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Kidney Transplantation: Topical Issues and Current Trends (Review)

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Abstract This article presents current approaches and trends in renal transplantation. The authors reviewed publications in specialized search engines PubMed, Web of Science, Embase, Google Scholar, etc., on the issues of kidney transplantation. Early kidney transplantation, a younger donor age, and optimal graft function in the first year are of paramount importance for long-term transplant survival. Measures on solving these issues (careful selection of donors, preventive kidney transplantation and efficient immunosuppressive protocols) are still a priority and optimal graft function during the first year are very important for the long-term survival of the graft. Improving the diagnostics, treatment and identification of the causes of unfavorable outcomes after kidney transplantation, as well as ways to prevent complications in the pre- and postoperative periods remain extremely relevant issues of modern renal transplantation.

Keywords Chronic kidney disease, Hemodialysis, Kidney transplantation, Donor, Recipient

According to world statistics, today the number of patients suffering from terminal kidney diseases in the world exceeds more than 4 million people, at the same time, the number of surgical interventions aimed at replacing an organ that has lost its functions is steadily growing (UNOS, the USA) [1].

Over the past ten years, the number of publications on solid organ transplantation has been increasing every year. Thus, in 2023 alone, the number of publications in specialized search engines PubMed, Web of Science, Embase, Google Scholar, etc., on the issues of kidney transplantation (KT) already totals more than 7,000 scientific and practical sources.

Considering the fact of the significant advantages of KT from a living donor and its recognition as the first line for patients with end-stage kidney disease, however, issues related to graft and patient survival, which are influenced by many interdependent factors both in the pre-transplantation period, remain unresolved (donor eGFR, donor type, socioeconomic status, HCV infection in the recipient, type of immunosuppression, etc.) [2] and in the post-transplant period (urological complications; rejection, infection, viral nephropathy, post-transplant diabetes mellitus, cancer invasion, renal interstitial fibrosis, etc.) [3-6]. and the existing factors of discrepancy in the degree of relationship, anthropometric indicators, HLA and ABO systems, etc. with living donation, create a large number of controversial issues and more detailed evaluation criteria for treatment results [7-8].

One of the priorities at the present stage of the development of transplantology is the improvement of the related organ donation system for transplantation and at the same time a resource for the further development of transplant care in world practice.

If, with regard to cadaveric donation, the experience and successes of the global system for coordinating organ donation demonstrate proven potential and can be used in the development of this direction in regions where this implementation program is only at the embryonic stage, then with regard to transplantation from a living related donor, it continues to develop taking into account the accumulated experience and assessment of quality of life criteria, long-term prognosis, both in relation to the recipient and the donor. For example, in case of related donation, issues related to the influence of age and gender aspects on the survival of the transplant and the patient remain relevant [9-10]. Thus, C.M. Ø ien et al. (2007) conducted a study after 739 first-time performed KTs with an average follow-up period of 55.1 months. The authors found that episodes of acute rejection increased in transplant recipients from donors at the age of 65 and older (p= 0.009). And the risk factors for early episodes of acute rejection were, respectively, the age of the donor 65 years or older with the recipient's age less than 50 years, HLA matching and the female gender of the donor. During the first 5 years after KT, an additional risk factor was an episode of steroid-resistant rejection, and more than 5 years after transplantation, the only additional risk factor for graft loss was male donor gender. Nevertheless, the authors consider it is necessary to continue using older male and female living donors who meet carefully developed medical criteria and are highly motivated to donate [11].

A more detailed study was carried out by S.H. Lee et al. (2014) who examined the effect of age matching (age difference less than 10 years) on survival after living donor kidney transplantation in 211 patients after primary living

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donor kidney transplantation and divided into two groups: the same age (n = 123) and different age (n = 78). The authors noted differences between groups in graft survival (p=0.008) and death-censored graft survival (p=0.003). The one-, 3-, and 5-years transplant survival rates were 100%, 100%, and 97% in the same age group, respectively, and 97%, 90%, and 88% in the different age group, respectively. According to Cokc multivariate regression analysis, the age-matching variable was an independent predictor of both graft survival (β=1.325, p=0.017) and death-censored graft survival (β=2.217, p=0.021). The authors conclude that when selecting a living donor and recipient, the age difference between them should be minimized [9].

This is confirmed by the research of M.I. Bellini et al. (2022) who conducted a systematic review and meta-analysis in EMBASE, MEDLINE, Web of Science, BIOSIS, CABI, SciELO and Cochrane. The authors identified 5129 studies, of which 47 met the inclusion criteria and were analysed. There was no significant difference in 1-year recipient survival between recipients of donors aged <50 years compared with donors aged >50 years (HR = 0.65 95% CI:0.1–4.1) and recipients of donors aged < 60 years compared with donors aged >60 years (RR = 0.81 95% CI:0.3–2.3). Graft survival was significantly higher in recipients of transplants from donors under 60 years of age. The risk of acute rejection (RR = 0.62, 95% CI: 0.5–0.8) was significantly lower in recipients of transplants from donors aged <60 years. Recipients of male donors had lower 1-year serum creatinine (MD = 0.12 mg/dL, 95% CI: 0.2–0.1) and higher eGFR compared with male donors-women (p <0.00001) [10].

Studies on the influence of living donation relatedness degree on graft survival are noteworthy. An interesting fact is that long-term, mid-term and short-term follow-up of living related and unrelated kidney transplantation showed no significant difference in graft survival. In addition, the incidence of acute rejection was not significantly different between the groups [12-13].

S.A. Husain et al (2021) examined the association between donor-recipient biological relationship and allograft survival (n=86154) after primary kidney transplantation from a living donor performed in the United States, from January 1, 2000 to December 31, 2014. It was observed that among 72980 transplant donors and recipients, 43174 (59%) donors and recipients were biologically related and 29806 (41%) were unrelated. Donors related to their recipients were younger (mean [IQR] age 39 (31-48) vs. 44 (35-52) years) and with fewer women (24848 (58%) vs 19142 (64%)). Related pairs had fewer HLA mismatches overall (median [IQR], 3 (2-3) vs. 5 (4-5)). In this study, KTs from living donors (after accounting for HLA matching) biologically related to their recipients had higher allograft failure rates than grafts from donors unrelated to their recipients. The authors believe that further research is needed to determine what genetic or socio-medial factors are associated with this finding [14].

One of the hotly debated and unresolved issues in KT from a living donor to date is the effect of HLA and ABO mismatch in donor-recipient pairs [15-16]. B.J. Orandi et al (2016) conducted a study in 22 centers and evaluated survival in 1025 renal transplant recipients from HLA-incompatible living donors who were matched with a control group (those who remained on the waiting list or received a kidney from a cadaveric donor). Based on the results of the study, it was noted that renal transplant recipients from incompatible living donors had a higher 1-year survival rate than either of the control groups (95.0% compared with 94.0% for the waitlisted or transplanted control group and 89.6% for the waitlisted-only control group); 3 years (91.7% vs. 83.6% and 72.7%, respectively); 5 years (86.0% vs. 74.4% and 59.2%) and 8 years (76.5% vs. 62.9% and 43.9%) (p<0.001 for all comparisons with two control groups). The survival advantage was significant after 8 years for all levels of donor-specific antibodies: 89.2% for renal transplant recipients from incompatible living donors who had a positive Luminex anti-HLA antibody test but a negative flow cytometry cross-sectional result [15].

The studies of B. Ribeiro et al. (2023) who evaluated all adults who underwent KT from a living donor between 2006 and 2018 are also interesting in this regard. Their HLA compatibility was classified according to the British Transplant Society system into low mismatch (LM) (level 1-2) and high mismatch (HM) (level 3-4). Outcomes of interest were acute rejection and overall or censored graft survival. The authors analyzed 1,068 renal transplant recipients and noted that in the study cohort, HLA level increased the risk of acute rejection regardless of the type of living donor. Nevertheless, the authors confirm the advantage of a living donor over a deceased one even with an elevated HLA [17].

However, tracing the distant period of renal transplants from HLA incompatible living donors, there were publications in the literature about the risk of cancer in this type of recipients, which was associated with preliminary massive immunosuppression and on this background desensitization to facilitate transplantation. In this regard, the publication by J.D. Motter et al. (2023), in which the authors examined cancer risk in a multicenter cohort with linkage to the U.S. transplant registry and 33 cancer registries (1997-2016), is of interest. The researchers evaluated 858 cases after HLA incompatible KT from living donors and 12239 cases after compatible KT from living donors. Among incompatible donor-recipient KT, the median follow-up time was 6.7 years (maximum 16.1 years) for invasive cancers and 5.0 years (maximum 16.1 years) for basal cell and squamous cell cancers. Invasive cancer occurred in 53 recipients (6.2%), and basal cell and squamous cell cancer occurred in 41 (4.8%). However, cancer risk did not differ according to the strength of donor-specific antibodies and in exploratory analysis was similar between the two compared groups for most cancer types and stage, except that "incompatible" KT had an increased risk of colorectal cancer. The authors conclude that the risk of cancer is not increased and is not a direct consequence of incompatibility, and the possible increased risk of colorectal cancer is unexplained and may indicate the need for specialized screening or preventive measures [18].

Attention should also be focused on studies related to the analysis of the characteristics of kidney transplant recipients, which show satisfactory graft function after 5-10 years of follow-up, in order to improve graft survival and ensure the best kidney function in the long term. B. Sayin et al. (2019) retrospectively evaluated the graft function and demographic characteristics of 288 patients who underwent KT. The authors found that 149 patients (51.7%) had excellent graft function, 88 patients (30.5%) had a functioning graft with GFR less than 60 ml/min and/or had evidence of renal graft dysfunction, and 45 patients (15.6%) lost the graft. Multivariate analysis showed that excellent predictors of graft survival after 5 years were negative panel reactive antibody levels, lower donor age, shorter duration of dialysis, no episodes of acute rejection, 3 or fewer HLA mismatches, and lower levels of immunosuppression [19].

Another issue discussed is the hypothesis that the relatively smaller size of the donor kidney relative to the size of the recipient leads to higher graft loss due to insufficient nephrons and hyperfiltration damage. A.J. Miller et al. (2017) conducted a study of data from the American Scientific Registry of Transplant Recipients. 21,261 from 115,124 renal transplant recipients, experienced death-censored graft failure (median graft survival time, 3.8 years; quartiles 1–3: 0.0 to 14.8 years). After multivariable adjustment, the highest relative risks of graft failure were observed in female recipients of male donor kidneys, and male recipients of female donor kidneys, in situations where the recipient was >30 kg heavier than the donor (HR, 1.50; 95% CI, 1.32 to 1.70; HR, 1.35; 95% CI, 1.25 to 1.45, respectively). The authors conclude that simultaneous donor-recipient body weight mismatch (donor<recipient) and donor-recipient sex are associated with a higher risk of graft loss with censored death at KT [20].

Another issue discussed in the literature is the evaluation of the possible benefits associated with early, preemptive or preventive KT. Studies evaluating the benefit to patient survival of preemptive kidney transplantation have compared it to postdialysis kidney transplantation. When comparing the survival of patients with preemptive kidney transplantation and those on the dialysis waiting list, there is a clear advantage in patient survival in favor of preemptive kidney transplantation. This advantage, according to some authors, justifies the promotion of preventive kidney transplantation [21-23].

The issue related to antibody-mediated rejection syndrome cannot be overlooked, which is a serious complication after KT that contributes to both short- and long-term damage [24-25]. Standard therapy for this complication combines plasmapheresis and intravenous immunoglobulins with or without steroids, with or without rituximab; however, despite such combined treatment, the effect is not always positive. In this regard, the study by L. Cabezas et al. (2022) who analyzed the PubMed literature and reviewed six studies including 117 patients and evaluated Tocilizumab, considering it the main humanized monoclonal drug targeting IL-6. Most studies report a significant reduction in donor specific antibody levels and a reduction in inflammation and microvascular lesions (found on biopsy). The authors believe that this drug may be an alternative for patients after KT complicated by this syndrome or as second-line therapy after treatment failure. Further randomized and controlled trials are needed to confirm these results [26].

One of the discussed issues regarding the prospects for the development of living donation is also the global kidney exchange, which, according to a number of world associations, allows to expand kidney transplantation from a living donor internationally for patients with immunological barriers. I.R. Marino et al (2022) proved that this concept is successful in a limited number of transplants. However, a number of misconceptions, according to the authors, have created obstacles to its development. The authors are convinced that the systematic application of this innovative tool will allow the cure of thousands of patients worldwide who are currently denied transplants and often even access to dialysis [27].

Studies related to solutions that improve access to KT from a multi-stakeholder perspective deserve special attention. So, R.V. Merweland et al. (2023) conducted a qualitative study using semi-structured interviews with both groups and individual participants. Participants were health care providers (geographically dispersed), patients and (former living) kidney donors, politicians and insurance companies. Stakeholders (n=87) were surveyed regarding their perceptions, opinions and attitudes towards access to kidney transplantation. According to respondents, more efforts should be made to inform health care providers and patients about clinical guidelines for kidney transplantation. The same applies to differences in medical inclusion criteria used in different transplant centers. Stakeholders identified opportunities for improvement based on psychological and social themes, especially with regard to the provision of information. Many stakeholders indicated the need to rethink the current economic model to improve access to KT [28].

The article by J. Augustine (2018), in which the author notes that there has been significant progress in KT over the last 20 years is of interest. The focus has shifted to using stronger immunotherapy rather than trying to minimize it. There is a recognition of the role of complications associated with infection and how to prevent and treat it. Induction therapy now has a greater emphasis so that maintenance therapy can be facilitated to reduce long-term toxicity. Perhaps the biggest change is the practice of screening for donor-specific antibodies at the time of transplantation so that predictable problems can be prevented or successfully managed if they occur. Such advances helped patients directly by extending the life of their transplanted organs [29].

One of the breakthroughs in the technical performance of solid organ transplants is the use of robotic KT. J.S. Slagter et al (2022) conducted a systematic search including 11 studies comparing 482 robotic KT procedures with 1316 open KT procedures. Robotic KT was associated with a lower risk of surgical site infection (hazard ratio (RR) = 0.15, $p < 0.001$), symptomatic lymphocele (RR = 0.20, $p = 0.03$),

less postoperative pain (mean difference (MD) = -1.38, $p < 0.001$), shorter incision length (MD = -8.51 cm, $p < 0.001$) and shorter hospital stay (MD = -1.69 days, $p = 0.03$) compared to open KT. No differences were found in kidney function, graft or patient survival [30].

One of the promising areas in kidney transplantology is the search and use of the most promising biomarkers for the early diagnosis of rejection of an allogeneic kidney transplant [31-33]. Thus, the National Center for Biotechnology Information (NCBI) proposes to continue the study of such biomarkers as: Lipocalin associated with neutrophil gelatinase [34-36]; Kidney damage molecule-1 [37-38]; Motif Chemokine 10 [39-40]; Cystatin C [41-42]; Osteopontin [43-44]; Clusterin [45], etc..

Another new direction that promises to minimize premature graft loss after KT is the strategy of genome-based precision medicine through precision approaches to matching the immunocompatibility between kidney donors and recipients. According to M. Yaghoubi (2023), the potential implementation of this technology requires important changes in clinical management processes and distribution policies. Such potential policy change decisions can be supported by decision models based on health economics, comparative efficiency research, and operations management. The author used a systematic approach to identify and extract information about models published in the kidney transplantation literature and provide an overview of the state of collective, model-based knowledge of the kidney transplantation process. 144 studies were included, most of which focused on one component of the transplant process, such as immunosuppressive therapy or donor-recipient matching and organ allocation policies. Pre- and post-transplant processes are rarely modeled together. The author emphasizes closer collaboration between disciplines and modeling of the whole disease, integration of precision medicine tools into kidney transplantation [46].

The following conclusions can be drawn from this review:

Early kidney transplantation, younger donor age and optimal graft function in the first year are of paramount importance for long-term graft survival.

Measures to address these issues (careful donor selection, preventive kidney transplantation and efficient immunosuppressive protocols) remain a priority and optimal graft function during the first year is paramount for long-term graft survival.

Improvement of diagnosis, treatment and identification of causes of unfavorable outcomes after kidney transplantation, as well as ways to prevent complications in the pre- and postoperative periods remain highly relevant issues of modern renal transplantology.

Conflict of interests

The authors declare no conflict of interest.

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