should be removed by laparoscopy continues to be the left, unless the CT angiogram shows vascular or urological alterations that could increase the risk in the recipient. Kidneys with multiple arteries or certain tumours may be accepted under specific circumstances after performing bench surgery. In the clipping of the donor renal artery, the use of hem-o-lok system is not recommended due to the death of a donor in an exceptional way, due to hemorrhage.[17]

The implantation of a double J catheter in the ureter is an increasingly recommended practice which reduces stenotic complications and urine leakage from the ureterovesical anastomosis, without increasing morbidity. Mesh placement should always be considered in obese recipients and those to be treated with m-TOR inhibitors.

The robotically assisted LDKT increases current options for recipients towards minimally invasive techniques. However, although it could be a promising technique in the future, at present, it is only suitable in a minority of patients.[18]

Incompatible donor: HLA, ABO and paired/pooled donation

LDKT is providing solutions for difficult cases in which donor and recipient have HLA and/or ABO blood group incompatibility. It is possible to go ahead with the transplantation of recipients with high HLA sensitisation if they have an HLA-identical living donor, even if they are ABO incompatible or if the recipient is a child.[19]

It has been possible to more precisely define the ideal moment for surgery after preconditioning of the incompatible LDKT (MFI titres and isoagglutinins), in addition to post-transplant follow-up through protocol biopsies for early diagnosis of possible rejection.

When no compatible living donor is available, but there is a willingness to donate, the condition of the donor-specific anti-HLA antibodies present in the recipient should be assessed and options of HLA desensitisation or paired/pooled donation kidney transplantation should be considered, the latter being the preferable option.[20] It is important to stress that paired/pooled donation and HLA desensitisation or ABO matching are complementary rather than competing initiatives, as most recipients included in paired/pooled donation kidney transplant programmes have few transplant options after being on the waiting list for more than a year, or not having found an option in four matching runs.[21]

The best results in LDKT with HLA or ABO incompatibility combine apheresis techniques with CD20 antibodies, polyclonal immunoglobulin and triple immunosuppression.

Last of all, the altruistic donor is the greatest expression of anonymous and disinterested solidarity. However, for validation as a donor, broad expert collaboration must be ensured to certify an optimal state of health and an exhaustive psychological evaluation to attest the motivation and post-donation mental health.[22] When they are declared suitable, altruistic donors are ideal for beginning chains of LDKT.[23]

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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