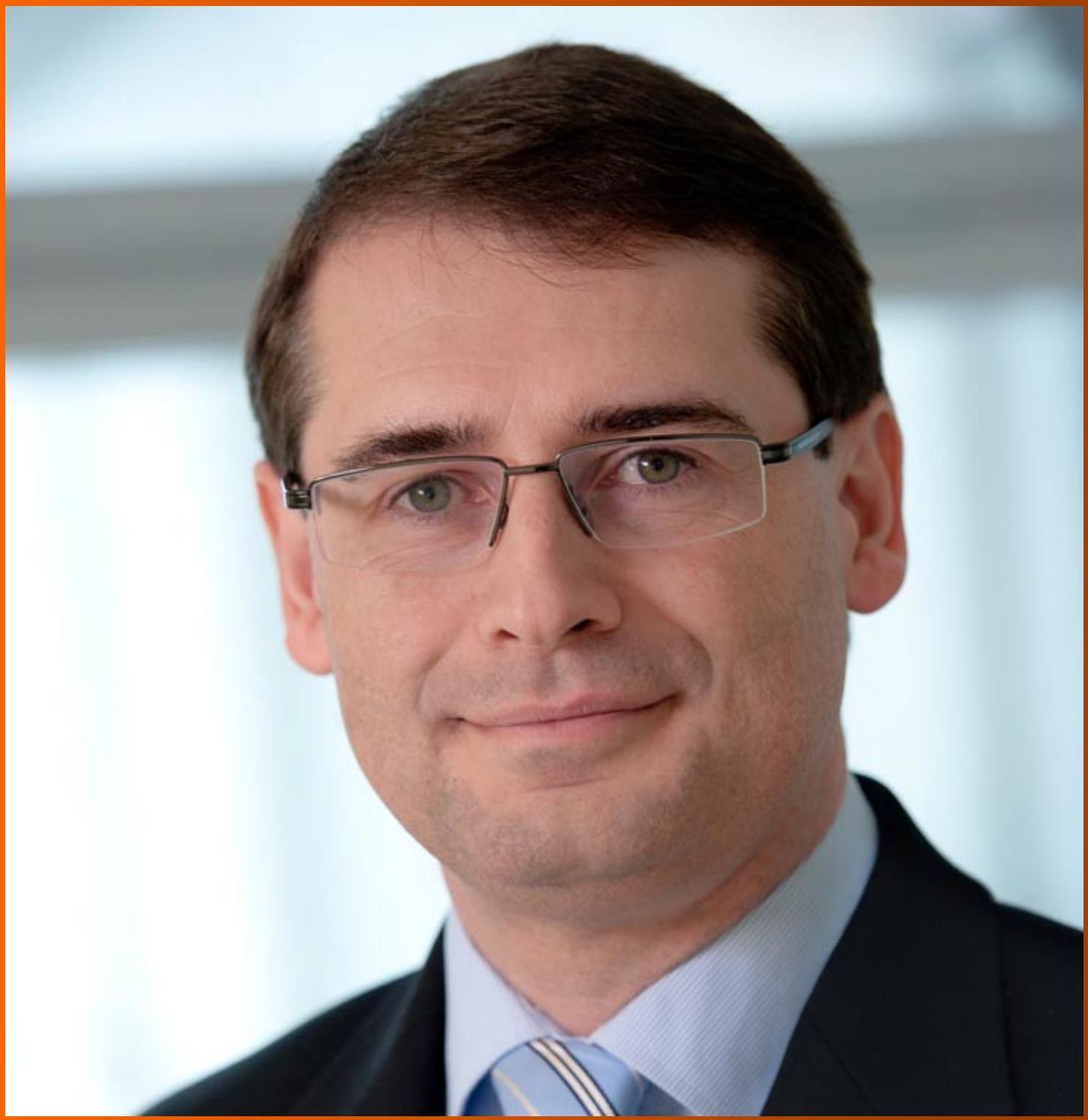
ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2015 June 24; 5(2): 38-72



Published by Baishideng Publishing Group Inc

WJT World Journal of Transplantation

A peer-reviewed, online, open-access journal of transplantation

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World Journal of Transplantation (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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World Journal of Transplantation is now indexed in PubMed Central, PubMed, Digital Object Identifier.

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NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Quarterly

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Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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PUBLICATION DATE
June 24, 2015

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2220-3230/g_info_20100722180909.htm.

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DOI: 10.5500/wjt.v5.i2.38

World J Transplant 2015 June 24; 5(2): 38-43
ISSN 2220-3230 (online)

EDITORIAL

Changing organ allocation policy for kidney transplantation in the United States

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Author contributions: Chopra B contributed to literature search, writing of the manuscript; Sureshkumar KK contributed to literature search, writing of the manuscript.

Conflict-of-interest: None.

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Received: January 22, 2015
Peer-review started: January 26, 2015
First decision: February 7, 2015
Revised: February 14, 2015
Accepted: March 16, 2015
Article in press: March 18, 2015
Published online: June 24, 2015

Abstract

The new kidney allocation scheme (KAS) in effect since December 4th 2014 was designed to overcome the shortcomings of previous system. A key feature of the new KAS is preferential allocation of best quality organs to wait-list candidates with the longest predictive survival in a concept called longevity matching. Highly sensitized recipients would get extra points and enjoy widespread sharing of organs in order to increase accessibility to transplant. Wait-list candidates with blood group B will be offered organs from donors with A2 and A2B blood type in order to shorten their wait-list time. Time on the wait list will start from day of listing or date of initiation of dialysis whichever comes first which should benefit candidates with limited resources who might be late to get on the transplant list. Pay back system has been eliminated in the new KAS. These changes in organ allocation policy may lead to increase in median half-life of the allograft and increase the number of transplants; thus resulting in better utilization of a scarce resource. There could be unintended negative consequences which may become evident over time.

Key words: New kidney allocation scheme; Longevity matching; Highly sensitized; Kidney donor profile index; Expected post-transplant survival

Core tip: The new kidney allocation system (KAS) was recently implemented in the United States in an attempt to improve the utilization of deceased donor kidneys. A key feature is preferential allocation of best quality organs to wait-list candidates with the longest predictive survival in a concept called longevity matching. Attempts were also made to improve access to kidney transplantation by giving priority points to highly-sensitized recipients and by giving consideration to dialysis vintage. Simulation model has predicted a modest increase in median allograft and patient life-years with the new KAS. Potential limitations and unintended consequences are also discussed in the article.

Chopra B, Sureshkumar KK. Changing organ allocation policy for kidney transplantation in the United States. *World J*

Transplant 2015; 5(2): 38-43 Available from: URL: http://www.wjgnet.com/2220-3230/full/v5/i2/38.htm DOI: http://dx.doi.org/10.5500/wjt.v5.i2.38

THE NEED FOR A NEW ALLOCATION SYSTEM

Kidney transplantation extends life and improves quality of life for most individuals compared to patients on the waiting list undergoing dialysis[1]. In the United States, an increasing number of candidates on the kidney transplant waiting list without a corresponding increase in the availability of suitable organs have led to a gradual widening of the gap between demand and supply of organs. This along with the shortcomings observed in the organ allocation system during the last two decades led to the development of the new kidney allocation scheme (KAS) for deceased donor (DD) kidney transplantation. New KAS was approved by the organ procurement and transplantation network (OPTN) in June 2013 and subsequently implemented for clinical use starting on December 4th 2014. In the previous allocation system, candidates who accrued the longest waiting time received the kidney transplant irrespective of their expected long-term outcomes. As a result, many older transplant recipients died with a functioning allograft while several younger recipients failed their older donor kidneys with return to waiting list in a short duration[2]. There was less emphasis regarding the level of HLA sensitization of candidates. The minority candidates who have difficulty in navigating the complex transplant process got listed late and hence had to wait longer to receive a transplant, whereas the educated affluent candidates generally got listed as soon as glomerular filtration rate (GFR) is < 20 mL/min and hence had better access to this scarce resource. This resulted in some disparity in allocation of kidneys between various socio-economic and racial groups[3-5]. The candidates with blood type B waited much longer as compared to blood type A[6]. The geographic disparity in different donor serving areas has worsened over time with the increased demand and limited supply of organs[7]. Over the last 10 years, the kidney transplantation committee of united network of organ sharing has worked on identifying and rectifying the limitations of the previous allocation system and designing the new KAS[8].

PRINCIPLES INVOLVED IN DESIGNING A NEW ALLOCATION SYSTEM

The two main principles involved in designing an allocation system are utility and equity[2]. A system that focuses on maximizing the outcomes after the transplant is a utility based system whereas the principle of equity is designed to prioritize equal access of organs to all irrespective of the long-term outcomes. In the context of organ shortage and long waiting times, the previous allocation system was heavily weighed on the principle of equity with less stress on measures of utility such as life years after transplant. If the new allocation system were entirely to focus more on utility, older patients with end stage renal disease would have decreased access to transplant. Thus a balance between equity and utility was necessary in the designing of new KAS, such that there is access for transplant to every one while maximizing the benefit of this scarce resource.

MAIN CHARACTERISTICS OF THE NEW KAS

In the new KAS, an attempt was made to match the donor and recipient characteristics in such a way that the best quality donor kidneys are preferentially given to recipients who are expected to have the longest post-transplant survival[9]. All the available DD kidneys will be given a score ranging from 0%-100% termed kidney donor profile index (KDPI). The 10 factors influencing KDPI are donor age, height, weight, ethnicity, history of hypertension and diabetes, cause of death as cerebro-vascular accident, serum creatinine level, hepatitis C status, and donation after circulatory death (DCD) status. Lower the KDPI score better is the quality of the kidney. Expected post-transplant survival (EPTS) is calculated to risk-stratify all wait-listed patients. EPTS ranges from 0%-100% and takes into account four factors including candidate age, dialysis duration, prior solid organ transplant, and diabetes status. Lower the EPTS score better is the post-transplant survival. The aim is to have patients with the top 20th percentile of EPTS receive organs with $\leqslant$ 20% KDPI in a concept called longevity matching. The formulae for calculating KDPI and EPTS are shown in Table 1. The KDPI is derived by utilizing the donor specific elements from the kidney donor risk index (KDRI) developed by Rao *et al*[10] in 2009. KDRI was validated by applying the formula to first time transplant recipients from 1995 to 2005 in the national Scientific Registry of Transplant Recipients (SRTR) data base. The KDRI was considered to be a substantial improvement in interpreting the graft outcomes based on donor related factors as compared to the expanded criteria donor (ECD) and standard criteria donor (SCD) terminology. The EPTS score was developed by the SRTR upon request from the OPTN Kidney Transplantation Committee. For the sake of simplicity, the committee requested that the score only include the four factors described above. The formula was derived using a Cox proportional hazards model to quantify the associations between the four factors and patient survival after transplant[11].

New KAS allocates kidneys in 4 steps after stratifying the organs based on the KDPI scores: $\leqslant$ 20%, 21%-34%, 35%-85%, > 85%. The recipients are matched based on their EPTS. In each of the

Table 1 Formulae for calculating Kidney Donor Profile Index and expected post-transplant survival

KDPI

KDPI = exp (-0.0194 × I[age < 18 year] × [age - 18 year] + 0.0128 × [age - 40 year] + 0.0107 × I[age > 50 year] + 0.179 × I[race = African American] + 0.126 × I[hypertensive] + 0.130 × I[diabetic] + 0.220 × [SCr - 1 mg/dL] - 0.209 × I[SCr 1.5 mg/dL] × [SCr - 1.5 mg/dL] + 0.0881 × I[cause of death = CVA] - 0.0464 × [{height - 170 cm}/10] - 0.0199 × I[weight < 80 kg] × [{weight - 80 kg}/5] + 0.133 × I[donation after cardiac death] + 0.240 × I[hepatitis C] - 0.0766, where I is equal to 1 if the condition is true and I is equal to 0 if the condition is false

EPTS

EPTS score = 0.047 × MAX (age - 25. 0) - 0.015 × Diabetes × MAX (Age - 25.0) + 0.398 × Prior Organ Transplant - 0.237 × Diabetes × Prior Organ Transplant + 0.315 × log(Years on Dialysis + 1) - 0.099 × Diabetes × log(Years on Dialysis + 1) + 0.130 × (Years on Dialysis = 0) - 0.348 × Diabetes × (Years on Dialysis = 0) + 1.262 × Diabetes

EPTS: Expected post-transplant survival; KDPI: Kidney donor profile index.

Table 2 Points awarded to wait-listed candidates in the new kidney allocation system

Candidate features	Points awarded
The waiting time (date of listing with GFR < 20 mL/min, or date of initiation of dialysis)	1 per year (1/365 per day)
Pediatric candidates at time of match with 0- ABDR mismatch donor	4 (if child is 0-10 yr) 3 (if child is 11-17 yr)
Pediatric candidate at time of match if KDPI < 35%	1
Prior living donor	4
Level of sensitization (cPRA ⩾ 20%)	0-202, see description
Single HLA-DR mismatch with donor	1
Zero HLA-DR mismatch with donor	2

cPRA: Calculated panel reactive antibody; GFR: Glomerular filtration rate; KDPI: Kidney donor profile index; HLA: Human leukocyte antigen.

KDPI class, first preference is given based on HLA sensitization: in patients with calculated panel reactive antibody (cPRA) of 100%, kidney is allocated at local, regional or national level, followed by cPRA of 99% and 98%. The zero HLA mismatch gets the next preference, followed by prior living donors, and then pediatric recipients. If a donor organ with KDPI ⩽ 20% is still unused after running down the list, it will then be offered to candidates with EPTS in the bottom 80%. A kidney with KDPI > 85% not used locally will be offered at a regional level before discarding.

In the new system, the time on the wait list for a candidate starts to accrue from the time of listing when the GFR < 20 mL/min or from the date of initiation of dialysis. The latter should benefit candidates with limited resources who might be late to get on the transplant list to accrue wait time from the date of initiation of dialysis. Points are assigned to each candidate as described in Table 2. In sensitized patients, points are given based on the level of sensitization. Patients with cPRA of 100% are awarded 202 points. Similarly for cPRA of 99%, 98%, 97%, 96% and 95%, points awarded are 50, 24, 17, 12 and 10 respectively. As the cPRA goes down, points are given in a decreasing order till the cPRA reaches a minimum of 20%. More the points accumulated by a candidate, higher the priority for receiving the next compatible kidney offer.

KEY DIFFERENCES BETWEEN NEW KAS AND OLD ALLOCATION POLICY

Many concepts of the new KAS are similar to the old policy but there are some key differences (Table 3). In the new KAS, an attempt is made to move away from the terms such as SCD, ECD and DCD. Instead the KDPI will be a more accurate way of assessing the donor risk index in a graded manner. The wait time for a potential recipient on the list is variable based on the geographic region and availability of organs. Traditionally blood types B and O candidates experienced the longest wait time in every region because blood type B is the least common and blood type O kidneys are also given to other blood type recipients if there is a zero-HLA mismatch. Blood types AB, A, O, and B have mean wait times of 2, 3, 5, and 6 years, respectively[12]. A blood type comprises of A1 and non-A1 (A2) blood sub-types. A2 blood type may be less immunogenic when compared to A1 blood type. Studies have shown increased rate of transplantation with reduced waiting time along with similar graft and patient outcomes when A2 or A2B DD kidneys were transplanted to wait-listed patients with B blood type when compared to B recipients of a B kidney[13-15]. In order to decrease the wait times for blood group B candidates, kidneys from donors with A2 and A2B blood types will be offered to blood group B candidates in the new KAS[9]. In the past, if an organ procurement organization (OPO) from a particular region received a kidney from another OPO because of a combined organ transplant or zero-HLA mismatch kidney, the receiving OPO had to pay-back to the national pool. This pay back system is eliminated now. National priority sharing of organs for highly sensitized patients and those with zero-HLA mismatch will help reduce the geographic disparity and better utilization of scarce resource for optimizing the-long

Table 3 Comparison of old *vs* new allocation policies

Old kidney allocation system (effective 1988 - 12/3/2014)	New kidney allocation system (effective 12/4/2014 onwards)
Wait list time starts from time of listing	Wait list time starts from time of listing or date of initiation of dialysis, whichever comes first
The quality of organs described based on the terms SCD, ECD and DCD kidneys	The quality of organs assessed by a KDPI score (0%-100%)
No metric was involved in allocating kidneys depending on the expected long- term outcomes of the transplant candidates	Longevity matching is used to allocate kidneys depending on the KDPI and EPTS scores
Only 4 priority points were given for HLA sensitization for a cPRA ⩾ 80%	Gradation of priority points given based on HLA sensitization for cPRA ⩾ 20% range from 1-202, which can bring the recipient much higher on the list
Long wait time for blood group B candidates	In order to decrease wait times for B blood group candidates, A2/A2B blood type donors acceptable
Pay back system present	Pay back system eliminated
Priority given to pediatric candidates: share 35 (donor age < 35 yr)	Pediatric candidates still get priority for kidneys with KDPI < 35%
National and regional sharing for sensitized patients was not mandated	National, regional and local priority sharing of organs for highly sensitized patients with cPRA of 100%, 99% and 98% respectively
High discard rate existed for marginal ECD/ DCD kidneys	Regional sharing of marginal kidneys (KDPI > 85%) is proposed

cPRA: Calculated panel reactive antibody; DCD: Donation after circulatory death; ECD: Extended criteria donor; EPTS: Estimated post-transplant survival; KDPI: Kidney donor profile index; SCD: Standard criteria donor.

term outcomes.

PREDICTED OUTCOMES FROM THE CHANGE IN ALLOCATION POLICY

It will take time to understand the real impact of the change in organ allocation policy in DD kidney transplantation. A simulation study was recently published which compared the long-term outcomes of transplant recipients by simulating distribution of organs based on the principles of the old and new kidney allocation policies[16]. Modeling was done using the software system called kidney-pancreas simulated allocation model (KPSAM) which is routinely used by the OPTN committees to assess policy proposals[17]. The characteristics of the recipients and donors were similar in both categories and similar to the actual transplants performed in 2010. The new allocation policy showed an increase in median survival of +0.23 years (an increase of 4.6%) when compared to wait-list candidates. There was also a slight increase in the number of transplants, *i.e.,* 68 more per year (0.58% more transplants per year). The model predicted an increase in the number of transplants by 18% in diabetics and by 11% in recipients with a dialysis vintage > 4 years while using the new allocation system. Median life span post-transplant increased by 0.83 years. The overall prediction was a 7.0% increase in median patient life years per transplant and a 2.8% increase in median allograft life years with the new allocation model. Assuming 11000 DD kidney transplants occur annually; this could result in a net gain of 9130 life-years of patient survival and 2750 years of allograft survival. The model also predicted an increase in the number of transplants for recipients in the age group 18-49 years, whereas the number of transplants would decline by 4.1% in 50-64 year olds and by 2.7% for those ⩾ 65 years. An increase in the rate of transplantation from 12.7% to 17.7% among blood type B candidates was also predicted by the model. A decrease in wait-list mortality predicted with the new allocation system despite an overall decrease in the transplantation rate for patients > 50 years could possibly be due to some unknown assumptions since it is less likely that the wait-list mortality would decrease despite fewer transplants in that age group. Simulation model in this study used various assumptions, and results were generated by the single software KPSAM. The reliability of these predictions in a dynamic environment can be questioned[18]. All the comparisons of the simulation were made to the transplants and outcomes from 2010, but all the outcomes from that year may not be a true reflection of what the results are each year. The practice patterns may change or vary with the changes in allocation policy which will alter the simulated results.

POSSIBLE LIMITATIONS AND UNINTENDED CONSEQUENCES OF THE NEW KAS

It is unclear how the information regarding major determinants of KDPI such as donor hypertension, diabetes mellitus and serum creatinine would be obtained in the setting of DD organ procurement. Blood pressure and blood sugar can increase under the stress of various clinical situations in a terminally ill potential donor and can erroneously give a diagnosis of underlying hypertension and diabetes. Serum creatinine is subjected to change over short period of time in critically ill patients and it is unclear which creatinine will be used for KDPI calculation since a baseline serum creatinine many not be available for most donors at the time of organ procurement. Procurement kidney biopsy findings, which can provide useful predictive information, are not part of KDPI since many kidneys are not biopsied. However, a recent study showed significant correlation between degree of glomerulosclerosis on

procurement biopsy and KDPI score[19]. The average glomerulosclerosis was 3.1% ± 4.4% among donors with a KDPI below 85 and 16.6% ± 11.7% for donors with KDPI ⩾ 85 (P < 0.01). Recipient cardiovascular status, a strong predictor of survival, is not directly incorporated in the calculation of EPTS. There could be other determinants of post-transplant survival that are not included in the computation of EPTS.

Unintended consequences are always a possibility while implementing any new system. For example, potential recipients with EPTS < 20% will have higher likelihood of getting organs with KDPI < 20%, within a relatively short time-frame and such recipients might decide not to pursue living donation. Wait-listed candidates > 50 years of age might feel disadvantaged with the potential decline in the number of transplants in their age groups. The effect of dialysis initiation on pre-emptively wait-listed candidates in the new KAS was reported by Schold *et al*[20]. Their analysis revealed that majority of patients pre-emptively listed are younger, privately insured, highly educated, Caucasian, non-diabetic females who would qualify for the top 20% KDPI organs. Counter intuitively, initiating dialysis in this group while on the waiting-list will lower their EPTS score further by 4%-5% for another 5 mo, which allows them to enjoy the priority status of receiving better quality organs. On the other hand, only very few diabetic patients would have EPTS < 20%, and initiating dialysis in these patients immediately increases their EPTS by about 6%, further disadvantaging them. The new KAS with its proposed local, regional and national sharing of organs may or may not decrease the geographic disparity in kidney transplantation as is expected. The cold ischemia time might increase with distant sharing of organs. Antibodies to HLA-DPB and HLA-DQA are not routinely considered in the cPRA calculation. Wait-listed patients with these unmeasured HLA antibodies might get offers from donors with HLA-DPB and/or HLA-DQA and could result in "unexpected" positive cross-matches and poor outcomes if decided to proceed with transplantation[21]. About 63% of the wait-listed candidates with cPRA > 98% had significant antibodies against HLA DPB or DQA subtypes which disproportionately affected women and minorities[22]. This may prevent the intended higher transplant rates in highly sensitized patients unless HLA DPB and HLA-DQA antibodies are routinely incorporated into cPRA estimation.

CONCLUSION

Donor kidney is a scarce resource and optimal utilization while maintaining equitable distribution is challenging. The changes in the new KAS are created with an aim to minimize the mismatch between allograft and recipient longevity. The new scoring systems of EPTS and KDPI give a gradation for the expected longevity of the potential recipient and allograft respectively. Priority sharing of organs for highly sensitized candidates and considering waiting time from time of initiation of dialysis will be advantageous for these waitlisted candidates. As a tradeoff, the rate of transplants in potential recipients > 50 years of age might decline. Regional sharing of high KDPI organs will hopefully lower the high discard rate of marginal organs. The simulation analysis looks promising but the dynamic practice pattern changes and other unknowns might result in some unanticipated results. We will need more methods to assess the outcomes of this new allocation policy, and with time the transplant community will learn the benefits and shortcomings of the new KAS.

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P- Reviewer: Ahn C, Fulop T, Marino IR **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Transplantation

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v5.i2.44

World J Transplant 2015 June 24; 5(2): 44-51
ISSN 2220-3230 (online)

REVIEW

Philosophy of organ donation: Review of ethical facets

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Author contributions: Dalal AR authored the paper.

Conflict-of-interest: None.

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Received: August 21, 2014
Peer-review started: August 21, 2014
First decision: September 16, 2014
Revised: February 6, 2015
Accepted: March 16, 2015
Article in press: March 18, 2015
Published online: June 24, 2015

Abstract

Transplantation ethics is a philosophy that incorporates systematizing, defending and advocating concepts of right and wrong conduct related to organ donation. As the demand for organs increases, it is essential to ensure that new and innovative laws, policies and strategies of increasing organ supply are bioethical and are founded on the principles of altruism and utilitarianism. In the field of organ transplantation, role of altruism and medical ethics values are significant to the welfare of the society. This article reviews several fundamental ethical principles, prevailing organ donation consent laws, incentives and policies related to the field of transplantation. The Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death outline criteria for death and organ retrieval. Presumed consent laws prevalent mostly in European countries maintain that the default choice of an individual would be to donate organs unless opted otherwise. Explicit consent laws require organ donation to be proactively affirmed with state registries. The Declaration of Istanbul outlines principles against organ trafficking and transplant tourism. World Health Organization's Guiding Principles on Human Cell, Tissue and Organ Transplantation aim at ensuring transparency in organ procurement and allocation. The ethics of financial incentives and non-financial incentives such as incorporation of non-medical criteria in organ priority allocation have also been reviewed in detail.

Key words: Transplantation; Ethics; Organ donation; Incentives for donation; Organ trade; Presumed and explicit consent

Core tip: Transplantation ethics is philosophy that involves systematizing, defending and recommending concepts of right and wrong conduct related to organ donation. As the demand for organs increases, it is essential for the society to ensure that new and innovative laws, policies and strategies of increasing organ supply are bioethical. In the field of organ transplantation, role of altruism and medical ethics values are significant to the welfare of the society. This article reviews the fundamental ethical principles to prevailing organ donation consent laws, incentives and policies.

Dalal AR. Philosophy of organ donation: Review of ethical facets. *World J Transplant* 2015; 5(2): 44-51 Available from: URL: http://www.wjgnet.com/2220-3230/full/v5/i2/44.htm DOI:

http://dx.doi.org/10.5500/wjt.v5.i2.44

ALTRUISM

Organ donation is founded on the pillars of altruism. When the moral value of an individual's actions are focused mainly on the beneficial impact to other individuals, without regard to the consequences on the individual herself, the individual's actions are regarded as "Altruistic". Auguste Comte[1] coined the word "Altruism" (French, altruisme, from autrui: "other people", and also derived from Latin alter: "other"). He was the French founder of positivism and described his views in Catéchisme Positiviste[2], where living for others was "Altruism". Altruism can be classified into two types-obligatory and supererogatory. Obligatory altruism is defined as a moral duty to help others. *Supererogatory* altruism is defined as morally good, but it is not morally required-going "above and beyond" one's duty. The act that maximizes good consequences for all of society is known as utilitarianism[3].

Altruistic behavior and happiness are reciprocal in nature. In fact, neuroscientists have found neural bases for altruism[4]. With functional magnetic resonance imaging, it has been shown that the subgenual cortex/septal region, which is intimately related to social bonding and attachment, gets activated when volunteers made altruistic charitable donations[4].

The opposite of altruism is egoism[5]. Egoism is the sense of self-importance. Psychological egoists claim that each person has his/her own welfare on their priority agenda. Some form of self-interest, such as intrinsic satisfaction, ultimately motivates all acts of sharing, helping or sacrificing. Other motivating criteria are expectation of reciprocation, and/or the desire to gain respect or reputation, or by the notion of a reward in life after death.

MORAL OBLIGATIONS

Ethically, doctors are professionally responsible to adhere to medicine's unique moral obligations. The Hippocratic tradition is the origin of several tenets of medical ethics. One of them is the commitment to nonjudgmental regard. Health professionals are professionally responsible to render care to patients without being affected by any judgment as to the patient's worthiness[6].

Another medical ethical tenet is Primum non nocere or "first, do no harm". This principle is clearly embodied in the Hippocratic oath for physicians. This principle of non-maleficence is the most serious ethical concern in living donor transplants, due to the potential of doing medical harm to the donor. Many donors experience significant pain and short-term disability. The risk of surgical complications in living donor surgery is 5% to 10% risk and the risk of death is 0.5% to 1%[7].

A doctor has a duty of beneficence that constitutes a professional obligation to benefit patients, placing their good before his or her own. Fiduciary responsibility encompasses use of knowledge, powers, and privileges for the good of patients[6]. This is the essence of medicine's fiduciary responsibility and commitment to beneficence.

DEATH AND ORGAN RETRIEVAL

Prior to the establishment of brain death criteria in 1968, the main source of grafts was donation after cardiac death (DCD)[8]. Thereafter, donation after brain death (DBD) soon became as the leading source of organs mostly due to the improved graft quality and potential for multiple organs. However, due to organ shortage, there was a renewed interest in cardiac/circulatory death. The potential for Donation after Circulatory Determination of Death programs is enormous. It is a very effective way to increase the grafts pool in both, adult as well as pediatric population[9]. A critical pathway for deceased donation, both DBD and DCD, was developed in 2011[10].

In 2012, a statement on Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death was structured[11]. Determination of death can be made after the cessation of circulation and respiratory function for 2 min. Underlying ethical principles considered were: (1) acts that promote the opportunity to donate viable organs respect the patient's potential interest in becoming an organ donor; (2) the legitimacy of surrogate decision making for critically ill patients whose wishes are unknown extends to decisions regarding organ donation; (3) if real or perceived conflicts arise between the goals of providing optimal end-of-life care and the goals of procuring organs, delivery of quality end-of-life care should take priority. The dead donor rule emphasizes that the recovery of donated organs shall not cause the donor's death.

PRESUMED CONSENT

World Health Organization (WHO) defines presumed consent as a system that permits material to be removed from the body of a deceased person for transplantation and, in some countries, for anatomical study or research, unless the person had expressed his or her opposition before death by filing an objection with an identified office or an informed party reports that the deceased definitely voiced an objection to donation[12].

Implicit consent[13] is consent without some specific move denoting consent, and inaction is itself a sign of consent. An example would be when the chairperson of a board meeting announces a motion carried unless there are any objections. It is important to emphasize that implicit consent is still real or actual. Those attending the meeting are aware that their silence will be inferred as consent, unless they specifically object[14].

Many ethicists believe that actual consent is not essential for organ donation[15]. The default position should be that one would want to donate organs as it is for the good of the society[16]. They also believe that it is immoral for an individual to decline consent for donation of his or her organs[13].

Presumed consent was first introduced in Spain by law in 1979. Spain has the highest deceased donation rate per million populations (35.3 p.m.p. in 2011)[17]. However, Organizacion Nacional de Trasplantes (ONT), Spain's governing transplantation organization, confers this success to its "Spanish Model" rather than its legislation[18,19]. Success factors of the Spanish Model include its legal approach and a comprehensive program of education, communication, public relations, hospital reimbursement, and quality improvement[20,21]. Intensive care unit doctors or anesthesiologists work part-time as in-hospital transplant coordinators[22]. The hospital pays them bonus salaries for organ donations they undertake[23]. The Spanish ONT explicitly denies that this factor alone causes the success seen in Spain[24,25]. This model differs significantly from that in the United States where transplant coordinators are part of the Organ Procurement Organizations (OPO).

In Spain, there is no national non-donor registry[21]. Approximately nineteen of twenty-five nations with presumed consent laws have some provision for individuals to express their desire to be an organ donor[22]. However, health professionals in only four of these nations (Belgium, France, Poland and Sweden) acknowledged that they do not override a deceased's expressed wish if the family objects[22]. A de facto family veto is significant to the choice between consent processes in cases where opt-in and opt-out schemes have a different after-effects on families subsequently vetoing organ removal[26,27]. If the family vetoes, then the opt-out case becomes much weaker.

Some ethicists feel that a duty to donate or feeling of obligation to the society aids transition from presumed consent to conscription for organ donation[28]. In the conscription model, every individual is under compulsion to donate organs[29]. The individual's body and organs are owned by the State. However, such a model may not be compatible with democracy, as it is recipe for totalitarianism[30]. Totalitarianism is usually portrayed by the coincidence of authoritarianism, *i.e.*, state decision-making and ideology are not framed by the ordinary citizens, *i.e.*, a pervasive scheme of values are announced and promoted by institutional means to control and direct all aspects of life[31].

Though presumed consent laws have been accepted in Spain and other European nations, they have been consistently rejected in the United States. Presumed consent has been considered in the United States, but not beyond initial considerations. The Ethics Committee of the United Network for Organ Sharing (UNOS) developed a white paper on presumed consent in 1993[32] and repeated those findings in 2005. It noted there was no clarity whether a large proportion of the population was primed for this type of system. At least three states, Delaware, Colorado, and New York, have considered modifying their laws to presumed consent stances (Nytimes.com 2010), but these efforts quickly fizzled out.

EXPLICIT CONSENT

WHO defines explicit consent is defined as a system in which "cells, tissues or organs may be removed from a deceased person if the person had expressly consented to such removal during his or her lifetime"[12].

Explicit consent policies require an individual to "opt-in" by proactively stating their wishes to be a donor such as signing a donor card or clearly accepting a donor status on a driver's license. Any person 16 years age and above, may consent, in writing with a signature at any time. Verbal consent is also permissible in the presence of a least two witnesses during the person's last illness. The consent has to specify that the person's organs can be used post-mortem for therapeutic purposes, medical and scientific education or research[33].

Explicit consent is recorded as advanced directives on state registries, by the issue of donor cards, and on the driving license. If one does not explicitly consent to donate on the form, the default setting is that one has not consented at all. Many people, however, do not record their decision to donate. Unfortunately, many organs are buried rather than donated. This is because potential donors and their families believe that the organ distribution system is unfair and potential donors may receive less aggressive medical care[34]. In the United States, African Americans, Catholics and Hispanics are less likely to be registered as organ donors[35].

Issues with registering explicit consent at the Department of Motor Vehicles (DMV) include inertia and people's predictable bias towards choosing options that require least effort where they are just trying to complete the license application process[36]. Most people find the DMV to be either stressful or simply an unpleasant place to be. After waiting for a long time to be seen, it is easy to become tired, eager to leave, anxious, frustrated, and even angry[37]. Some, rationally or not, may fear that they might bring about their own death through a motor vehicle accident by deciding to donate at the DMV. Individuals are isolated from connections to family members and other trusted and beloved people whom they would want to be present when making an important decision regarding their death[38]. Even when people do opt in by checking off "donor" on their driver's license, OPOs will often follow the negative wishes of the family of the deceased, overriding a recorded decision to donate[36,39].

However, by the end of 2013, with increasing awareness and education, 117.1 million people in the United States enrolled in state donor registries. This represents 48% of all United State residents age 18 and over[40].

Donate Life Statistics state that 76% of Australians have pointed out that they are willing to become organ and tissue donors[41]. In 2013, the Australian donor rate was 16.9 donors per million people[41]. The Australian organ donation outcome in 2013 was 10% higher than in 2012[42]. If the family is aware that the deceased was likely to consent to organ donation, then they are more likely to donate. Ninety-three percent of Australians stated that they would certainly endorse their loved one's wishes if they knew what the wishes were[41].

ORGAN TRADE

In the United States, Anatomical Gift Act and the National Organ Transplant Act of 1984, prohibit the buying and selling of organs[43,44]. Unfortunately, illegal organ trade and transplant tourism still persist in many other countries despite many laws made and enforced against it[45]. The organ vendors are promised paltry sums of money, and they are frequently deceived out of some of the procurement fee. The surgery for organ procurement and the post-transplant care is often substandard[46,47]. Paid vendors experience social stigma for having sold a part of their body as well as emotional and physical damage[46,47].

If a person owns her body, then she has the right to autonomy, *i.e.*, to sell her body parts. Limits on autonomy are placed to protect individuals from themselves. A good example would be that we do not allow individuals to be slaves so that the moral dignity of the individual is preserved[48]. Additionally, it be possible that the individual is acting involuntarily or is being coerced due to circumstances that are unfair[49]. Respect for autonomy[50] permits one to question an individual's decision when it is against the individual's best interest. An individual may make a decision that is contrary to his or her own interest due to miscalculation, coercion, undue influence or simply misinformation. Though the organ vendor harms himself, and this harm is not inflicted on others, we as a human society, place ourselves in a substandard position, if we allow vulnerable persons to sell their body organs on the grounds of commodification[49].

Transplant tourism results in corruption, coercion and crowding out[51]. It enhances corruption by allowing the sale of organs to go forward in that it may "dehumanize society by viewing human beings and their parts as mere commodities"[52]. Crowding Out occurs by allowing the sale of organs which will cause individuals who would have donated organs to instead sell them, thus reducing the number of donated organs, or it will cause individuals to refuse to donate at all, leading to an overall reduction in procured organs[53]. Organ brokers or recipients often coerce poor sellers, who have no other reasonable economic alternative, to sell their organs[54].

In May 2008, The Transplantation Society and the International Society of Nephrology convened an international summit meeting on organ trafficking and transplant tourism in Istanbul. More than 150 professionals from 78 countries attended this meeting. The text of the Declaration of Istanbul (DoI) on Organ Trafficking and Transplant Tourism was published simultaneously in "Transplantation", and "The Lancet". In 2010, the World Health Assembly updated WHO's guiding principles on human cell, tissue and organ transplantation to add principles aimed at vigilance and safety in transplantation and at ensuring transparency in organ procurement and allocation[55].

Several professional and governmental bodies voluntarily adhere to the principles of the DoI and WHO. The DoI and WHO guidelines have also been incorporated into national laws and regulations[56]. In 2008, the Government of India amended and fortified its Transplantation of Human Organs Act[57]. In Philippines, Anti-Human Trafficking Law was launched in June 2009[58]. Pakistan and Egypt also passed similar laws in 2010[59,60]. Latin American Society of Nephrology[61], and the Society of Transplantation of Latin America and Caribbean, have endorsed the DoI[61,62]. In 2012, Brazil specifically mentioned the DoI in its national regulations[63]. UNOS policy based on the DoI requires all non-United States citizen transplant waiting-list registrants to specify whether the United States is their primary place of residence or whether they have come to the United States for the purpose of transplantation or any other reason[64].

PRISONERS AS ORGAN DONORS OR RECIPIENTS

The United States Constitution's Eight Amendment states that inmates have a right to healthcare. Some argue that prisoners are less deserving for consideration as transplant recipients. Many contend that it is a poor use of a limited resource, since a prisoner, whose life is saved by transplant, may re-enter a life of crime. Should a prisoner's right to transplant depend on the nature of the crime or the terms of his/her incarceration-such as white-collar crimes against capital crimes, or first time offenders *vs* repeat offenders?

Donation benefits both prisoner as well as society by compensating for crimes against society. It would give the prisoner an opportunity to prove to himself and others that he can do something worthwhile. On the other hand, prison environment may prohibit free and voluntary consent. Reduction of sentence for organ donation could be misused as a form of coercion. It may be more acceptable if the decision to donate was made before the prisoners conviction and that the organs to go the recipient *via* UNOS matchlist. But then, would the recipient agree to accept the organs if he/she was aware that the donor was a prisoner on a death row sentence? In April 2011, MSNBC news conducted a survey in which almost 80% of 86736 voters responded "yes" to the question, "Should death row inmates be allowed to donate their organs?"[65]. Patients would

appreciate it, *e.g.*, Patients on Dukes Lung Transplant List were asked whether they would accept lungs from a death row inmate if the organ was good, and 75% replied in the affirmative[65].

FINANCIAL INCENTIVES

The UNOS Ethics Committee defines financial incentives as any material gain or valuable consideration obtained by those directly consenting to the process of organ procurement, whether it be the organ donor himself (in advance of his demise), the donor's estate, or the donor's family[66].

Financial Incentives can be direct or indirect. Regulated organ sale, tax credits, *etc.*, are some of the direct financial incentives. Reimbursement for funeral expense, life and disability insurance are some indirect financial incentives[67]. For living donors, incentives could include: tax credit, long-term health care, tuition or job training; employment; or payment[68]. The convention on human rights and biomedicine of the Council of Europe has favored compensation for donor expenses incurred[69]. This has also been supported by the World Medical Association[70] and the WHO[12]. Several United States states have passed legislations that provide paid leave to organ and bone marrow donors. The laws also offer tax benefits for live and deceased organ donations and to employers of donors. However, a study stated that these provisions did not significantly impact the quantity of organs donated[71].

Some believe that financial incentives will increase the supply of organs. A form of "donor insurance", has been suggested. In this method, a person agrees in advance to organ donation after his or her death. Payment is made to his beneficiaries or his estate after the donation[66]. Financial incentives are also rationalized based on whether they pertain to obligatory or supererogatory altruism. To charge money for one's organ would be wrong if an altruistic kidney donation were morally obligatory. On the other hand, if altruistic donation were supererogatory, then to charge money for one's organ would not be wrong. Rather, demanding money would be non-supererogatory. It would be categorized as perhaps not good, but not wrong, and morally permissible[72].

Decreased emotional gain for the donor family, decreased respect for the sanctity of the human body and life itself, and a loss of the personal touch that currently exists in the altruistic donation process are some of the reasons cited for opposing the provision of financial incentives. There is also a fear of creation of organ markets where the poor would be harvested for the rich. Financial approaches to organ donation may start "the ultimate slide down the slippery slope" - *i.e.*, the human body actually becoming a commodity to be bought, sold and exchanged for in a manner similar to any other good or service[66].

Financial incentives are officially permissible in Iran. A controlled living unrelated kidney donors (LURDs) transplant program has been initiated. If the patient has no living related donor, she is referred to The Kidney Foundation of Iran to find a suitable LURD. The Iranian Society of Organ Transplantation monitors this program to ensure that there is no broker introducing donors to recipients, nor there is any transplant tourism[73]. In Iran, this program has been effective in reducing the kidney transplant waitlist[74]. The kidney donors register in the Dialysis and Transplant Patients Association. After the donation, they are rewarded with the equivalent of $ 1200 United States dollars and 1 year of medical insurance by the government[75].

In Philippines, from 2002 to 2008, a regulated system of incentives for living organ donors was implemented[76]. The program offered a sizable "gratuity package". Transparency, ethics, monitoring of transplant facilities and maintaining a donor registry was mandated. Unfortunately, the intended outcomes differed from reality. The black market was not eliminated and organ brokers or middlemen continued to be involved[77].

In 2010, China launched a financial incentives compensation policy in five pilot provinces and cities. Two forms were considered for financial compensation. The "thank you" form expresses gratitude on behalf of the Red Cross Society of China for subscription to organ donation. The "help" form is social welfare support for underprivileged families[78]. This initiative has been criticized due to involvement of an extremely vulnerable group. Additionally, there was no public campaign to endorse social change making this new initiative ethically objectionable[79].

In 2012, The Working Group on Incentives for Living Donation developed guidelines for development of a regulated system of incentives for living and deceased donation. These guidelines state that each country should have a regulatory and legal framework for implementing incentives and the entire process must be transparent and overseen by international and governmental authorities[68].

NON-FINANCIAL INCENTIVES

The Israeli Organ Transplant Law is a novel approach to increase supply of organ to meet the escalating demands. Historically, Israel's organ donation rate was very low. Jewish law condemns violation of the dead. This has been interpreted that Judaism prohibits organ donation. Rabbinic issues surrounded the concept of brain death. Thus, many patients died waiting for organs. But in the Talmud, saving a life supersedes almost everything. Many commandments may be overstepped if saving a life is the goal. Therefore, it could be argued that organ donation actually fulfills a very high religious virtue[80].

So Israel decided to implement a new approach and became the first country in the world to incorporate "nonmedical" criteria into the priority system based on medical criteria. In 2008 two new laws relevant to organ transplantation were introduced. The Brain-

Respiratory Death Law defines the precise circumstances and mechanisms to determine brain death. The Organ Transplantation Law bans reimbursing transplant tourism involving organ trade. Registered donors are given priority for organs, should they ever need one. Disincentives for living donation are removed by providing insurance reimbursement and social supportive services[81].

First priority is granted to candidates whose first-degree relatives donated organs after death. It is also granted to candidates who have been themselves have registered as kidney or liver-lobe donors. Second priority is granted to candidates who have registered as organ donors at least 3 years prior of being listed. Third priority to candidates whose first-degree relatives have registered as organ donors at least 3 years prior to their listing[82]. A Parliamentary amendment was recently made to this clause that has broadened the prioritization to any living donor. Prior kidney, liver lobe or lung lobe donors, who now need an organ, are granted first priority in the allocation of these organs[83].

This law is based on the ethical principle of reciprocal altruism[84] where by those in the society who are willing to help others will in turn be helped. This effectively works as an incentive for many to become registered donors[82]. It also derives some features from UNOS policy, which allows living donors of organs priority to receive a transplant from a deceased donor should they ever need one[85]. The Singapore's Human Organ Transplant Act grants priority to a person who did not register any objection in respect of organ donation *vs* organ allocation over a person who has opted out from organ donation[86].

This law has been criticized on ethical grounds, as one's chances of obtaining priority points may potentially increase with greater number of first-degree relatives and may be disadvantageous to those with fewer siblings. Additionally, it introduces the potential for individuals to register solely to assure priority points in the future, while advising their families to decline donation in the event of their death[87].

When this law was implemented, an organ donation public awareness campaign was also launched. Television, radio, billboard and newspaper advertisements were introduced promoting the new priority system. The perception that Jewish law forbids donation was countered. Shopping centers and coffee houses were overwhelmed with information regarding organ donation. This resulted in an overwhelming response from the Israeli population. Seventy thousand Israelis registered for organ donation cards within the first 10 wk of the campaign[80]. In 2011, the Israeli organ donation rate increased from 7.8 to 11.4 donors per million populations[81]. Israeli transplant tourism to China to receive organs has now ceased[88].

CONCLUSION

The gap between organ demand and supply is forever widening. It is essential to review ethical facets of every new law, strategy or policy initiated to increase the organ donation. Ethical reflections of organ donation quandaries promote and advance this field in a bioethical manner that ultimately benefits humanity and the well-being of the society.

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P- Reviewer: Gordon CR, Zielinski T **S- Editor**: Gong XM
L- Editor: A **E- Editor**: Wu HL

World Journal of Transplantation

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5500/wjt.v5.i2.52

World J Transplant 2015 June 24; 5(2): 52-67
ISSN 2220-3230 (online)

REVIEW

Update on ischemia-reperfusion injury in kidney transplantation: Pathogenesis and treatment

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Author contributions: Salvadori M coordinated the study; Rosso G reviewed the literature; Bertoni E edited the manuscript; all authors wrote and approved the final graft.

Conflict-of-interest: None.

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Received: November 27, 2014
Peer-review started: November 28, 2014
First decision: December 26, 2014
Revised: January 16, 2015
Accepted: April 27, 2015
Article in press: April 29, 2015
Published online: June 24, 2015

Abstract

Ischemia/reperfusion injury is an unavoidable relevant consequence after kidney transplantation and influences short term as well as long-term graft outcome. Clinically ischemia/reperfusion injury is associated with delayed graft function, graft rejection, chronic rejection and chronic graft dysfunction. Ischemia/reperfusion affects many regulatory systems at the cellular level as well as in the renal tissue that result in a distinct inflammatory reaction of the kidney graft. Underlying factors of ischemia reperfusion include energy metabolism, cellular changes of the mitochondria and cellular membranes, initiation of different forms of cell death-like apoptosis and necrosis together with a recently discovered mixed form termed necroptosis. Chemokines and cytokines together with other factors promote the inflammatory response leading to activation of the innate immune system as well as the adaptive immune system. If the inflammatory reaction continues within the graft tissue, a progressive interstitial fibrosis develops that impacts long-term graft outcome. It is of particular importance in kidney transplantation to understand the underlying mechanisms and effects of ischemia/reperfusion on the graft as this knowledge also opens strategies to prevent or treat ischemia/reperfusion injury after transplantation in order to improve graft outcome.

Key words: Ischemia-reperfusion; Delayed graft function; Inflammatory response; Acute kidney injury; Innate and adaptive immune response; Anti-inflammatory strategies

Core tip: In kidney transplantation the ischemia reperfusion injury is a severe unavoidable consequence that may impact the graft outcome. The underlying mechanisms are not completely understood and new findings are continuously being discovered. These involve the biological cellular mechanisms and the gene related response to injury as ischemia and reperfusion. Therapeutically, is extremely important to control this severe complication. Several drugs and strategies are now available and a number of international trials are ongoing. In addition future therapies are now in the pipeline and will be described in this manuscript.

Salvadori M, Rosso G, Bertoni E. Update on ischemia-reperfusion injury in kidney transplantation: Pathogenesis and treatment. *World J Transplant* 2015; 5(2): 52-67 Available from: URL: http://www.wjgnet.com/2220-3230/full/v5/i2/52.htm DOI: http://dx.doi.org/10.5500/wjt.v5.i2.52

INTRODUCTION

Ischemia reperfusion injury (IRI) is a relevant factor in determining high morbidity and mortality in several diseases among which, the myocardial infarction, the ischemic stroke, the acute kidney injury (AKI) and trauma. In organ transplantation, as well as in major surgery IRI is a relevant challenge, that importantly influences the clinical outcome (Table 1). A reduced metabolic supply with respect to the demand within an ischemic organ, causes a severe hypoxia associated with micro vascular dysfunction[1,2]. Paradoxically, the subsequent reperfusion does not restore the normal conditions, but further enhances the damage activating several mechanisms, among which the innate and the adaptive immune response and the cell death programs[3]. Recently, important advances in understanding the basis at molecular level of the ischemia and reperfusion have been made. This new relevant knowledge probably will lead to new therapeutic strategies for treating patients affected by ischemia and reperfusion-associated tissue inflammation. This will have a particular relevance in the field of organ transplantation[4].

In this paper the main consequences of IRI that may influence the course of the transplanted kidney will be examined. After analyzing the main clinical factors that affect IRI and the clinical consequences, the biologic mechanisms at the basis of IRI will be discussed. Finally new exciting and promising therapeutic strategies will be described.

CAUSES AND CONSEQUENCES OF IRI

IRI is a step frequently occurring during kidney transplantation and is principally caused by blood flow disturbances. Impairment of blood flow starts with the brain death and is due to severe hemodynamic disturbances in the cadaveric donors. These disturbances already causes in the donor activation of complement cascade and of the innate immune system. The clamping of renal artery causes a short, but severe renal ischemia during the harvesting operation. In addition, the cold ischemia during allograft kidney storage may also cause a further ischemic damage[5-7]. The allograft kidney transplantation from living related donors is also subjected to warm ischemia, but in such condition disturbances related to brain death are not present and cold ischemia is also shorter: indeed IRI is less frequent and less severe in transplantation from living donors.

The final and biologically more severe stage of the injury occurs during the reperfusion as a consequence of the blood flow reconstruction[8].

Table 1 Examples of ischemia and reperfusion injury

Affected organ and surgical procedures	Example of clinical manifestation
Heart	Acute coronary syndrome
Kidney	Acute kidney injury
Intestine	Intestinal ischemia and reperfusion
Brain	Stroke
Cardiac surgery	Acute heart failure after cardiopulmonary bypass
Thoracic surgery	Acute lung injury
Peripheral vascular surgery	Compartment syndrome of extremity
Major vascular surgery	Acute kidney injury
Solid organ transplantation	Acute graft failure; early graft rejection

The delayed graft function (DGF) is one of the more frequent early complications after the deceased-donor kidney transplantation and is primarily a consequence of post-ischemic acute tubular necrosis caused by IRI[9]. As aforementioned the degree of IRI is related to several factors that may happen in the donor, during transplantation and later in the recipient[10]. DGF is a severe complication that frequently occurs in the initial post-transplant period. In addition to the acute complications related to the renal failure and the associated costs of prolonged hospitalization, several studies document an association between the occurrence of DGF and the subsequent acute and chronic allograft dysfunction. However is not clear whether the DGF directly affects the long-term graft survival[11,12].

The IRI determines a two-step injury in the transplanted kidney. The first step that happens immediately after transplantation is related to the ischemic damage, while the second step occurs later and is linked to the IRI related activation of the innate and adaptive immune response and may cause either antibody-mediated rejection (ABMR)[13] and cell mediated rejection[14].

Recently, Curci *et al*[15] documented that IRI might also cause renal fibrosis due to the endothelial-to-mesenchimal transition (EndMT) mediated by the complement anaphylatoxins and by the Akt pathway. Due to the relevance of the consequences of IRI, the Food and Drug Administration (FDA) held an open workshop to summarize the current status of knowledge related to IRI upon the outcomes in kidney transplantation[16].

The workshop identified the following factors as relevant causes affecting IRI and DGF: (1) donor factors: Relevant donor-related factors that increase the risk of DGF are the donor age, the biopsy findings at the implantation[17] and the cardiac or brain death[18]; (2) recipient factors: Most relevant recipient-related factors that influence the incidence and severity of IRI and DGF are the male gender, the African American race, body mass index greater than 30 and high panel reactive antibodies[19]; and (3) storage preservation.

The duration of storage and cold ischemia time correlate with DGF. An adequate preservation of renal allograft during the cold storage is also important to prevent the DGF. Recently also the pulsatile hypothermic machine perfusion has been documented by several authors to significantly reduce the DGF, even if a meta-analysis comparing static cold storage and hypothermic machine perfusion did not document a different influence on long-term outcomes[20,21].

Similarly the FDA workshop and further studies[22] documented the clinical consequences of IRI on the kidney graft function and survival rate. Clinically, IRI is associated with the DGF, the graft rejection and the chronic graft dysfunction with a progressive interstitial fibrosis: (1) delayed graft function; The DGF is a result of IRI related ischemic graft damage that impacts upon the short-term and the long-term outcome of the kidney graft [12,23]. However, due to the lack of clarity of the DGF definition, the impact of the DGF on the long-term graft survival is controversial[12]. Clearly, if DGF determines an impaired graft function at discharge, this represents an independent predictor of a poorer long-term graft outcome[24]; (2) graft rejection: The inflammatory response that follows the IRI after the kidney transplantation causes also an increased immunogenicity of the graft[25]. In addition, the IRI may amplify the humoral immune response to antigens. This amplification is also favored by a facilitated cross-talk between T and B cells. The consequence is an increased ABMR rates. In addition, the facilitated antigen presentation by the dendritic cells to the naive T cells may further enhance the immunogenicity of the graft leading to the T cell-mediated rejections[26]; (3) chronic graft dysfunction: The IRI results in progressive interstitial fibrosis of the kidney graft in experimental kidney transplantation models[15,27]. In the humans, the development of interstitial fibrosis/tubular atrophy is also associated with IRI. However, is not clear whether in a specific graft transplantation the severity of the chronic damage should be related to the severity of the IRI itself or to a genetic predisposition of the graft[22].

The physiopathology of the ischemia reperfusion (I/R) should be distinguished from the physiopathology of the injury caused by the ischemia-reperfusion injury (IRI).

PHYSIOPATHOLOGY OF ISCHEMIA REPERFUSION

The I/R occurs when the blood flow supply is either interrupted or severely disturbed. During the process of transplantation the organs are subjected to hypoxic and ischemic injury during the procurement, the pre-servation and after the reperfusion. This principally occurs for the kidneys retrieved from brain dead donors. A recent study comparing kidneys retrieved from living donors and deceased donors (DD) documented that immediately after retrieval from DD there is a high increase of pro-inflammatory genes as interleukin-1 beta (IL-1β), IL-6, P-selectin and monocyte chemotactic protein 1 (MCP-1)[28].

The I/R is a pathological condition characterized by an initial reduction of the blood supply to an organ followed by the subsequent perfusion with consequent re-oxygenation. In any organ the blood flow reduction leads from one hand to the reduction in oxygen and nutrient deliveries, from the other hand to the reduction of waste product removal[29].

Ischemia is an event always associated to the kidney transplantation. Ischemia begins already in the donor with the brain death, principally when is associated with severe hemodynamic disturbances. In addition, the ischemic tissue injury is increased by hypothermic kidney storage. The final stage of the ischemia injury occurs in the reperfusion stage, during which the repair and regeneration processes occur, together with the cellular death[30].

At cellular level two phases should be distinguished: the damage occurring during the ischemia and the damage occurring after the reperfusion. The vast majority of the studies concerning the aforementioned processes have been conducted on the heart, but the same phenomena occur also in the kidney.

Ischemia

The first change induced by the ischemia is the decrease in the oxygen delivery. This will induce a switch from the aerobic to the anaerobic metabolism[30]. The anaerobic metabolism does not meet the demand of aerobic tissues and, as a consequence, the intracellular ATP levels rapidly fall. In addition, the intracellular acidosis may be enhanced by lactic acid that increases because of the lactate-dependent ATP production.

These processes lead to (1) the destabilization of lysosome membrane with the leakage of lysosome enzymes and the breakdown of the cell structure[31]; and (2) the inhibition of the membrane-bound Na^+-K^+-ATPase activity[32,33]. The latter process causes a large intracellular increase of Na^+ ions and water, with consequent edema[30]. Along with Na^+ ions accumulation into the cell, the intracellular Ca^{2+} levels are also increased because of the stop of pumping Ca^{2+} out of the cells[34] and because ATP depletion inhibits the Ca^{2+} re-uptake[35]. The calcium overload causes the activation of calcium dependent proteases such as calpains. Calpains remain inactive because of the acid environment, but may damage the cells after pH normalization at the reperfusion[36]. Another effect of Ca^{2+} overload is the generation of reactive oxigen species (ROS) at mitochondrial level during the ischemia. This causes the opening of the mitochondrial transition pore (mPTP) after reperfusion, with apoptosis and cell death[37,38].

During the hypoxia phase, only exiguous amounts of ROS are produced because of redox-reduction of the cytochromes[39], nitric oxide (NO) synthases[40], xanthine oxidase and NADPH oxidase activations[41,42].

Despite all the aforementioned processes, during the ischemia only a small quantity of cells is lost with

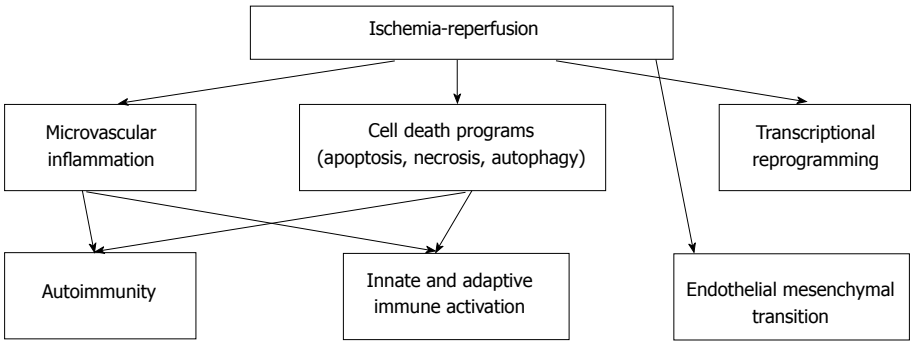

Figure 1 Biological consequences of ischemia-reperfusion.

respect to the reperfusion phase. In a study *in vitro* on cardiomyocytes[43] 4% and 17% of cardiomyocytes viability were lost after 1 and 4 h of ischemia in comparison to 73% of viability loss after 3 h of re-perfusion.

Reperfusion

Upon reperfusion, we observe both an increase in oxygen levels and extracellular pH normalization. This normalization is dangerous for cells previously undergone the ischemia. Indeed, after reperfusion there is a further increase of cytoplasm and mitochondrial calcium overloads that activate the calpains, which cause the cell structure impairment and the cell death. The return to normoxia causes a large production of ROS and a reduction in antioxidant capacity level[41,44]. ROS contribute to damage membranes and cytoskeleton[45]. Together, the ROS increase and the increased mitochondrial calcium content cause the mPTP opening. Once opened the mPTP lead to cell death through different mechanisms as apoptosis, necrosis and autophagy[45,46].

A recently described and relevant factor is the hypoxia-inducible factor (HIF) that might defense cells against I/R[47]. HIF is now considered to be the principal mechanism of defense, controlling the cellular response to hypoxia and regulating several genes involved in the metabolic cell cycle. The HIF pathway is to date the topic of many researches as a possible target for many clinical conditions as I/R.

PHYSIOPATHOLOGY OF ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury may cause cell damage through several pathways (Figure 1).

Cell death, apoptosis, necroptosis and autophagy

The ischemia-reperfusion activates different programs of cell death, which may be categorized in necrosis, apoptosis, or autophagy associated cell-death.

The necrosis, characterized by the cell swelling with subsequent rupture of surface membranes[48], is a frequent consequence of the I/R. The necrotic cells stimulate the immune system and lead to tissue infiltration of inflammatory-cells with consequent cytokine release. In contrast, the apoptosis activating a complex caspase signaling cascade induces a self-limiting program of cell death. Generally the apoptosis process was considered as less immunostimulating than the necrosis process[49]; however recent data have documented that the extracellular release of ATP from the apoptotic cells may attract phagocytes[50,51]. Programmed cell death has been a synonymous of apoptosis until recently, when new pathways of regulated necrosis (RN) have been described. The best studied RN pathway is the necroptosis that is activated by disturbances of the caspase-8-mediated apoptosis and is the consequence of an interaction between the protein kinases 1 and 3 (RIPK1/RIPK3) and their receptors[52,53]. In this condition the necroptosome is formed, which is able to promote the inflammatory injury and to activate the innate and adaptive immunity[54]. In addition, Goncalves-Primo *et al*[55] recently found that the apoptosis-related gene expression levels (*BAX, BCL2*) in pre-implantation biopsies are predictors of kidney DGF.

Finally, in response to the ischemic injury, the cells may maintain their metabolic functions and avoid the death. A recent review highlights that the autophagy is one of the principal tool adopted by the injured cells to maintain their viability[56]. According to this review, the autophagy may be regarded as a protective response to pathological injuries and its stimulation may therefore improve the graft outcome[57]. However, other studies[58] highlight that the stimulation of autophagy may not necessarily protect the graft.

Micro vascular dysfunction

The ischemia and reperfusion are associated with a vascular dysfunction with increased vascular permeability and endothelial cell inflammation. In addition, the recruitment of polymorphonucleates (PMN) and other cells, and the activation of coagulation and the complement system cause further injury. At vascular level, the I/R leads to endothelial cell swelling, loss of glycocalyx, breakdown of the actin cytoskeleton. This leads to lose of the endothelial cell-cell contacts and,

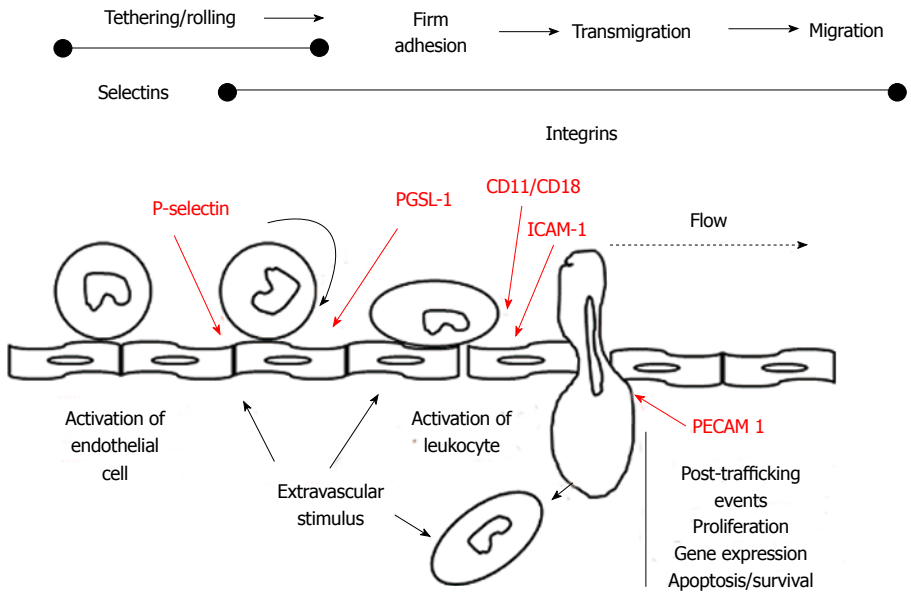

Figure 2 Rolling, firm adhesion and diapedesis of leukocytes. Leukocyte rolling is initiated by increase in endothelial P-selectin and its interaction with the leukocyte receptor PGSL-1; integration of integrins CD11a/CD18 with endothelial ICAM-1 results in leukocyte adherence; Leukocyte transmigration, facilitated by PECAM-1. PGSL-1: P-selectin glycoprotein 1-ligand; ICAM-1: Intercellular adhesion molecule 1; PECAM-1: Platelet endothelial cell adhesion molecule-1.

as a consequence of the increased micro vascular permeability, there is a fluid loss in the interstitium[59]. Furthermore, the I/R promotes vasoconstriction by inducing the endothelial productions of vasoconstrictor substances (platelet derived growth factor-B and Endothelin-1)[60]. The increased vascular permeability induced by hypoxia may also be generated by the production of several adenosine receptors, among which the A2BAR. Recent studies have documented that the repression of the A2BAR also selectively increases the endothelial leak in response to hypoxia *in vitro*[61]. The IRI is characterized by leukocyte activation, chemotaxis, leukocyte-endothelial cell adhesion and transmigration[62]. The leukocytes interact with the vascular endothelium in different steps. First we have the leukocyte "rolling" on the endothelium, then the firm adherence of leukocytes to the endothelium and, finally, the endothelium transmigration of the leukocytes[63] (Figure 2).

The leukocyte rolling is induced by the increase of endothelial P-selectin (CD62P) surface expression, which interacts with P-selectin glycoprotein 1 (PSGL-1) located on the leukocytes. A firm leukocyte adherence is a consequence of the interaction of the leukocyte beta 2 integrins CD11a/CD18 and CD11b/CD18 with the endothelial intercellular adhesion molecule 1. The leukocyte transmigration into the interstitial compartment is then facilitated by the platelet-endothelial cell adhesion molecule 1. Later on, in the interstitial compartment the activated leukocytes release toxic ROS, proteases and elastases, so causing several further injuries as an increased micro vascular permeability, edema, thrombosis and parenchyma cell death[62]. The PMN accumulation in the extra vascular compartment is also facilitated by the IL-8 releases by the hypoxic tissues. Indeed IL-8 realizes a chemotactic gradient that facilitates the neutrophils moving from the intravascular space towards the hypoxic interstitium[64].

The vasoconstriction is increased by a reduced NO production in the reperfusion phase, associated with a reduction in the production of the eNOS protein and other vasodilator substances, which are no more produced by the damaged endothelium[65]. In addition, the vasoconstriction is intensified by increased arterioles reactivity to vasoconstrictor substances such as angiotensin Ⅱ, thromboxane A2, prostaglandin H2, leukotrienes C4 and D4 and adenosine[1,66].

After reperfusion, the activated endothelial cells produce the vascular adhesion molecule 1 as well as the P and E selectins on the endothelial membranes[67]. Mechanistically, the E-selectin activation by E-selectin ligand 1 induces the polarized, activated $\alpha_M\beta_2$ integrin clusters at the leading edge of crawling neutrophils, so inducing the increased adherence of circulating erythrocytes and platelets[68].

The attenuated vascular relaxation, after reperfusion, in addition to a sustained pericyte contraction[69] may result in a "no reflow phenomenon" characterized by an increased impedance of micro vascular blood flow after the restoration of the normal conditions.

Transcriptional reprogramming

The transcriptional reprogramming is a consequence of the I/R that should be regarded as a defense mechanism and not as an injury. This phenomenon has been principally studied in the I/R of organs as liver, brain or heart.

The ischemic period is associated with significant alterations in the transcription control of the gene expression. The ischemia is associated with an inhibition of

the oxygen-sensing prolylhydroxylase (PHD) enzymes that require oxygen as a co-factor. Hypoxia-associated inhibition of the PHD enzymes leads to the post-translational activation of hypoxia and of the inflammatory signaling cascades, which control the stability of the transcription factors HIF and nuclear factor-κB (NF-κB), respectively[70]. In particular in hypoxic conditions, the HIFs move to the nucleus, where, binding to a hypoxia response promoter element (HRE), induce the transcription of numerous genes, among which the genes that induce NF-κB and toll-like receptors (TLRs). This represents an additional attempt to restore oxygenation and to help the tissue to adapt to the hypoxia[71].

Recently, it has also been found that the protective phenotype in response to the ischemia depends on an integrated response at the genomic, molecular, and cellular and tissue levels. This finding has been called "genomic reprogramming" following ischemic preconditioning[72].

Innate and adaptive immune system

The innate immune system is an overlapping response to conditions of disturbed tissue integrity as happens in IRI. Numerous cells and mechanisms are involved in the innate immunity.

Cells: Following reperfusion, the neutrophils adhere to the endothelium and migrate into the tissue. The neutrophils react to any unspecific injuries and release proteases, ROS and pro-inflammatory cytokines as IL-4, IL-6, interferon-γ, tumor necrosis factor-α[73]. Similarly, also the macrophages produce proinflammatory cytokines and may be found in the damaged tissues since the early stages of the IRI[74]. The natural killer (NK) cells play a central role in the renal IRI and the perforin dependent killing of tubular cells by the NK cells is a major mechanism of the renal IRI[75]. The dendritic cells (DCs) represent an essential step in the pathogenesis of the IRI. Indeed DCs undergo an antigen-independent maturation process induced by damage-associated or pathogen-associated molecular proteins (DAMPs, PAMPs). In addition, the DCs represent the connecting bridge between the innate and the adaptive immune activation. In renal transplantation, where the deceased donor undergoes an oxidative stress induced by brain death, the donor DCs are activated favoring the subsequent activation of the recipient T cells[76].

TLRs: The TLRs are small proteins, located on cell membranes or into the cytoplasm that are able to recognize the pathogen-associated molecules. Once activated, the TLRs recruit adapter molecules within the cytoplasm able to generate several kinases that, on turn activate transcription factors, as NFκB. The transcription factors may induce an inflammatory response[77]. In addition to the microbial-associated molecular patterns, the TLRs may be also activated by the endogenous molecules called DAMPs. Several DAMPs are able to activate TLRs and might be associated to IRI. Among them only the nuclear protein High Mobility Group Box 1 (HMGB-1) has been documented to be linked to the pathogenesis of the IRI[78,79]. HMGB-1 binds the DNA and regulates the transcription and the chromatin modeling. In deceased-donor kidneys where the IRI is more frequent and more severe, the TLR-4 has been found to be up-regulated and tubular HMGB-1 is detectable[80]. The TLR-4 exerts a crucial role in the IRI. Indeed, the activation of TLR-4 on the leukocytes, the vascular endothelial cells and the tubular epithelial cells leads to an increased production of pro-inflammatory cytokines and adhesion molecules, which realize an inflammatory response in both the renal microvasculature and the interstitial space. This intensifies the kidney damage already initiated during the ischemic phase through a massive leukocyte infiltrations and generating further cytotocicity. The increased endothelial and epithelial cell damage accelerates the antigen processing and presenting. Therefore the immunogenicity is increased and an immune reaction is generated. The tubules and vasculature severely damaged might promote fibrosis, and all these molecular events may predispose to chronic allograft failure[81].

Strictly connected with the TLRs are the inflammasomes. The inflammasomes are multiprotein complexes present in the cells of the kidney. The inflammasomes respond to DAMPs and may be activated by any cellular damage. For example, the NOD leucine-rich repeat pyrin domain containing NLRP, named NLRP1, activates the caspase-1 cascade producing pro-inflammatory cytokines. Other inflammasome like NLRP3 seems to exert a protective effect in mice[82].

Complement: A central role of the innate immunity is exerted by the complement. The complement is involved in the IRI. The DAMPs may activate all the three complement pathways, binding either to C1q, or to C3 or to mannose-lectin[12]. When the complement pathways are activated the anaphylatoxins C3a and C5a are released and the MAC (C5b-9) is formed. As a result, chemokines are induced and a neutrophil activation and infiltration occur leading to cell injury, apoptosis and necrosis[83].

It has been recently documented that in the complex setting of the IRI, there is a close cross-talk between the complement and the TLRs, another component of innate immunity[84].

The complement may be activated by the brain death and the complement component C5a, generated by the donor brain death, acts directly on the C5a receptor which is also expressed on the DCs, resulting in the cell activation and subsequently enhances its capacity for the allo-specific T cell stimulation[85]. Li *et al*[86] suggest that the donor epithelium bound C3 may up-regulate the alloimmune response. It is postulated that the surface bound C3 interacts with the complement receptors on the alloreactive T cells or on the antigen presenting cells to increase the allo-immune

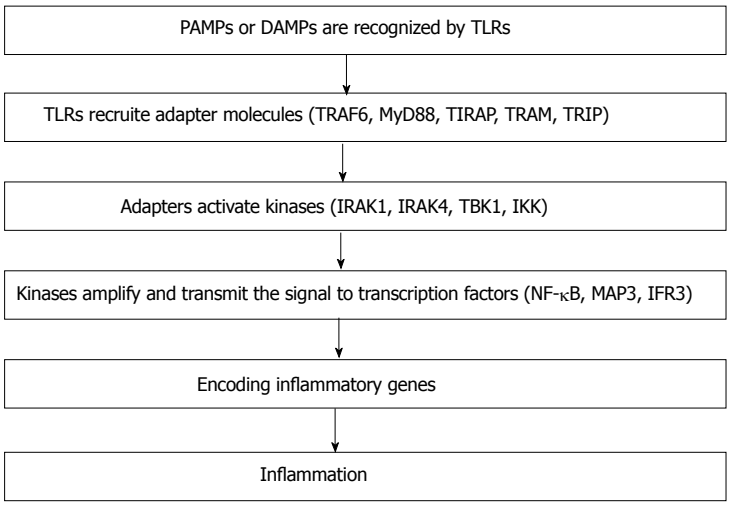

Figure 3 Schematic view of innate inflammatory response. PAMPs: Pathogen associated molecular patterns; DAMPs: Danger associated molecular patterns; TLRs: Toll-like receptors; TRAF6: TNF receptor-associated factor 6; MyD88: Myeloid differentiation primary response 88; TIRAP: Toll-interleukin 1 receptor (TIR) domain containing adaptor protein; TRAM: TRIF-related adaptor molecule; TRIF: TIR domain containing adaptor protein inducing interferon β; IRAK1: Interleukin 1- receptor-associated kinase 1; TBK1: TANK binding kinase 1; IKK: Inhibitor of nuclear factor kappa-B kinase; NFκB: Nuclear factor kappa B; MAP3: MAP3 kinase; IFR3: Interferon regulatory factor 3.

stimulation.

Finally, it should be considered that the majority of transplanted kidneys are retrieved from cadaveric donors. In such kidneys C3 may be present in the organ already before retrieval because of donor suffering. Damman *et al*[84] found higher gene expression of C3 and increased deposition of C3d in kidney biopsies obtained from graft from deceased donors. It has been documented that the complement component C3 is capable of modulating the rejection of the renal allograft *in vivo* and of regulating the T-cell responses *in vivo* and *in vitro*[14,87].

While the activation of the innate immune system takes places within minutes, the adaptive immune response is generated after a longer period. The T-cells involved in either antigen-specific or antigen-unspecific responses play a key role in the kidney IRI[88].

Summarizing the chain of the events that happen as a consequence of the I/R and the consequent activation of the immune system, two steps should be distinguished: (1) activation of the innate system: The recognition receptors of the innate immunity are principally the TLRs (both intra and extracellular), the intracellular receptors, NOD-like receptors and retinoic acid-inducible gene 1 receptor. TLRs are essential in recognizing the PAMPs or DAMPs. The TLRs activate a number of kinases [IL-1-receptor-associated kinase 1 (IRAK1), IL-1-receptor-associated kinase 4 (IRAK4), TANK binding kinase 1, inhibitor of NFκB kinase] recruiting in the cytoplasm adaptor molecules [myeloid differentiation 88 (MyD88), Toll/IL receptor containing adaptor protein, TIR domain-containing adaptor inducing interferon (TRIF) and TRIF-related adaptor molecule]. The kinases amplify and transmit the signal to the transcription factors NFκB, MAP3 kinase (MAP3) and interferon regulatory factor 3. Finally the transcription factors encode the genes regulating the inflammatory cells[12] (Figure 3); and (2) activation of the adaptive system: In tissues affected by innflammation, the DCs become mature, bind the antigen and migrate to the lymph nodes where they may present the antigen to the T cells. The activation of T cell is mediated by signals generated by the T cell receptor and the co-stimulation molecules. The strict interaction between T and B cells may generate an alloimmune response (Figure 4). Recently, has also been documented that the renal IRI may amplify the humoral immune response generating an antibody mediated rejection (ABMR)[13]. Indeed, following the I/R an amplified IgG response, antigen specific, may be generated in the presence of functional alternative pathway of the complement.

Autoimmunity is principally referred to the adaptive immune system. However several studies reveal that also the innate immune system, under specific circumstances may be self-reactive and may initiate the reaction against self-tissues similarly as occurs with pathogens. This specific event is referred as "innate autoimmunity"[89]. Several studies have linked the reperfusion injury to the occurrence of the so-called "natural" antibodies, leading to the activation of the complement system. These natural antibodies are produced in the absence of any immunization and are principally composed of IgM and, in some cases, IgG[90].

In mouse models, non-muscle myosin and heavy chain type Ⅱ A and C have been identified as a self-target for natural IgM in the initiation of reperfusion injury[91]. More recently, additional neoepitopes have been identified as the soluble cytosolic protein annexin Ⅳ[90]. These studies indicate that these neoepitopes generated by the ischemic tissue may become the targets for the natural antibodies principally during the reperfusion phase, thus causing complement activation, neutrophil recruitment and tissue injury.

EndMT

EndMT has been recently described in different human diseases[92]. During the EndMT, the endothelial cells (ECs) acquire a mesenchimal phenotype characterized by the loss of specific endothelial markers and by the gain of mesenchymal markers, such as the fibroblast specific protein 1, the neuronal cadherin (N-cadherin) and the alpha-smooth muscle actin (α-SMA). Under these conditions, the ECs move from their normal organized cell layer and invade the underlying tissue inducing

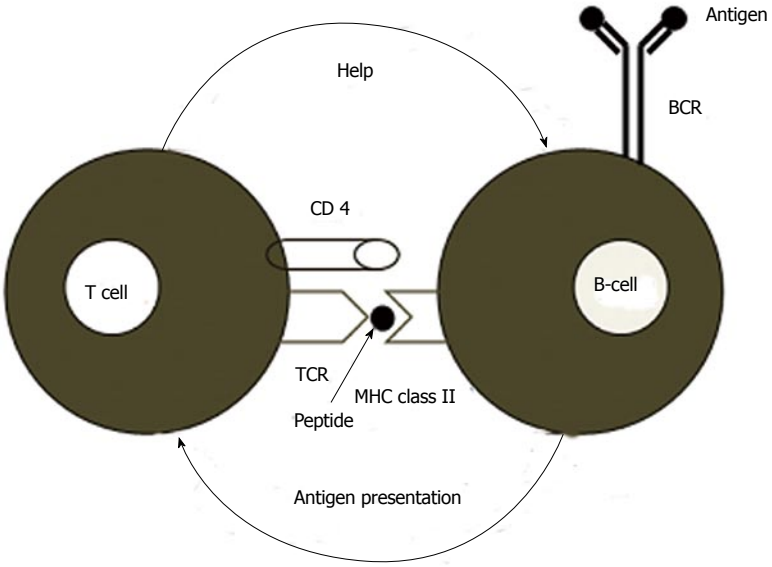

Figure 4 Adaptive immunity. Interrelationship between T and B cells. TCR: T cell receptor; MHC: Major histocompatibility complex; BCR: B cell receptor.

interstitial fibrosis and favoring the development of chronic kidney disease[93,94].

To date, we are aware of the possible role of the EndMT in the renal IRI but little is known about the pathogenetic factors regulating its development after IRI at renal level. In a recent study, Carney[95] documented that, during the IRI, the activation of the classical and the lectin pathways of the complement system occur primarily at the endothelial cell level. These authors analyzed in large mammals the role of complement in the induction of EndMT by using recombinant C1 inhibitor *in vivo*. Their data documented that the activation of the serine/threonine-specific protein kinase (Akt) was essential to induce EndMT *in vitro*. In accordance, inhibition of complement *in vivo* abrogated the Akt signaling, with inhibition of EndMT and of tissue fibrosis. These data document for the first time that the process of EndMT and the vascular rarefaction at the renal level are activated by the IRI through the priming of the complement system and the subsequent activation of the Akt pathway leading to renal fibrosis[15].

PROPHYLAXIS AND TREATMENT

Medical products that limit the short term deleterious effects of the IRI and improve the long term allograft survival are urgently needed.

To date 34 clinical trials are ongoing over this issue[96]. The targets, as we have documented may be quite different.

Donor management

An optimal management of the deceased donor is essential to reduce the risk and the consequences of the IRI, as well as an accurate surgical technique, a reduced cold ischemia time, and an optimal allograft perfusion.

The ischemic preconditioning implies a first period of organ ischemia "tolerizing" the graft to a subsequent second ischemia period. In this period, the administration of thymoglobulin (rATG) to rats with brain death reduced the expression of pro-inflammatory cytokines and ameliorated the renal damage[97]. The supplementation of Klotho, a transmembrane protein with pleiotropic functions, may protect from the IRI and may suppress the fibrosis[98]. The ischemic preconditioning in a recent systematic review on kidney animal models has been effective in reducing the IRI[99]; however it did not translate by now into clinical transplantation.

Storing donated kidney

Historically, the cold static preservation has been the standard preservation method, principally for kidney transplantation but hypothermic machine perfusion is now used more frequently. A large trial has demonstrated that the use in machine perfusion results in better outcomes principally in the case of deceased donor kidneys, with reduced rates and intensity of DGF and improved outcomes[100,101]. These studies were recently confirmed by Gill *et al*[102].

Therapeutic gases

Several therapeutic gases have been used for the treatment of the I/R, among which hydrogen (H_2), NO, hydrogen sulfide (H_2S) and carbon monoxide[4]. The best studied is NO because this gas is also synthesized in the endothelial cells by the endothelial NO synthase. NO principally acts on the endothelial function; in addition, contributes to maintain the blood oxygenation through hypoxic pulmonary vasoconstriction. Patients inhaling NO during liver transplantation had an improved liver function also related to a reduced apoptosis of the hepatocytes[103]. Similarly, the administration of nitrites stimulating NO signaling attenuated the IRI in a rat kidney transplant model[104].

Metabolic and anti-inflammatory strategies

During the ischemia phase, the energy metabolism switches from fatty acid oxidation to glycolysis, allowing the tissues to remain viable. This switch is controlled

Table 2 Anti-complement agents on clinical trials for ischemia-reperfusion-injury

Complement inhibitor	Target	Major mechanism of action
Eculizumab	C5	Inhibit the formation of C5b-9 and C5a
rhC1-INH	C1r, C1s, Plasmin, C3b, Kallikrein, Xia, XIIa, MASP1, MASP2	Regulatory effect on coagulation Inhibition of the alternative pathway Control of the release of bradykinin
sCR1	C3b, C4b	Inactivation of C3 and C5 convertase

rhC1-INH: Recombinant C1 inhibitor; MASP1: Mannan-binding lectin-associated serine protease1; MASP2: Mannan-binding lectin-associated serine protease 2; sCR1: Soluble complement receptor 1.

and improved by the HIF transcription factor whose stability is regulated by the oxygen-sensing PHD enzymes. The treatment with pharmacological doses of PHD inhibitors results in an increased tolerance of the kidneys to the ischemia[105]. In addition, the inhibition of PHD2 has been documented to be able to restore the tumor oxygenation and inhibit metastasis *via* endothelial normalization[106].

The erythropoietin (EPO) has also been tested in the prevention of the renal IRI. A study by Imamura[107] documented that EPO increases the HIF-1α and attenuates the tubular hypoxia. The protective effect of heme oxygenase 1 (HO-1) in the renal IRI has also been tested. In a mice transplant model, HO-1 induction in the donor attenuated the consequences of donor brain death and increased graft survival rate[108].

Adenosine is a well-known anti-inflammatory molecule. Activation of the adenosine receptor A2ABR expressed on the DCs leads to the inhibition of NFkB. Recently it has been documented that the administration of the selective A2ABR agonist (BAY 60-6583), attenuates the renal IRI *via* a tolerizing effect on the DCs[61,109].

Antioxidant therapy

The enzyme superoxide dismutase (SOD) scavenges the superoxide anions on free radicals produced during the tissue injury and catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide[110]. The SOD administered intravenously during transplantation, significantly reduced the incidence of acute rejections and improved the long term outcomes of renal transplanted patients. These results were reviewed ten years later and the beneficial effects of SOD were confirmed. In a small trial, renal recipients were assigned to receive treatment with N-acetylcysteine or to receive a control solution. DGF incidence rate was significantly lower among the treated group as well as the markers of oxidative stress[111].

Inhibition of innate inflammatory response

Manipulation of the dendritic cells: The DCs have a relevant role in the immune response as they may operate as a link between the innate and adaptive immunity. The rATG inhibits the DCs function[112]. In addition, in a primate model of IRI, the rATG administered prior to the reperfusion, resulted in a reduced expression of ICAM-1, platelet endothelial cell adhesion molecules, CD11b and E selectin[113].

A recent study documented a more powerful protection against the renal IRI by the T-cell-specific NFkB inhibition[114].

TLRs: Experimental studies showed that the prevention of the activation of the innate immunity may be achieved by inhibiting TLR2, which is expressed on the tubular epithelial cells together with the TLR4. The inhibition of the TLR2 with a new monoclonal antibody might significantly reduce the IRI consequences in models of myocardial IRI[115]. After a successful phase I study in man[116], a placebo-controlled study to evaluate the safety and efficacy of OPN-305, the monoclonal antibody anti TLR2, in preventing DGF, is now ongoing (Identifier: NCT01794663). Another possible target is the TLR4[81]. To date, only one study has been performed to inhibit TLR4 in renal IRI. It has been documented that the blockade of TLR4 by "eritoran" reduced the renal IRI in terms of renal function and histology[117]. Other possible targets are the adaptive molecule MyD88[118], the natural killers and the inflammasomes[10]. More recently, Kondo *et al*[119] reported his experience with the use of a novel IRAK-4 inhibitor. The IRAK-4 inhibitor, in addition to block the toll like receptor pathway, was able to attenuate the progression of the chronic kidney disease[120].

Complement inhibition: Several molecules are currently tested in clinical trials attempting to inhibit the complement that is a relevant component in the innate immune response[83] (Table 2).

Eculizumab is a humanized monoclonal antibody directed against the C5 component of the complement cascade, already used to treat the atypical hemolytic uremic syndrome (aHUS) and the ABMR. Renal damage due to complement activation occurs in two phases after transplantation: during reperfusion after that the donor kidney has undergone significant period of ischemia and during the acute rejection once the innate and adaptive immune system has recognized the donor antigens. In both conditions the complement may play a relevant role. C5 cleavage is a key step in the pathogenesis of IRI and its block could be an effective prophylactic tool to prevent acute kidney injury (AKI). The eculizumab might be used to prevent IRI. Four clinical trials to evaluate eculizumab in the prevention and treatment of the IRI in kidney allograft are currently ongoing[121].

The beneficial effect of recombinant C1 inhibitor (C1-INH) on the IRI has been widely studied by Castellano

et al[122]. Purified or recombinant C1-INH is a host serine protease inhibitor that is able to block the complement cascade acting either at level of classical or lectin pathway[123].

To date, a trial with C1-INH was started (NCT02134314) to prevent DGF in patients receiving deceased donor kidney transplant. In addition, the use of C1-INH to inhibit the Akt pathway has been documented to be effective on the EndMT[15].

The soluble CR1 is among the proteins that regulate the C3 convertase. CR1 is a cell-surface glycoprotein, expressed on several cells, among which monocytes, APCs, T and B cells and podocytes. As a consequence, soluble complement receptor 1 (sCR1) may modulate the complement cascade at multiple levels on all cells expressing on their surface CR1[124].

In normal conditions only small quantities of sCR1 are in circulation. Li *et al*[125] administered high sCR1 in patients undergoing cardiopulmonary by-pass to inhibit complement activity. sCR1 has been recently used in renal diseases and in renal transplantation.

The effect of Mirocept (APT070) (sCR1) has been widely described by Sacks *et al*[126] and is currently the subject of a large scale study in kidney transplantation to test the superiority of Mirocept in the prevention of the IRI in cadaveric renal allograft[127].

In addition, administration or targeting of other complement regulator proteins such as CD59, CD55 or CD46 might be a potential way to reduce renal injury during renal transplantation, but to date these molecules are not yet object of clinical trials in the IRI[84].

Future IRI therapies

A recent paper by Columbia University Medical Center reviewed the novel therapies in managing IRI[128].

Diannexin: Phosphatidylserine is a phospholipid normally absent from the endothelial cell surface. The IRI and the consequent ATP depletion cause the translocation of phosphatidylserine to the endothelial cell surface[129]. Once expressed, the phophatidylserine binds leukocytes and platelets. A recombinant annexin A5, Diannexin, binds with higher affinity to phosphatidylserine with respect to the endogenous annexin and is able to reduce the IRI as documented in a study on mice[130]. To date a phase Ⅱ/Ⅲ clinical trial is ongoing to assess the efficacy and safety of diannexin in *de novo* renal transplant recipients[131].

Recombinant P selectin glycoprotein ligand Ig fusion protein (rPSGL-Ig): The rPSGL-Ig efficiently binds P and E-selectin and prevents the granulocyte adhesion and the sequestration to the site of injury. Two multicenter, randomized, placebo-controlled phase Ⅰ/Ⅱ studies (YSL0001) were performed to clinically evaluate the possible use of YSPSL in the prevention of the IRI in deceased-donor renal transplant recipients[132,133]. No differences in the DGF rate were found, but treated patients had a significantly lower serum creatinine. Cheadle *et al*[134] documented that the pre-reperfusion intravenous YSPSL, significantly reduced the induction of both MCP-1 and tumor growth factor beta.

15NP: The inhibition of p53 after cell damage causes a delayed cell death. Experiments in animal models have documented that the p53 inhibition causes a significant protection on proximal tubule cells[135]. 15NP is a synthetic small interfering ribonucleic acid (siRNA) designed to inhibit the p53 (RNAi) pathway[136]. After preclinical studies in rats, a double blind, multicenter, placebo-controlled trial is ongoing to assess the safety and efficacy of 15NP in men[137].

IAC: The ROS production is an important cause of I/R. A non-peptidyl low molecular weight radical scavenger (IAC) has documented to have anti-oxidant properties in different mice and human models of induced ischemia[138]. A preliminary study on mice documented an IAC protective effect over IRI[139].

Heat shock protein 70: Despite the evidence that heat shock protein 70 (Hsp70) induction can mediate renal protection after the IRI[140], current researches in this area did not document how to enhance the protective Hsp expression strategies in the recovering from the renal IRI. A better understanding on the recovery phase therapy may arise from better understanding of how Hsp70 induction acts on the cells involved in the renal IRI.

After transplantation the recipient circulation carries continuously inflammatory cells to the kidney. These cells are possible treatment targets because of their capacity to either maintain or resolve tissue inflammation[1]. The induction of Hsp70 often may occur in immune cells far from the kidney after heat shock and might have a relevant role in increasing Treg responses in the renal IRI[141,142].

Future anticomplement drugs: Compstatin is an agent that prevents cleavage and activation of the complement protein C3. The drug is to date studied for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in humans[143]. Its major limitations are the instability and the short plasma half-life. Chen *et al*[83] are now testing the compstatin efficacy in renal allotransplant monkey models to investigate the effect on the ABMR. No clinical trial is ongoing to test the efficacy on the IRI.

Yunnan-cobra venom factor (Y-CVF) acts as a more stable C3 convertase, causes consumption of C3 and its eventual depletion. The drug has been used to enable renal allograft accommodation in presensitized non-human primates[144]. Major concerns are its potential toxicity, its immunogenicity and its capacity to generate anaphylatoxins. No clinical trial is ongoing to test its efficacy in the IRI.

Vaccinia virus complement control protein prevents the activated C3 (C3b) and C4 (C4b) from trigger-

ing further steps in the complement cascade. An improvement in kidney structure and function in rats after IRI has been documented[145,146]. Also for this molecule no clinical trial is to date ongoing for the human IRI.

CONCLUSION

Ischemia-reperfusion injury is a frequent and severe consequence of both major surgery and organ transplantation. In the case of renal transplantation the IRI occurs principally with kidneys from a deceased donor. Indeed, the impairment of blood flow starts with brain death and is related to the severe hemodynamic disturbances. Warm ischemia after kidney vessel clamping and the cold ischemia after refrigeration also reduce oxygen and nutrients supply to the tissues. The reperfusion further aggravates the state of oxidation and inflammation created by the ischemia.

The principal causes of the IRI are related to the donor and recipient factors and the storage preservation.

The principal clinical consequences of the IRI in clinical transplantation are the DGF, due to tubular dysfunction, the graft rejection, related to enhanced graft immunogenicity and the chronic graft dysfunction related both to the chronic rejection and to endothelial mesenchymal transition.

Ischemia-reperfusion injury may cause cell damage through several pathways as cell death, micro vascular dysfunction, transcriptional reprogramming, activation of innate and adaptive immune system, autoimmunity and EndMT.

The distinction of the above mentioned pathways is relevant for the different therapeutical approaches.

These include an optimal management of donor and recipient, anti-inflammatory strategies and antioxidant therapies with L-arginine and N-acetylcysteine.

The activation of the innate and adaptive immune system has a central role in the pathogenesis of the IRI. Indeed the danger signals released by the dying cells alarm the Toll-like receptors which encode the genes regulating the inflammatory cells and the mediators. In the inflammatory environment the DCs intercept the antigen, migrate to lymph nodes and present the antigen to immunocompetent cells, so activating the adaptive immunity and favoring the rejection. As a consequence, the interference with the signals leading to activation of innate immunity, the inactivation of complement or the manipulation of DCs are promising therapeutic options for the next future.

Finally the pipeline is filled with possible future therapies. Many of them are the object of current ongoing clinical trials or are in preclinical phases.

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DOI: 10.5500/wjt.v5.i2.68

World J Transplant 2015 June 24; 5(2): 68-72
ISSN 2220-3230 (online)

CASE REPORT

Successful endovascular treatment of transplant intrarenal artery stenosis in renal transplant recipients: Two case reports

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Ethics approval: Ethics approval was not required.
Informed consent: Informed consent was obtained prior to initiation of procedure.
Conflict-of-interest: None.

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Received: October 29, 2014
Peer-review started: October 31, 2014
First decision: November 14, 2014
Revised: February 2, 2015
Accepted: March 18, 2015
Article in press: March 20, 2015

Published online: June 24, 2015

Abstract

Transplant renal artery stenosis (TRAS) is a relatively rare complication after renal transplantation. The site of the surgical anastomosis is most commonly involved, but sites both proximal and distal to the anastomosis may occur, as well. Angioplasty is the gold standard for the treatment of the stenosis, especially for intrarenal lesions. We report two cases of intrarenal TRAS and successful management with angioplasty without stent placement. Both patients were male, 44 and 55 years old respectively, and they presented with elevated blood pressure or serum creatinine within three months after transplantation. Subsequently, they have undergone angioplasty balloon dilatation with normalization of blood pressure and serum creatinine returning to baseline level. Percutaneous transluminal balloon renal angioplasty is a safe and effective method for the treatment of the intrarenal TRAS.

Key words: Transplant renal artery stenosis; Intrarenal stenosis; Hypertension; Renal transplantation; Allograft dysfunction; Angioplasty; Endovascular treatment

Core tip: Transplant renal artery stenosis is a relatively rare complication after renal transplantation and usually affects the site of the surgical anastomosis. Intrarenal stenosis is rather uncommon, manifesting with uncontrolled hypertension and rise in serum creatinine. Angioplasty is the gold standard for the treatment of the stenosis, especially for intrarenal lesions.

Koukoulaki M, Brountzos E, Loukopoulos I, Pomoni M, Antypa E, Vougas V, Drakopoulos S. Successful endovascular treatment of transplant intrarenal artery stenosis in renal transplant recipients: Two case reports. *World J Transplant* 2015; 5(2): 68-72 Available from: URL: http://www.wjgnet.com/2220-3230/full/v5/i2/68.htm DOI: http://dx.doi.org/10.5500/wjt.v5.i2.68

INTRODUCTION

Transplant renal artery stenosis (TRAS) is a rare complication after renal transplantation. Its incidence varies between 2.7%-23%[1]. Its clinical consequences are renal dysfunction which occurs with elevation in serum creatinine or refractory hypertension. The ultrasound is the first tool for the diagnosis of the stenosis but the angiography is method of choice for the confirmation of the diagnosis[2]. Angioplasty is the gold standard for the treatment of the disease and allows the placement of intraluminal stents to maintain patency of the stenosed segments[3,4]. It can be localized at the site of the anastomosis, proximal or distal to the anastomosis at the iliac artery. Rarely the site of the stenosis can be localized into the renal parenchyma. We present two patients who underwent renal transplantation from cadaveric donors and who developed renal artery stenosis at the intrarenal segment of the transplant artery during the early postoperative period.

CASE REPORT

Case 1

A 44-year-old man received a first cadaveric renal allograft. He suffered end-stage renal disease due to chronic pyelonephritis. Demographic characteristics are shown in Table 1. Immunosuppression included induction therapy with basiliximab and triple regimen (cyclosporine, mycophenolate mofetil and corticosteroids). The patient had immediate recovery of graft function. The ultra-sound routinely performed on day 3 was normal. Four months after transplantation the patient presented with elevated blood pressure (180/100 mmHg) and elevated serum creatinine (4.2 mg/dL) and readmitted to the hospital. The ultrasound revealed a severe stenosis at the midportion of the renal transplant artery. Angiography confirmed 70% stenosis at the intrarenal portion of the branch which supplies the middle and lower portion of the kidney (Figure 1A), and angioplasty was performed using a 3.5 mm balloon (Figure 2A). One week after the transplantation the serum creatinine was at 2.3 mg/dL and the blood pressure was normal. Sequential values of serum creatinine are plotted in Figure 3. Since then the recipient has good renal graft function during follow-up for 14 mo.

Table 1 Demographic characteristics

	Case patient 1	Case patient 2
Donor type	Cadaveric	Cadaveric
Donor age (yr)	67	42
Donor gender	Male	Male
Donor co-morbidities	Hypertension	None reported
Donor smoking habit	No	Yes
Recipient age (yr)	44	55
Recipient gender	Male	Male
Recipient primary renal disease	Chronic pyelonephritis	Membranous Glomerulopathy
Time on hemodialysis	5 yr	7 yr
Number of antihypertensive agents following repair of intrarenal transplant artery stenosis	One (amlodipine)	One (amlodipine)

Case 2

A 55-year-old man with end stage renal disease due to membranous glomerulopathy received a cadaveric kidney. Induction therapy was administered with basiliximab followed by triple immunosuppressive regimen (cyclosporine, mycophenolate mofetil and corticosteroids). Two months after transplantation during the routine follow-up, an elevated serum creatinine was discovered (4.7 mg/dL). An ultrasonography raised suspicion of severe stenosis at the intrarenal portion of the two main branches of the renal transplant artery. The finding was confirmed by angiography (Figure 1B) and subsequently the patient was submitted to angioplasty dilatation using a 5 f balloon (Figure 2B). Five days after the angioplasty the serum creatinine was 1.8 mg/dL. Sequential values of serum creatinine are plotted in Figure 3. During a one year follow-up the patient is well with satisfactory renal graft function.

DISCUSSION

The incidence of TRAS varies between 2.7% to 23%[1]. Risk factors for its development are poor anastomotic technique, traction injuries on the renal artery at the time of retrieval, intimal damage at the time of perfusion and atheroma at the site of the anastomosis. The role of acute rejection is controversial but chronic allograft nephropathy may play a role[5]. In our study both of the recipients were not older than 55 years old, there was not acute rejection episode, the stenosis was located distal to the anastomosis and into the renal parenchyma, and it occurred early after the transplantation. So it is difficult to consider one of the above mentioned factors as responsible for the arterial stenosis.

The clinical presentations of stenotic lesions are variable. Most of them present with progressive accelerated hypertension with or without biochemical evidence of renal allograft dysfunction, or they discovered incidentally during the routine follow-up examination[3].

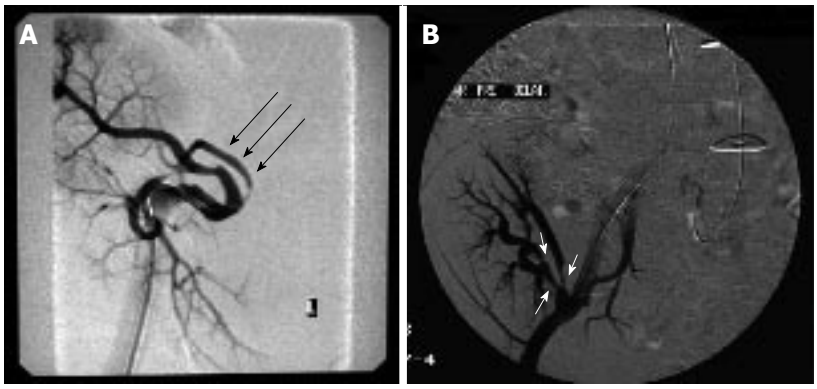

Figure 1 Angiography of renal allograft. A: Angiography of renal allograft (Case patient 1) showing significant stenosis of intrarenal branches of renal artery indicated by black arrows; B: Angiography of renal allograft (Case patient 2) showing significant stenosis of intrarenal branches of renal artery indicated by white arrows.

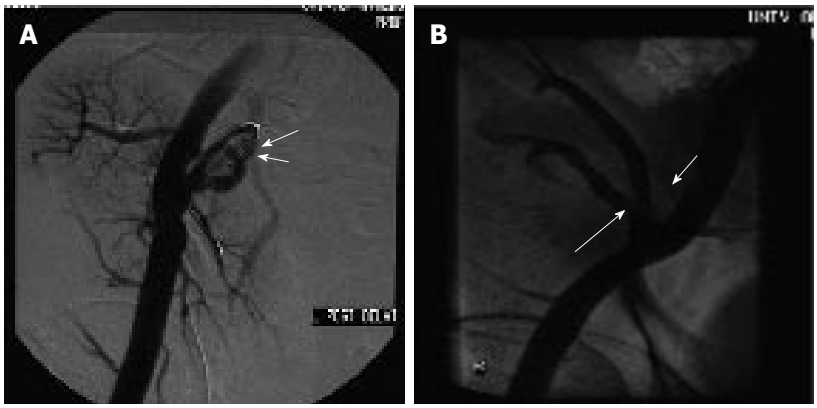

Figure 2 Angioplasty with balloon dilatation of stenotic intrarenal lesion and restoration of patency of renal allograft artery. A: Angioplasty with balloon dilatation of stenotic intrarenal lesion and restoration of patency of renal allograft artery indicated by white arrows; B: Angioplasty with balloon dilatation of two stenotic intrarenal lesions and restoration of patency of renal allograft artery indicated by two white arrows.

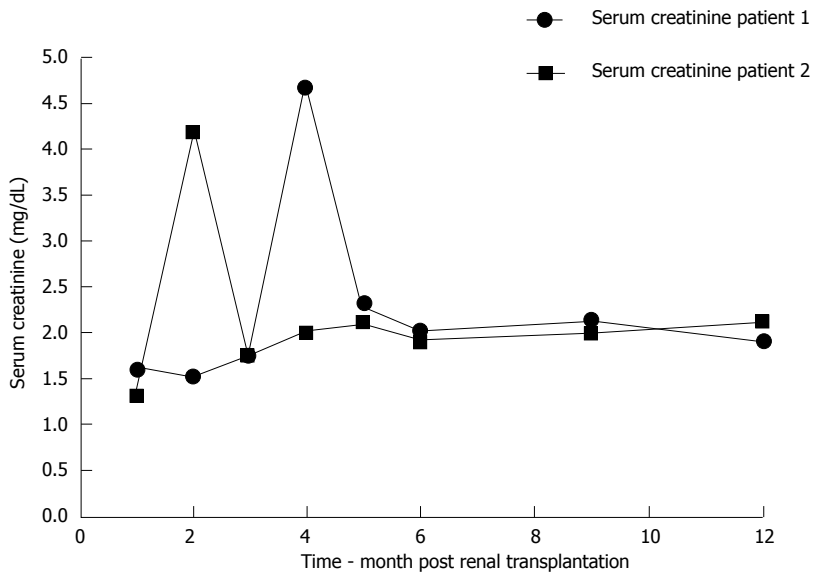

Figure 3 Sequential values of serum creatinine during one year of follow-up post renal transplantation.

The Doppler and color flow Duplex ultrasound are highly sensitive for the diagnosis of TRAS[6,7]. Of course both of them are operator dependent, but are also non invasive and can give some extra information of anatomical details. In our study the ultrasound was able to demonstrate not only the stenosis but also to pinpoint

the exact segment and the degree of the stenosis.

Angiography is still the method of choice for the confirmation of the diagnosis of a stenosis, even in cases that non invasive methods have demonstrated its existence. It allows the complete visualization of the graft vasculature, and also the proximal ipsilateral arterial segments. There are potential complications, such as thromboembolism, haematoma formation, pseudoaneurysm and AV fistula formation. None of these complications occurred in our patients.

Percutaneous transluminal balloon renal angioplasty is considered to be the gold standard for the treatment of TRAS. Moreover there is the possibility of intraluminal stent placement for the preservation of the patency of the vessel lumen mainly in cases of refractory or recurrent stenosis. The success of the procedure is manifested by the improvement of the blood pressure control, the discontinuation of the anti-hypertensive medications and the normalization of the serum creatinine levels. The success rate immediately after the procedure has been reported to be greater than 80%[5,8]. Long term follow-up at one year is reported to be 63%-82%, with the rate of recurrence stenosis after PTA range from 10% to 36%[8-10].

In both of our cases, the PTA procedure was successful in controlling the blood pressure and normalization of the serum creatinine levels without stent placement, and this result is maintaining more than one year follow-up. No complications such as haematoma, aneurysm thrombosis were observed, although in the first case there was a longitudinal stenosis, and in the second there were two separate stenosis in the renal parenchyma.

The other option for the confrontation of TRAS would be the surgical procedure. The short term success results after surgery is reported to be 81%-95% and the long term patency is maintained in 63%-92% of cases[1]. It must be emphasized however that despite these good success rates surgery is difficult to repair surgically in cases that the location of the stenosis is into the renal parenchyma. In such cases the PTA with or without stent placement is probably the only procedure which could resolve the problem.

Renal graft artery stenosis is a relatively rare complication after renal transplantation, the localization of the stenosis into the renal parenchyma is rather uncommon. The PTRA offers the possibility for a safe treatment with good long term results in such cases were it would be difficult or even impossible for a surgical procedure to be undertaken.

COMMENTS

Case characteristics

Two renal transplant recipients presenting shortly after renal transplantation with uncontrolled blood pressure and elevated serum creatinine.

Clinical diagnosis

Renal transplant artery stenosis.

Differential diagnosis

Renal allograft rejection, CNI toxicity, interstitial nephritis, recurrence of primary renal disease.

Laboratory diagnosis

Case 1: Serum Creatinine: 4.2 mg/dL; Case 2: Serum Creatinine 4.7 mg/dL.

Imaging diagnosis

Ultrasound revealed severe stenosis after the orifice of the renal transplant artery.

Angiography diagnosis

Angiography showed 70% stenosis at the intrarenal portion of the branch of renal transplant artery.

Treatment

Angioplasty with balloon dilatation.

Related reports

Intrarenal transplant artery stenosis in rather rare in renal transplant recipients especially when diagnosed relatively recently post renal transplantation.

Term explanation

Angioplasty is the method of choice in repairing renal transplant artery stenosis especially for intrarenal lesions.

Experiences and lessons

Uncontrolled blood pressure in renal transplant recipients should prompt for laboratory exams and further imaging studies.

Peer-review

Authors refer two cases of post-transplant intrarenal artery stenosis leading to renal insufficiency and once elevated blood pressure as well. The applied percutaneous transluminal angioplasty in this condition looks to be safe and long-lasting solution even without stent implantation, so the described cases are worth to be published.

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P- Reviewer: Fulop T, Nemcsik J **S- Editor**: Song XX **L- Editor**: A
E- Editor: Wu HL

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