Can we improve the results and increase the number of renal transplants?

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Introduction

The two main aims of the transplant community are to improve the results of organ transplantation and to increase the number of donors. Here we will consider first the main factors that can influence the results of renal transplantation and then the possible measures to counteract the shortage of donors.

Factors influencing the results of renal transplantation

There is a long list of factors that may affect the outcome of kidney transplantation. We will discuss, however, only the most important variables.

Centre effect

A retrospective investigation of >27000 cadaveric renal transplants made in different centres in the US has shown that the 1-year allograft survival ranged between 52 and 100%, with a graft half-life ranging between 3 and 25 years [1]. At present, the centre effect is considered the most important variable influencing the results of renal transplantation, after transplant between HLA-identical siblings [1].

Age of the recipient

A recent report of the EDTA–ERA showed that the 5-year graft survival rate is significantly worse in recipients aged 20 years or less [2]. On the other hand, patients aged >54 years have an inferior survival compared with patients aged between 15 and 54 years [3]. The poorer graft survival in children is caused mainly by more frequent and severe rejection; the poor results in older patients must be attributed to a higher mortality.

Pre-formed antibodies

The greater the number of pre-formed lymphocytotoxic antibodies, the higher the risk of graft failure. Feucht and Opelz [4] reported a minimum risk if patients had <10% antibodies, an intermediate risk if antibodies ranged between 11 and 50%, and a high rate of graft failure if antibodies exceeded 50%. In hyperimmunized patients, the HLA compatibility strongly influences the results. The pre-transplant removal of pre-formed antibodies with immunoadsorptive columns or plasma exchanges may improve the results in patients with an elevated titre of circulating antibodies [5].

Primary disease

Idiopathic glomerulonephritis (GN) may recur after transplantation and can lead to graft failure. The risk is particularly elevated for childhood focal glomerulosclerosis which is responsible for graft failure in 24% of cases. Mesangiocapillary GN type II is responsible for graft failure in 19% of cases, while the other GNs account for 4% of graft failures. With the exception of focal glomerulosclerosis that destroys the kidney within 2 years in two-thirds of cases, graft failure occurs after several years in the other types of GN [2].

When compared with patients with standard primary disease, the graft survival is lower in patients with analgesic nephropathy, amyloidosis and polyarteritis. The difference is accounted for mostly by a higher death rate [2]. Patients with lupus nephritis or Wegener granulomatosis have a graft survival comparable with that of patients with primary renal disease [2].

HLA compatibility

The recent data of the Collaborative Transplant Study showed that, even in the era of cyclosporin, there is a stepwise decrease in the cadaveric graft survival rate as the number of HLA mismatches increases [6]. On the other hand, factors such as the centre effect and second transplants may have a even greater influence than HLA compatibility on the outcome of the transplant.

Donor age

The UNOS data show that the best results in cadaveric renal transplants can be obtained with donors aged between 18 and 34 years. The 3-year graft survival rate is 12.2% lower with donors aged between 50 and 64
Can we increase the number of renal transplants?

years, and 20.9% lower with donors aged more than 65 years. The difference is less striking with living donors, 3.5% lower with donors aged between 50 and 64 years, and 55% with donors older than 65 years, as compared with donors between 18 and 34 years [7].

Gender of the donor

Kidneys from female donors have a 3-year graft survival 5% less than kidneys from male donors [8]. The difference is even greater for second transplants. These results may depend on a lower nephronic mass that could cause a more rapid progression of renal insufficiency.

Cause of death

Kidneys from donors who have died due to cranial trauma have a 1-year survival 4% better than those from donors who have died due to cerebral haemorrhage [9]. Although statistically significant, this difference has little clinical relevance.

Difference in age of donor and recipient

A retrospective analysis showed that the 1-year graft survival was 66% if the cadaveric donor was 5 years older than the recipient, 84% if the donor was 5 years younger than the recipient, and 72% if the difference in age was within ≤5 years [9].

Difference in body weight of donor and recipient

The following factors reduce the 1-year graft survival to 3–9% according to an analysis of the UNOS [10]: recipient body weight 40 kg greater than that of donor, height 40 cm more, body mass index twice as great and body surface twice as great.

Second transplant

The risk of graft failure is more elevated with second transplants, particularly if the previous transplant was lost because of acute rejection and/or if the patient developed circulating antibodies [6]. The results of second transplants are significantly better for living than for cadaveric donors [2].

Delayed graft function

A delayed graft function is associated with a poorer graft survival in the long term [11]. The risk of delayed graft function is higher if Eurocollins solution was used, and if the anastomosis time was longer than 45 min [12]. Some studies found that a donor age of more than 50 years and cold ischaemia time longer than 24 h were associated with a greater risk of delayed graft function [12], but others did not [6,8].

Duration of dialysis

In our experience, long duration of dialysis was an independent variable associated with poorer results of transplantation in the long term [11].

Acute rejection

The development of an acute rejection may reduce the half-life of a kidney allograft, from 12.5 to 6.6 years [13]. However, if a rejection is completely reversible with a post-rejection plasma creatinine <130 μmol/l, there is no difference in the 6-year graft survival rate between patients who did or did not have acute rejection [14].

Immunosuppression

There is controlled evidence that cyclosporin (CsA) allows better graft survival than azathioprine, not only in the short term but also in the long term [15]. There is no significant difference in the 4-year graft survival between regimens based on CsA alone, CsA plus steroids, or CsA plus steroids plus azathioprine [16]. New drugs such as neoral [17], FK506 [18] and mofetil mycophenolate [19] have been shown to be able to significantly reduce the risk of acute rejection when compared with the old formulation of CsA. Further progress is expected from the use of sirolimus, brequinarn, leflunomide and/or monoclonal antibodies against the interleukin-2 receptors.

Compliance

Bad compliance with therapy represents the third cause of late graft failure [20]. It is possible that the rate of failures due to bad compliance is even more than usually estimated, as many patients are reluctant to confess their mistake. Young patients and those with a poor function of the transplanted kidney are those with a lower compliance.

Concomitant disease

It is obvious that patients with severe extrarenal diseases have an increased risk of complications which can be responsible for death or the need for modifications of immunosuppression which favour the onset of irreversible rejection [11]. Thus, a careful clinical evaluation of the recipient is of utmost importance in influencing the results.

In summary, a renal transplantation will have the greatest chance of success if performed in a centre with a high level of competence and organization, on a young adult in excellent clinical conditions, having good HLA compatibility with a young donor, who died from cranial trauma, with body weight and surface similar or superior to those of the recipient. An organ allocation based on these criteria of medical utility may give the best results. On the other hand, if these criteria had absolute priority, the principles of equity would be violated, thus damaging elderly recipients, patients on long-term dialysis, patients with pre-formed antibodies, etc. It is necessary that transplant organizations regularly verify and review the criteria for the scores used to assign each combination of cadaveric donor–recipient, in order to allow good results without violating the principles of equity.
**Shortage of donors**

All over the world, the increasing success of transplantation is paralleled by the increased size of the waiting list. The legal, religious and logistic problems, which are different in different countries, will not be discussed here. At present, we can follow three main routes to increase the donor pool: use of marginal donors; use of non-heart-beating donors; and use of living donors.

**Marginal donors**

A number of potential donors are rejected because of anatomical abnormalities, arterial hypertension, renal dysfunction, prolonged cold ischaemia time or advanced age.

Some vascular and/or urological abnormalities do not represent a contraindication. A number of kidneys with multiple vessels, benign cysts and other urological abnormalities have been transplanted with success [21,22].

There is little information about the outcome of kidney donation from hypertensive donors. Good results have been reported in some small series [23]. We suggest that hypertensive patients should not be discarded unless there is evidence of pre-existing renal dysfunction, decreased size of kidney hyperecogenicity at ultrasound and/or severe retinopathy.

Many transplant units reject donors with renal dysfunction before operation. However, in a retrospective analysis of French data, Alexandre et al. [24] found no difference in the 1-year graft survival rate between patients with the last plasma creatinine concentration greater or less than 200 μmol/l. A review of 1157 renal transplant patients showed that neither oligoanuria of the donor nor hypotensive episodes influenced the risk of delayed graft function [12]. Pokorná et al. [25] found similar graft survival and plasma creatinine concentrations in patients who received a kidney from donors with stable haemodynamic conditions and normal renal function or from donors with unstable haemodynamic status and plasma creatinine concentration > 160 μmol/l.

A cold ischaemia time (CIT) longer than 24 h is usually regarded as a major risk factor for delayed graft function and poor results. By reviewing the data of CTS, Opelz [26] found that the 5-year graft survival of patients with a CIT of 0–6 h was similar to that of grafts with a longer CIT, being between that of grafts with a CIT of 25–36 h and of >48 h.

The use of older donors is still under discussion. As already mentioned, older age may be associated with a poorer cadaveric graft survival [7]. However, good results have been reported with elderly living donors [27] and, in some series, even with cadaveric donors older than 60 years [8,28]. It has been pointed out, however, that age alone cannot be considered as an exclusion criterion for selecting donors. In a retrospective analysis, it was shown that creatinine clearance was the sole independent predictor of graft survival. A donor creatinine clearance <50 ml/min was associated with ultimate graft loss [28]. In this regard, it is reassuring that recipients of living-donor kidneys older than 55–60 years have similar or even better graft survival than recipients of younger kidneys, providing that the donor undergoes a complete and exhaustive work-up [27,29]. The main objection to the use of older donors is represented by the potential risk of a late graft failure caused by the reduced nephron mass, which can be diminished further by rejection, hypertension, CIT and nephrotoxic agents. This risk may be minimized by transplanting the kidney in a recipient with a small body surface [30] or by allocating the kidney to a pool of aged recipients with a shorter life expectancy.

The adoption of more flexible criteria for accepting marginal donors might reduce the 1–2 year graft survival by ~10–20% compared with the ideal cadaveric donor [31], but could increase the number of cadaveric transplants by 20–50%.

**Non-heart-beating donors (NHBD)**

The initial results with NHBD were poor, probably as a consequence of severe renal injury. Recently, however, improved immunosuppression and methods aimed at minimizing ischemic injury have allowed results comparable with those achieved with conventional cadaveric donors to be obtained. Wijnen et al. [32] reported similar 1-year graft survival and renal function in 57 renal transplant patients who received their kidney from NHBDs and in 114 who received a kidney from heart-beating donors. The technique consisted of inserting, after 10 min of asystolia, a balloon catheter at the fork of renal arteries, which is then inflated and refrigerated. Probably <6% of patients dying in hospitals are diagnosed as brain dead. Far larger is the proportion of potentially suitable donors who die from cardiac arrest. Daemen et al. [33] evaluated the magnitude of the potential pool of NHBDs at the University Hospital of Maastricht. They scored the medical suitability and logistic availability. Including rates of consent refusal and rates of technical failures, the calculated annual number of NHBDs was 2–4.5 times the projected number of kidneys from donors diagnosed as brain dead.

Clearly, the use of NHBDs may give rise to problems because families have only a short time to decide about organ donation. A legal system based on presumed consent, that allows preservation of organs without consent, would enable optimal availability of the pool of potential NHBD kidney donors [33].

**Living donors**

Even after the advent of CsA, the results of renal transplantation are better with living donors than with cadaveric donors. Cecka and Terasaki [34] reviewed the data of UNOS. For patients with no HLA incompatibility, the 5-year graft survival was 85% for living transplants and 74% for cadaver transplants. The graft
half-lives were respectively 24.8 vs 16.1 years. For patients with 1–3 HLA incompatibilities, the 5-year survival was 72% for living transplants vs 60% for cadaver transplants. The half-lives were 13.1 vs 8.8 years. It is of interest that the results with unrelated living donors were slightly better than those reported with haploidentical living donors and similar to those observed in HLA-identical cadaver donors, the 5-year graft survival being 75% and the graft half-life 15.0 years.

The most troubling question with the use of living donors concerns the risks for the donor. Nephrectomy is a major surgical procedure which may have post-operative complications. However, most of these are minor. Major complications occur in <2% of cases [35]. The risk of death has been calculated to be ~0.03% [36], a risk of dying which has been estimated to be similar to that to which an average Ohio citizen has of dying of a vehicular or pedestrian accident for each 4 years of residence in Ohio [35]. What about long-term risks? Najarian et al. [36] compared the outcome of subjects who donated a kidney at least 20 years earlier with that of their healthy siblings. The renal function, and the prevalence of proteinuria and hypertension were similar in the two groups. Similar conclusions were reached in other studies. Furthermore, the vast majority of donors believe that their health has not been adversely affected by donation [37].

Some physicians still refuse to accept kidneys from living donors, especially if genetically unrelated to the recipient. Most ethicists, however, believe that the transplant centre must evaluate and advise, but in general the individual who is most at risk—the competent donor—should make the final decision. This approach respects and promotes individual autonomy over medical paternalism [37]. On the other hand, concern about motivation should be no greater for emotionally related donors than for genetically related ones. According to Thiel [38], there are several arguments in favour of emotionally related living donors: (i) the increasing waiting list for cadaveric kidneys; (ii) the excellent results of spouse transplantation with up to >90% success rates after 1 year; (iii) the strong motivation of a spouse donor comparable with that of parents donating to their children; (iv) the personal advantage for the donor which is certainly greater for a spouse than for a brother; (v) the possibility of bypassing dialysis completely; (vi) the experience that donation from spouses causes fewer psychological problems than transplantation from siblings; and (vii) the surprisingly few ethical objections and psychological resistance from the medical and nursing staff within a hospital also involved in cadaver kidney transplantation. On the basis of these considerations, the attitudes of many transplant physicians have changed over the last few years. In a recent survey, 90% of 154 responding US transplant centres replied that they would accept spousal donors, and 60% encourage donation from spouses or friends [39].

References

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