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Kidney transplantation in the elderly

Przeszczepianie nerek u osób w wieku podeszłym

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S u m m a r y

In this paper current state of the art in kidney transplantation in the elderly is discussed. Due to ageing of the society, including patients with end-stage renal disease, kidney transplantation in individuals over 65 years of age becomes more and more common. Organ allocation policy in accordance with the applicable Polish regulations, including the "old-for-old" principle concerning preferential transplantation of kidneys from donors over 65 years of age to recipients over 60 years old, is discussed. The use of kidneys obtained from elderly donors entails major medical problems and the personnel involved in the process should minimise the negative effects of the donor's age and the cold ischaemia time on the recipient's prognosis. The recipient's elderly age affects the mechanisms of repair, function of the immune system, and pharmacokinetics of immunosuppressive medications.

Key words: kidney transplantation, elderly donors and recipients, immunosuppressive treatment, acute rejection

S t r e s z c z e n i e

W pracy przedstawiono aktualny stan wiedzy na temat przeszczepiania nerek u osób w wieku podeszłym. Wobec starzenia się społeczeństwa, w tym populacji ze schyłkową niewydolnością nerek, coraz powszechniejsze staje się przeszczepianie nerek u osób powyżej 65. roku życia. Omówiono zasady alokacji narządów zgodnie z obowiązującym w Polsce stanem prawnym, w tym zasadę *old-for-old* stosowaną w celu preferencyjnego przeszczepiania nerek od dawców powyżej 65 lat biorcom ponad 60-letnim. Wykorzystanie nerek pochodzących od starszych dawców rodzi istotne problemy natury medycznej, a zadaniem personelu zaangażowanego w ten proces jest zminimalizowanie negatywnego wpływu wieku dawcy oraz czasu zimnego niedokrwienia na rokowanie u biorcy. Starszy wiek biorcy wpływa na upośledzenie mechanizmów naprawczych, zmiany w układzie immunologicznym oraz zaburzoną farmakokinetykę leków immunosupresyjnych.

Słowa kluczowe: przeszczepianie nerek, biorcy i dawcy w podeszłym wieku, leczenie immunosupresyjne, ostre odrzucanie

Kidney transplantation is a recognised and efficacious method of renal replacement therapy in patients with end-stage renal disease (ESRD), cheaper than dialysis therapy and allowing for longer survival. As Wolfe et al. (1) (1999) demonstrated in their classical study, the survival time of kidney transplant recipients is longer than that of dialysed patients or those dialysed and placed on the list of patients awaiting transplantation. However, at the time of publication only 1% of Americans aged over 70 years received a kidney from a dead donor; in addition, advanced age has always been a factor negatively affecting participation of the patients in clinical trials.

Over the last 20 years the demographic situation in the world, including Poland, has changed. According to Polish statistical data, in 2030 people over 65 years of age will constitute ca. 24% of the society; the number of elderly patients with chronic renal disease is also increasing, due to longer life as well as concomitant diseases such as diabetes mellitus and arterial hypertension which, if poorly controlled, affect kidney function. Aging of the society results in older recipients as well as donors – due to the widespread shortage of organs.

According to the "Poltransplant" bulletin (2), by the end of the year 2011 the National Waiting List included 2623 individuals awaiting kidney transplant, including 453 patients aged over 60 years (for the comparison: in 2008 there were 192 patients in this age group); despite a stable number of newly added patients, the number of awaiting elderly patients grew significantly, which also increased the mean age of patients awaiting kidney transplant

– 47 years and 3 months at present. The Polish system of kidney allocation for recipients placed on the waiting list is based on medical criteria and functions in accordance with the regulation of the Minister of Health of December 4th, 2009, concerning the national list of patients awaiting transplantation. One criterion of preferential donor-recipient matching is transplantation of a kidney obtained from a donor more than 65 years old to a recipient over 60 years of age (so-called obligatory transplantation, regardless of the score including HLA compatibility, duration of dialysis therapy, the need of retransplantation, and other factors). Such a system for allocation of "old" kidneys is consistent with the European Senior Program (ESP) introduced by Eurotransplant on 1.01.1999 (3). The aim of this program was to increase the number of kidneys obtained from elderly donors and shorten the time of waiting for transplantation for elderly recipients without a negative effect on the organ's or patient's survival. In order to shorten the cold ischaemia time and minimise the related risk of ischaemic damage, "old-for-old" transplantations may be possible within local waiting lists; the compatibility of main blood groups is mandatory and the PRA (panel-reactive antibody) value must be less than 5%, while HLA compatibility is not taken into account in the program. Initially the member states of Eurotransplant entered the program voluntarily; after two years the system became mandatory as a part of the European Kidney Allocation System (ETKAS).

A patient awaiting kidney transplant has a chance to receive an organ from a living donor, a deceased donor below 65 years of age, or a deceased donor over 65 years old. In 2011 in Poland 1002 recipients received kidneys from deceased donors, while only 40 patients were transplanted with a kidney from a living donor; therefore, elderly recipients have virtually no chance of receiving a kidney from a living donor. The possibility of discontinuation of dialysis therapy is mainly associated with the "old-for-old" principle, as kidneys from young donors are seldom transplanted to elderly recipients. It must be remembered that the aim of kidney transplantation in a young person is to allow for long-time survival of the patient (and the transplanted organ) and, should the organ cease to function, for retransplantation. A geriatric recipient's chance for retransplantation is low and the aim of transplantation is to prolong life and increase its quality in comparison with that of a peer on lifetime dialysis.

Kidney transplantation in the elderly is associated with the term "marginal donor", introduced as early as in 1991, (4) changed in 2002 to "expanded-criteria donor" (ECD) (5, 6): a deceased donor over 60 years of age without concomitant diseases or a deceased donor 50-59 years old meeting at least 2 out of 3 criteria: creatinine concentration over 1.5 mg/dl at the time of death, cerebrovascular death, or a history of arterial hypertension. As a rule, transplantation of a kidney from an ECD is associated with a 70% higher risk of graft failure in comparison with transplantation from a standard-criteria donor (SCD).

PHYSIOLOGICAL AGEING OF THE KIDNEYS

What is the difference between a kidney of an older donor and a younger kidney? The process of ageing affects all organs, including the kidneys (7-9). The weight of a kidney, increasing from birth to ca. 400 g in the 5th decade of life, then continuously falls by ca. 20-30% up to the age of 80 years. This affects in particular the cortical layer, with thinning and changed echostructure (due to scarring secondary to vascular lesions). Lesions typical for the ageing kidney are similar to those observed in other organs: arteriolosclerosis (accumulation of hyaline deposits), fibroblastic hypertrophy of the intima and media of the arcuate arteries and arterioles, and thickening of the basal membrane. Secondary to vascular lesions focal glomerulosclerosis, atrophy of the tubules (mainly proximal), and interstitial fibrosis (mainly in the cortex) develop. Arteriosclerosis is also observed and high pulse waves inflict additional damage on the walls of small vessels. The number of the glomeruli decreases with age (from a mean of 1 million per kidney) by 30-50%, with an increased proportion of "physiologically" sclerotic glomeruli, resulting in compensative hypertrophy and hyperfiltration of the medullar glomeruli, with their secondary segmental and global sclerosis.

The Poltransplant data indicate that in the years 2006-2011 the most common cause of death of donors in Poland were cerebrovascular conditions, i.e. haemorrhagic or ischaemic stroke (59%), and the mean age of a dead donor in 2011 was over 44 years; therefore, transplantation of organs from dead ECDs, mainly to elderly recipients, is a fact and the personnel involved in the process of donor preparation and the operation should minimise the negative effects of the donor's age and health on the recipient's prognosis.

QUALITY OF KIDNEYS OBTAINED FROM ELDERLY DONORS

Provided that the probability of the organ being obtained from an ECD increases with the donor's age (10, 11) and the possibility of transplantation of a kidney from a living donor whose organ – even if not young – is still of better quality than that of a deceased donor (12) is very small, the quality of an "old" kidney becomes very important. Age-related physiological changes in the kidneys combined with the donor's past diseases, the risk of ischaemic injury, and potential nephrotoxicity of immunosuppressive medications result in the risk of primary graft insufficiency (13). The mechanism of this injury is unclear, although ageing seems to limit the repairing properties of epithelial cells. The number of

glomeruli without tubules also increases, as demonstrated in patients with chronic allograft nephropathy (14). Therefore, the correlation of the donor's age and the cold ischaemia time becomes critical for the recipient's prognosis. Is it possible to "predict" lower quality of an elderly kidney before transplantation if, as demonstrated by the Third National Health and Nutrition Survey (NHANES III) performed in the USA, only in 7.6% of individuals 60-69 years old and in 25.9% of those aged over 75 years eGFR is below 60 mlmin/1.73 m^2 (15)? Preimplantation kidney biopsy is not a new idea (16) – histological assessment of the organ may facilitate the decision to reject an organ or the choice between single and dual kidney transplantation (SKT vs. DKT) in order to increase the final eGFR value. Remuzzi et al.(17) assessed kidney biopsy specimens obtained from potential donors aged over 60 years using a scale concerning specific features (in which 0 represented no abnormalities and 12 – advanced interstitial lesions): kidneys scoring 0-3 were used for single transplantations, those scoring 4-6 – for dual transplantations, and the remaining organs were rejected. After 3 years of follow-up the results of DKT were better than those of SKT for elderly donors. Another "cut-off" parameter may be the number of sclerotic glomeruli. Andres et al. (18) evaluated kidneys obtained from donors aged 60-75 years and performed SKT if the proportion of sclerotic glomeruli was lower than 15% and DKT if the proportion was 15-50%. After a year the kidney survival rate was 90% in the SKT group and 95% in the DKT group.

In Poland in 2011 the DKT procedure was applied in 4 recipients.

On the margin of this review the study by Kasiske and Snyder (19) should be recalled. The authors demonstrated that the prognosis is determined not by the recipient's age but the donor's age – the results of "old-for-old" transplantations were better than "old-for-young".

SELECTION OF GERIATRIC RECIPIENTS

On the recipient's side concomitant diseases and the transplant waiting time were more significant predictors of post-transplant complications than the recipient's chronological age. It is known that the sooner the recipient undergoes transplantation (i.e. the shorter their waiting time), the better the prognosis. An American study (published in 2006) concerning this problem (20) demonstrated that the probability of transplantation for elderly patients was the highest in the first year after placement on the waiting list, while those remaining on the list for 5 years had a 4 times lower chance of transplantation of a kidney from a standard donor than recipients 18-39 years old (this is the opposite relationship to that observed in young people, for whom it "pays off" to wait longer for a better organ). In that study patients with diabetes comprised a specific group benefiting from quick transplantation. Similarly, in a large American study (21) published in 2007 the eldest donors (above 70 years of age) benefited from quick transplantation – even from an ECD – in comparison with their peers still undergoing dialysis therapy. Elderly patients are less often placed on the waiting list (22) and the chronological age criterion may "replace" the patient's actual biological age and their physical (e.g. heart failure, emaciation, bone complications of renal disease) and mental abilities. However, considering that in the first year after kidney transplantation 35% of deaths of recipients aged over 60 years are due to cardiovascular complications (23), caution in offering kidney transplantation to elderly patients is hardly surprising.

IMMUNE SUPPRESSION IN THE ELDERLY

There is no specific immune suppression regimen dedicated to recipients over 65 years of age. Immunosuppressive treatment in any age group consists in balancing between too strong immune suppression resulting in infectious complications (among recipients over 60 years of age 38% of deaths in the first year after transplantation are due to infection!) (23) and malignancies, and too weak suppression resulting in acute graft rejection. In elderly recipients this is combined with physiological changes due to ageing, the immune potential of kidney transplantation from an elderly donor, and lower histological quality of an organ obtained from an ECD, which may result in a higher risk of delayed graft function and worse long-term graft function. Kidney transplantation in the elderly is also associated with a higher risk of nephrotoxicity of medications (especially calcineurin inhibitors – CNI) and, due to a high number of concomitant diseases, a higher probability of adverse drug-drug interactions.

Aging of the immune system involves (24, 25) involution of the thymus in which T cells learn to recognise autoantigens with adequate affinity. As a result, the number of naive lymphocytes and the TCR variability decrease; the proportion of thymus-dependent CD4+ and CD8+ cells shifts towards CD4+, and a decrease in number of naive cells is accompanied by an increase in number of the memory cells. The latter's potential to proliferate in response to stimulating factors, such as IL-2, is small and the expression of co-stimulating molecules, e.g. CD28, is lower (which may be the cause of different efficacy of induction treatment with basiliximab in elderly recipients). For post-transplant patients clonal expansion of highly differentiated T cells specific against CMV, with low CD28 and CD27 expression, is also of importance. With age the number of B cells capable of antibody production as well as the number of circulating memory B cells decrease. Production of specific classes of antibodies changes – the concentrations of IgM and and IgE decrease, while that

of IgG grows. The expression of MHC antigens on antigen presenting cells decreases.

Therefore, the mechanism and course of acute graft rejection in elderly recipients is different from that observed in younger age groups. In general, the immune response in elderly recipients is weakened, but when acute rejection occurs, its effect on long-term prognosis will be more significant than in younger recipients (26, 27). This is due to the kidney injury itself and limited repairing properties as well as adverse effects of treatment of acute rejection (infectious and malignant complications due to more intensive immune suppression). Moreover, the older the donor, the more immunogenic the kidney, according to the physiology of ageing discussed above. Therefore, the risk of acute graft rejection is higher for a geriatric donor (28, 29). Pratsche et al. (28) demonstrated a higher incidence of acute rejection episodes in recipients in the ESP program in the first year after transplantation (42% vs. 30% in younger recipients of kidneys from SCD) which, however, did not affect the graft survival rate after a year (86% vs. 79% in the control group). The authors stressed also the possibility of effect of insufficient HLA matching in patients qualified for the ESP, despite wider application of induction treatment. Higher immunogenicity of older kidneys was previously demonstrated in studies in animals (30).

What, therefore, should be safe immune suppression in the elderly? According to American data (31), in 2010 90% of patients (regardless of age) received tacrolimus as a de novo calcineurin inhibitor, and mycophenolates essentially supplanted azathioprine. Therefore, a typical treatment regimen includes glucocorticosteroids, a calcineurin inhibitor and sodium/ /mofetil mycophenolate, with or without induction.

Danovitch et al. (32) proposed a term of "the evil axis", representing the processes of infection, rejection, and malignancies in the elderly. The authors reminded that elderly patients more often suffer from conditions increasing the risk of infections: colonic diverticulosis, urinary tract infections, heart failure, and diabetes mellitus. Citing the study by Meier-Kriesche et al. (33) the authors noted that mortality due to infections among recipients over 65 years of age was only slightly higher than among their peers awaiting transplantation – 16.7 vs. 20/1000 individuals (for the comparison: the respective numbers in the group of recipients 40-49 years old were 6.1 and 15.4). As discussed above, decisions concerning minimisation of immune suppression must therefore be taken with great care; otherwise treatment of acute rejection may easily squander the success of transplantation.

The risk of malignancies increases with age, also in transplant recipients. This is not surprising given impaired immune surveillance and increased incidence of infections, also those potentially oncogenic. Kasiske et al. (34) calculated that in patients undergoing transplantation in the USA in the years 1995-2001 malignancies (other than non-melanoma skin cancer) occurred three times more often in recipients aged 50-64 years and five times more often in the elderly in comparison with recipients 18-34 years old. However, no relationship between specific immune suppression regimens and malignancies was found.

From the clinical point of view, an important issue is safe dose adjustment of immunosuppressive medications in elderly recipients in whom ageing per se may affect pharmacokinetics, including drug absorption, distribution and metabolism. This may be combined with the negative aspects of transplantation of kidneys from ECDs discussed above and interactions with medications used in treatment of concomitant diseases. Danovitch (32) reminded that metabolism of calcineurin inhibitors is particularly sensitive to changes in blood flow in the liver and changed activity of the IIIA cytochrome isoenzymes as well as glycoprotein carriers. Similarly, pharmacokinetics of mycophenolate mofetil is affected by protein binding, lower by 15-25% in the elderly (25), which may result in increased blood concentration of mycophenolic acid. The toxicity of mycophenolate is increased in the state of hypoalbuminaemia. Cyclosporine in turn is lipophilic and its volume of distribution increases with increased amount of the adipose tissue in the body. Age-related renal excretion of medications is especially pronounced in recipients of elderly kidneys. Danovitch stressed also that changes in pharmacodynamics of immunosuppressive medications, i.e. the way in which they affect the ageing immune system, may be more important than their pharmacokinetics.

No recommendations concerning the use of specific doses of immunosuppressive medications in elderly recipients have been issued. This is at least partially due to exclusion of patients over 60 years of age from clinical trials and possible difficulties in objective evaluation of drug activity in a situation in which pharmacokinetics may be changed. Neither the study by Danovitch (32) cited above nor a recent review concerning organ transplantation in the elderly published in the American Journal of Transplantation in 2012 (35) make decisions easier – the authors stress the necessity of individual treatment planning in each patient. As far as induction treatment is concerned, there is no evidence for superiority of specific products in this age group of recipients. A study by Gill et al. (36), in which induction treatment in recipients aged 60 years or more who underwent transplantation in the USA in the years 2003-2008 was analysed, is remarkable. The authors discussed the use of IL-2 receptor antagonists (IL2RA), rATG and alemtuzumab in various subpopulations of recipients: a recipient of high immunological risk – a kidney from a low-risk donor,

a high-risk recipient – a high-risk donor etc. A high immunological risk in the recipient was defined as PRA above 20% or African origin, while a high risk in the donor meant an ECD, DCD (a donor after cardiac death – not applicable in Poland), or the cold ischaemia time exceeding 24 hours. In all groups higher incidence of acute rejection episodes was observed in patients treated with IL2RA in the first year after transplantation (a limitation of the study was the lack of data concerning the applied CNI doses). It should also be noted that even in low-risk recipients the episodes of acute rejection were more common in case of delayed graft function (DGF).

On the other hand, Danovitch (32) (2007) cited previous studies in which oncogenic and pro-infectious properties of anti-lymphatic agents were stressed, suggesting that IL2RA should be the medications of choice in induction therapy in elderly recipients. Regardless of the choice of a product, the aim of treatment is to reduce the risk of acute rejection as well as to reduce doses or discontinue nephrotoxic calcineurin inhibitors. In this context the study by Arbogast et al. (37) concerning the use of ATG and/or basiliximab in induction treatment is worth noticing. Administration of cyclosporine after at least 13 weeks following transplantation (in 42% of patients; those remaining did not require it) allowed for very good effects after 3 and 5 years of follow-up: the recipient/graft survival rate after 3 and 5 years was 87.7/77% and 87.7/70%, respectively. Delayed treatment with tacrolimus was similarly evaluated (38); however, in all cited studies induction treatment was used.

As mentioned above, mycophenolates practically replaced azathioprine and there is no doubt this group of medications is more efficacious, also in elderly recipients (39).

The use of mTOR inhibitors, despite their efficacy in prevention of development of malignancies in organ recipients, remains controversial in elderly patients due to their adverse effects, such as impaired wound healing, pulmonary complications, or lipid disorders (32).

A limited number of studies concerning the possibility of discontinuation of glucocorticosteroids in elderly patients, in whom the risk of infections, fractures, myopathy and diabetes is higher, does not allow for such a recommendation at present (35, 40).

Danovitch (32) proposed consideration of the following treatment decisions in elderly recipients:

1. Young donor – elderly recipient of low immunological risk: consider early discontinuation or dose reduction of glucocorticosteroids.
2. Elderly donor – elderly recipient of low immunological risk: consider dose reduction of CNI.
3. Consider induction treatment in regimens limiting the use of CNI; the author prefers IL2RA due to their better safety profile in comparison with ATG.
4. A recipient of high immunological risk: minimisation of immune suppression is not recommended; induction treatment, glucocorticosteroids, CNI and mycophenolate may be suggested.
5. Due to the risk of complications of treatment with glucocorticosteroids empiric treatment of suspected acute rejection episode without confirmation by means of biopsy is not recommended.
6. Following treatment of acute rejection, return to prevention of infections should be considered.

LONG-TERM PROGNOSIS

As mentioned above, the aim of kidney transplantation in an elderly patient is to prolong life and increase its quality in comparison with dialysis therapy. According to a review by EL Hartmann for the American Society of Nephrology (41), based on USRDS 2007 Annual Data Report, the life expectancy in patients aged 65-69 years was 3.9 years in those undergoing dialysis and 10.6 years following kidney transplantation; in individuals 70-74 years old the respective numbers were 3.3 and 8.9. European studies also indicate that kidney transplantation in the elderly will double their life expectancy in comparison with dialysed patients, which was stressed by the authors of the ESP summary after 5 years (25).

The study by Danovitch et al. (32) is worth citing again in this context. The authors stressed that general mortality among elderly recipients was higher than in those younger, but comparison with "typical" age-related mortality rates revealed no significant differences in survival in specific age groups. Oniscu et al. (42) noted that 8-year survival rate in recipients aged 60-65 years was 49%, in those aged 65 years or more – 33%, and in individuals 18-49 years old – 82%. However, an analysis similar to the one presented above revealed a survival rate of 70% in all groups.

Long-term prognosis in elderly recipients is affected by their susceptibility to serious infectious diseases (35), and the risk of death increases with the recipient's age. As mentioned above, infections are the leading (38%) cause of death in the elderly recipients in the first year after transplantation (23). The second (35%) cause of early mortality after transplantation are cardiovascular complications. Abecassis et al. (25) stressed that cardiological evaluation of the recipient before transplantation was focused on perioperative survival and it was not clear how long-term cardiovascular risk might be best predicted. There is no doubt that careful selection of the immune suppression regimen affects long-term survival of the organ recipient.

The ESP results after 5 years (3) indicate better survival of grafts and recipients who received younger kidneys than those qualified for the program (64/74% vs. 47/60%); however, these results cannot be compared with those in age-matched

dialysed patients. Such data are available in the USA as that country does not take part in the program and organ allocation according to UNOS (25) is left at the local level. According to the publications, (20) even transplantation of an "old" kidney to an elderly recipient results in better survival than dialysis therapy.

While the graft loss for immunological reasons is frequent in young recipients, the main cause of graft loss in elderly recipients is the patient's death (42). In omparison with recipients 18-29 years old, in patients above the age of 65 years the risk of death with a functioning graft is 7 times higher (44).

Therefore, kidney transplantation in patients above 65 years of age gives them a chance for life without dialyses for the price of a higher risk of delayed or worse graft function, and in recipients of kidneys obtained from geriatric donors – also more common episodes of acute rejection. Avoidance of long (over 24 hours) cold ischaemia time and individualisation of immune suppression may improve the quality of life of the recipients.

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