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AIM AND SCOPE

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REVIEW

Kidney exchange transplantation current status, an update and future perspectives

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Abstract

Kidney exchange transplantation is well established modality to increase living donor kidney transplantation. Reasons for joining kidney exchange programs are ABO blood group incompatibility, immunological incompatibility (positive cross match or donor specific antibody), human leukocyte antigen (HLA) incompatibility (poor HLA matching), chronological incompatibility and financial incompatibility. Kidney exchange transplantation has evolved from the traditional simultaneous anonymous 2-way kidney exchange to more complex ways such as 3-way exchange, 4-way exchange, *n*-way exchange,compatible pair, non-simultaneous kidney exchange,non-simultaneous extended altruistic donor, never ending altruistic donor, kidney exchange combined with desensitization, kidney exchange combined with ABO incompatible kidney transplantation, acceptable mismatch transplant, use of A2 donor to O patients, living donor-deceased donor list exchange, domino chain, non-anonymous kidney exchange, single center, multicenter, regional, National, International and Global kidney exchange. Here we discuss recent advances in kidney exchanges such as International kidney exchange transplantation in a global environment, three categories of advanced donation program, deceased donors as a source of chain initiating kidneys, donor renege myth or reality, pros and cons of anonymity in developed world and (non-) anonymity in developing world, pros and cons of donor travel *vs* kidney transport, algorithm for management of incompatible donor-recipient pairs and pros and cons of Global kidney exchange. The participating transplant teams and donor-recipient pairs should make the decision by consensus about kidney donor travel *vs*

kidney transport and anonymity *vs* non-anonymity in allocation as per local resources and logistics. Future of organ transplantation in resource-limited setting will be liver *vs* kidney exchange, a legitimate hope or utopia?

Key words: Kidney transplantation; Kidney exchange; ABO incompatible; Desensitization

Core tip: Reasons for joining kidney exchange transplantation are ABO blood group incompatibility, immunological incompatibility (positive cross match or donor specific antibody), human leukocyte antigen (HLA) incompatibility (poor HLA matching), chronological incompatibility and financial incompatibility. Here, we discuss recent advances in kidney exchange transplantation such as International kidney exchange transplantation in a global environment, three categories of advanced donation program, deceased donors as a source of chain initiating kidneys, donor renege myth or reality, pros and cons of anonymity in developed world and (non-) anonymity in developing world, pros and cons of donor travel *vs* kidney transport, need of algorithm for management of incompatible donor-recipient pairs and Global kidney exchange.

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INTRODUCTION

Chronic kidney disease is the global health problem with high prevalence rate of 11% to 13%[1,2]. Outcome of living donor kidney transplantation is two times better than deceased donor kidney transplantation. Kidney exchange transplantation is well established modality to increase living donor kidney transplantation and more useful in countries where deceased donor kidney transplantation is not well developed. Kidney exchange transplantation provides good quality of organs and increasingly used in developed[3-10] and de-veloping world[11-23]. Kidney exchange is more useful in countries with low deceased donation rates (China, South, Korea, Japan, India and Pakistan) due to cultural and regional factors. Reasons for joining kidney exchange programs are ABO blood group incompatibility, immunological incompatibility (positive cross match or donor specific antibody), human leukocyte antigen (HLA) incompatibility (poor HLA matching), chronological incompatibility and financial incompatibility. Kidney exchange transplantation has evolved from the traditional simultaneous anonymous 2-way kidney exchange to more complex ways. Table 1 shows types of kidney exchange. Table 2 shows key features of success in single center kidney exchange program in india. Table 3 shows key features of national kidney exchange program.

INTERNATIONAL KIDNEY EXCHANGE TRANSPLANTATION IN A GLOBAL ENVIRONMENT

Table 4 shows strength and weakness of international kidney Exchange. There is limited solution to O blood group patients with non-O donor and highly sensitized pairs in kidney exchange program due to blood group composition of the general and end stage kidney disease population[24]. International kidney exchange transplantation in a global environment of regulation imposed by World Health Organization and the Transplantation Society could increase transplantation for difficult to match donor-recipient pairs such as highly sensitized pairs and O blood group patients with non-O donor[25-28]. The heterogeneity in antigen antibody profile and blood group composition in different geographic area may be contributing factor for this increased transplant rate. International kidney exchange transplantation should be reviewed by the ethics committee according to international standards of Good Clinical Practice and as per local laws and regulations. It should be also abided by the Declaration of Helsinki and Declaration of Istanbul principles. National kidney exchanged may be first attempted to keep the logistics simple before participation in International kidney exchange transplantation. More studies are required about willingness of donor-recipient pairs, transplant professionals and society to participate in such kind on program in ethical and regulatory environment. There should be collaboration in the adjutant National kidney exchange registries in initial pilot project.

THREE CATEGORIES OF ADVANCED DONATION PROGRAM

Ethical concerns about advanced donation program include the management of uncertainty, the extent of donor and recipient consent, the scope of the obligation that the organization has to the kidney exchange recipient, and the potential to unfairly advantage the recipient[29-31].

Butt *et al*[32] reported "out-of-sequence donation" in which a donor donates in kidney exchange chain early because of time limits and their intended paired recipient receives a kidney transplant a short time later. The patient is already having identified matched kidney exchange donor but transplant could not be completed for whatever reason. The donating pair has to take calculated risk that other pairs will actually donate the kidney in short time. Flechner *et al*[33] reported "short-

Table 1 Types of kidney exchange

Simultaneous anonymous 2-way kidney exchange
3-way, 4-way, *n*-way exchange[13]
Compatible pair[14,21]
Non-simultaneous kidney exchange[16]
Non-simultaneous extended altruistic donor and domino[18]
Kidney exchange + desensitization therapy[15]
Kidney exchange + ABO incompatible transplant[18]
Acceptable mismatch transplant
Use of A2 donor to O patients[18]
Living donor-deceased donor list exchange[19]
National kidney exchange[20]
International kidney exchange[17]
Global kidney exchange[18]

term unmatched" donation in which recipient without a match at the time of his donation, was matched and transplanted few months later. The recipient then gets priority to be matched for a kidney.

Veale *et al*[34] reported first case of "voucher" donation in which a living donor donates a kidney to receive voucher for a intended named patient to be transplanted in the near future. Vouchers can be used for future kidney transplants to overcome "chronological incompatibility" between living donors and recipients in the modern era of living donor banking. However an exact time limit for matching cannot be guaranteed. The detailed written informed consent process of advance donation program should include the alternatives such as living donation, deceased donation, non-simultaneous extended altruistic donor chain and waiting until a transplant is indicated.

DECEASED DONORS AS A SOURCE OF CHAIN INITIATING KIDNEYS

Melcher *et al*[35] reported that deceased donor kidney can be used to start non-simultaneous extended altruistic donor chain. Standard criteria deceased donor kidney or deceased donor with kidney donor profile index below 35 should be used for optimum outcome.

DONOR RENEGE MYTH OR REALITY

It was standard practice to do surgery simultaneously when kidney exchange was started in 1986 in the traditional simplest form of 2-way exchange. The quality of kidney exchange matching and number of patients transplanted with kidney exchange improved further with increasingly complex strategies evolved utilizing non-simultaneous donor operations. Donor withdrawal is rare and has been minimized through careful and thorough medical evaluation including surgical, and psychiatric evaluations in addition to laboratory work, age-appropriate screening tests of potential donors, proper counselling, donor motivation, commitment, written informed consent; minimize time between consent and kidney donation and trust between transplant team and donor, and cryopreservation of donor blood preventing frequent laboratory visits for blood testing when new chains are constructed. The medical problems in donors such as pregnancy, trauma, prostate cancer, declined in glomerular filtration rate, donor or kidney declined by recipient surgeon can lead to donor withdrawal and broken chains. The logistics issues are less in short chain than longer chain decreasing the donor withdrawal. The optimum chain length is three and longer chain may not further increase quality of kidney exchange matching along with number of transplants. Decreasing the utilization of bridge donors and minimizing bridge donor wait time can also reduce donor renege. Cowan *et al*[36] reported a real-world renege rate of 1.5% and real-time swap failures as a subset of broken chains in 35% of cases in analysis of 1748 kidney exchange transplants from the National Kidney Registry from 2008 through May 2016. Gentry *et al*[37] estimated a bridge donor renege rate of 5% per month for non-simultaneous extended altruistic donor chains. The simulation was then run over 24 mo and resulted in 35% of chains broken by donor reneging, significantly higher than by recent study Cowan *et al*[36] of 1.7%. The data from India also reported donor renege rate of zero percent in single center study of 300 kidney exchange transplants. It shows that donor renege is rare and is not significant problem in modern kidney exchange practice.

PROS AND CONS OF ANONYMITY IN DEVELOPED WORLD AND (NON-) ANONYMITY IN DEVELOPING WORLD

There is disparity on standard practice of kidney exchange in developed and developing World in term of (non-) anonymity. There is variable practice on anonymity before and after surgery in different countries.

Conditional approach[38]: When the donor-recipient pairs give consent for meeting after surgery, they are allowed to meet each other after surgery in some countries such as the United States of America[39] and the United Kingdom[40]. In other countries, such as the Netherlands and Sweden[41], anonymity is absolute. Anonymity protects patients, donors and transplant hospital/ administration against the risks of revoking anonymity and prevents further commercialization of organs, and breach of patient donor privacy. An Ethical, Legal and Psychosocial Aspects of Organ Transplantation (ELPAT), a subsection of the European Society for Organ Transplantation reported that a conditional approach to anonymity should be possible after surgery[42]. Pronk *et al*[38] showed that most donor-recipient pairs who participated in anonymous donation process are in favour of a conditional approach to anonymity. Guidelines on how to revoke anonymity if both parties agree are needed and should include education about pros and cons of (non-) anonymity and a logistical plan on how, when, where, and by whom anonymity should be revoked.

Non-anonymous allocation[11,12]: Donor-recipient pa-

Table 2 Key features of success in single center kidney exchange program in India

Education, awareness, counselling of about risk and benefits of available transplant options[11-23]
Kidney exchange registry of incompatible pairs
Dedicated transplant team to overcome logistic problems
Uniform evaluation, care and follow-up
Complete work up of pairs before allocation avoids chain collapse
Standardization of HLA laboratory
Robust Immunological evaluation prevents unequal outcome in pairs
Non-anonymous allocation increases trust between pairs and transplant team
Exchange kidney of similar quality
Bonus for difficult to match and better HLA matched pairs
Use of short (≤ 4-way exchange) *vs* long chain minimises logistic problems
Simultaneous surgeries avoid risk of donor reneging
Improve program using key features of other successful programs
Legal, ethical, fair, transparent, equitable and patient centric policy by Competent Authorities

HLA: Human leukocyte antigen.

Table 3 Key features of national kidney exchange program

Country[3-10]	Key features of kidney exchange program
Australia[3-4]	High transplant rate for highly sensitized, HLA-incompatible pairs due to accepting ABO-incompatible donor matching with ABO titers ≤ 1:64, high-resolution HLA identification and virtual cross match
Canada[5]	Non-directed anonymous donors facilitate 62% of transplants
South Korea	Favourable due to less sensitized, more compatible pairs, more non-directed anonymous donors, non-O > O patients
United Kingdom[8]	Low transplant rate due to less use of altruistic donor, restriction on long chain, permit only ≤ 3-way exchange, donor travel
Johns Hopkins University, United States	Kidney exchange + desensitization increases transplant rate for difficult to match and difficult to desensitize pairs
San Antonio, United States[10]	Use of compatible pairs and A2 donors increases transplant rate even in single canter program
National kidney registry, United States	Longer chain are used in matching
Donor *vs* kidney transport	Donors travel is preferred in Netherlands and Canada, kidney transport is preferred in United Kingdom and Australia
Alliance for paired donation, United States	Global kidney exchange

HLA: Human leukocyte antigen.

irs are allowed to meet each other before allocation of donor for surgery and even after surgery. They can share medical reports of exchange donors before surgery and kidney transplant and donor surgery outcome after surgery. Donor-recipient pairs do not choose their match but donor-recipient pairs may decline a match or can withdraw from participation in the kidney exchange program at any time, for any reason. Non-anonymous allocation has the potential of commercialization of organs in case of compatible donor-recipient pairs along with breach in privacy of donor-recipient pairs. Kute *et al*[11,12] reported that donor-recipient pairs are willing for non-anonymous allocation process in single center study of 300 kidney exchange transplants in India. They reported that non-anonymity is more helpful in manual allocation in absence of computer software allocation which also increases trust between patients, donors and transplant hospital/administration and legal team. More long term prospective studies are required to explore the donor and recipient perspective on anonymity in living kidney donation in different socio-economic regions and countries.

PROS AND CONS OF DONOR TRAVEL *VS* KIDNEY TRANSPORT[43-48]

The cold ischemia time is more detrimental in deceased donor kidney transplant than live donor kidney transplant. There is no statistically significant difference in live donor kidney transplant survival in shipped *vs* non-shipped kidney in data from various National registries (Scientific Registry of Transplant Recipients registry in the United States, National Kidney Registry in the United States, and Australian kidney paired donation program). This is feasible strategy to improve the quality of matching such as HLA matching in kidney exchange program. However, more studies are required to define long term safety of shipping donor kidneys and willingness of donor-recipient pairs to participate in donor travel *vs* kidney transport

In Canada with wide geographic distribution, donor travel is accepted and preferred over kidney transport whereas, in Australia kidney transport is accepted and preferred over donor travel.

Disadvantages of donor travel are variation in donor

Table 4 Strength and weakness of international kidney exchange

Strength	Weakness
Increase access to better and effective health care of end stage renal disease patients for transplantation	Inequalities between donor recipient pairs from participating countries result from differences in regulatory, legal and reimbursement policy. Increase inequality and inequity in participating countries particularly for low/middle income countries
Quality of medical care increase from existing and participating National programs	Logistics are complex in immunological evaluation of pairs, management of clinical data and simultaneous surgery
Increase pool size, optimization and diversity of pairs increase quality of matching, number of transplants and increase transplant rate for difficult to match pairs who remain unmatched within their own country	Emerging less well established programs are likely to benefit less than well-funded established program. Limiting development of national program to become self-sufficient in organ donation and transplantation
Mutual learning between different National programs. Promote collaboration, best practice and spread of kidney exchange in interested countries	Adequate financial support for effective and equitable follow-up must be available in low/middle income countries
	Risk for donor recipient pairs with less adequate health care system to manage medical complications and long term follow up care
Facilitate legal, ethical expansion of kidney exchange program with International organ donation and transplantation community	Risks reducing the effectiveness and equity of existing well established program due to practical, logistical and organisational considerations associated with trans-national kidney exchange program
Dialysis is replaced with kidney exchange which is best and cost effective living donor kidney transplantation	Reputational risk and loss of public trust interest confidence in organ donation and transplantation if international kidney exchange involve Nations without appropriate legal and ethical policy to support best practice

workup and donor surgery side of donor nephrectomy (right *vs* left), surgical method (open, laparoscopic, hand-assist or robotic), lack of family support/familiar surgical team, surgical skills and experience are different in different transplant centers as per surgical training and less patient trust and donor satisfaction.

Advantages of kidney transport are familiarity with the transplant team, presence of family and friends for logistical support. Disadvantage of kidney transport is the effect of prolong cold ischemia time on long term kidney allograft survival. However recent studies have shown that cold ischemia time of 16 h has minimal/no effect on long term kidney allograft survival. Cold ischemia time is short in kidney exchange programs where donor travel is used. The Global Positioning System tracking devices can be used to monitor the location of shipped kidneys. Donor-recipient pairs should discuss the best option with the transplant team as per available resources. The participating transplant teams should make the decision by consensus about kidney donor travel *vs* kidney transport as per local resources and logistics. Donor travel rather than kidney transport is likely to be logistically simpler to execute in the Indian situation.

EDUCATION, AWARENESS AND COUNSELLING OF INCOMPATIBLE DONOR-RECIPIENT PAIRS

Variations in practice for management of incompatible donor-recipient pairs will inevitably occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to a clinical situation. There is need of clinical practice guideline document to be designed to provide information and assist decision-making in relation to kidney exchange *vs* desensitization. Each donor-recipient pairs should be given education, awareness, and counselling about risk, benefits and cost effectiveness of various renal replacement therapy options (ABO incompatible kidney transplantation *vs* kidney exchange, deceased donor kidney transplantation and dialysis) in an easy to understand format as early as possible in process of chronic kidney disease evaluation, treatment and transplant evaluation. This counselling can be performed by member of transplant team during dialysis sessions. Patients were encouraged for living donor kidney transplantation over deceased donor kidney transplantation. Patients with incompatible living donors should be encouraged for kidney exchange and ABO incompatible kidney transplantation depending on their phenotype. Infection is common cause of morbidity and mortality after kidney transplantation in developing world compared to developed world.

NEED OF ALGORITHM FOR MANAGEMENT OF INCOMPATIBLE DONOR-RECIPIENT PAIRS

The match/transplant rates for non-O group patients are higher with kidney exchange compared to O group patients. Such easy to match pairs (non-O group patients such as A donor and B recipient; B donor and A recipient and sensitised pairs) should be encouraged for kidney exchange over ABO incompatible kidney transplantation and desensitization protocol[11,12,49]. O group patients with ABO titer $\leqslant$ 128 or panel reactive antibody > 80% should undergo desensitization and ABO incompatible kidney transplantation with acceptable outcome[49]. O group patients with ABO titer > 128 should be first considered in kidney exchange than ABO incompatible kidney transplantation[49]. If no

Table 5 Advantages of global kidney exchange[50-53]

2-7 million people die World-wide from kidney failure due to poverty. Helping some of these poor patients would be good. GKE helps only those patients who have exhausted all the solutions in their home country and increases transplant opportunity for poor patients from low/middle income countries who are otherwise exposed to death[61-62]
GKE wants to support poor patients from low/middle income country legally, ethically, fairly and transparently following the rules established by the National Competent Authorities of each country
GKE does not induce donation but removes the financial barrier to donation for a willing donor recipient pairs where donor's motivation is altruistic and unpaid
Everybody wins in GKE: Low/middle income country's donor and recipient, low/middle income country's pre-and post-transplantation health care system, high income country's recipient, health care payers and high income country's Government and taxpayers
GKE can send high income country patient to high quality low/middle income country transplant centers, instead of reverse. This would be less expensive and build local infrastructure in low/middle income country and access to kidney transplantation to more low/middle income country patients
There can be oversight by organizations such as the World Health Organization and the Transplantation Society with strong International governance that is consistent with the highest ethical and legal standards

GKE: Global kidney exchange.

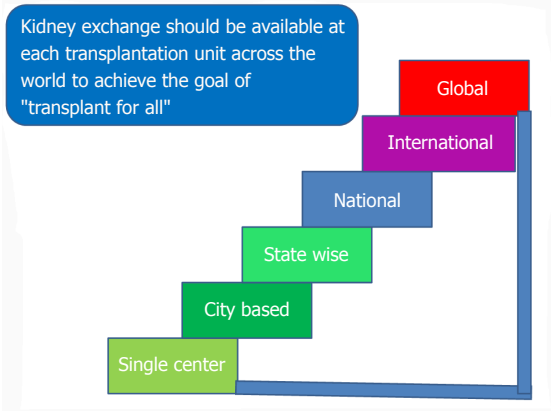

Figure 1 Stepwise progress in kidney exchange.

match is found with kidney exchange in a reasonable period of time they can be undergo ABO incompatible kidney transplantation with equally good results but with greater number of treatments and cost.

For sensitized donor-recipient pairs who have phenotypes that are either easy-to-match and/or difficult-to-desensitize are more likely to benefit from kidney exchange, whereas those who are either easy-to-desensitize and/or difficult-to-match should be considered for desensitization. For sensitized donor-recipient pairs with phenotypes that are both difficult-to-desensitize and difficult-to-match may benefit from a combination of kidney exchange and desensitization in which they are paired with a more immunologically suitable donor[49]. This will reduce waiting time for deceased donor kidney transplantation for patients with no living kidney donor. ABO incompatible kidney transplantation should continue to function in a complimentary way that enhances access to living donor kidney transplantation rather than competes with kidney exchange. ABO incompatible kidney transplantation should be performed after obtaining written informed consent of donor-recipient pairs. Patients with economic constrains; pre-transplant infections and baseline high ABO titer may be excluded from ABO incompatible kidney transplantation.

PROS AND CONS OF GLOBAL KIDNEY EXCHANGE

Table 5 Shows Advantages of Global Kidney Exchange (GKE). Figure 1 shows Stepwise Progress in Kidney Exchange. One third of donor-recipient pairs could not receive kidney transplantation due to immunological incompatibility (ABO incompatible or positive cross match/donor specific antibody). Financial incompatibility is much more common barrier to kidney transplantation than immunological incompatibility in developing countries in absence of universal access to health care for end-stage renal disease. Global kidney exchange increases access to living donor kidney transplantation for donor-recipient pairs from developing countries with financial incompatibility[50,51]. Global kidney exchange should be conducted in legal, transparent and an ethical way. Global kidney exchange will help rich donor-recipient pairs from developed countries with universal access to health care for end-stage renal disease and poor donor-recipient pairs from developing countries in absence of universal access to health care for end-stage renal disease. It should run in a way that enhances access to living donor kidney transplantation with kidney exchange along with national and regional KPD program. The collaboration of single center, regional, National, International and Global kidney exchange program should aim to provide cost effective kidney transplantation with better long term outcome for all patients with end-stage renal disease.

We believe that single center, regional, National kidney exchange program should be attempted before International and Global kidney exchange program to overcome transcultural and logistical issues with the later[52,53]. In addition, more studies are required for the definition of financial incompatibility and about willingness and feasibility of donor-recipient pairs from developing countries for International and Global kidney exchange program. Clearly, the heterogeneity in antigen-antibody profile of donor-recipient pairs from developing countries and developed countries increase

access to living donor kidney transplantation for difficult to match and highly sensitised donor-recipient pairs. The larger donor pool in International kidney exchange will increase HLA matching of donor-recipient pairs which is the best parameter to improve long- term kidney graft survival. Global kidney exchange appears to provide life-saving kidney transplantation to poor donor-recipient pairs from developing countries that otherwise could die due to economic constrain[50-53].

PAIRED EXCHANGE TO INCREASE LIVING DONOR LIVER TRANSPLANTATION

An exchange donor program for adult living donor liver transplantation appears to be a feasible modality for overcoming donor-recipient ABO incompatibility[54-56].

FUTURE OF ORGAN TRANSPLANTATION IN RESOURCE-LIMITED SETTING: LIVER *VS* KIDNEY EXCHANGE: LEGITIMATE HOPE OR UTOPIA?

Opportunity and necessity is the mother of invention. Suppose, there are two patients in developing countries with end stage kidney disease and end stage liver disease with no suitable living donors in family in area without deceased donor organ transplantation. The morbidity and mortality of end stage kidney disease and end stage liver disease is very high in developing countries in absence of national health care insurance, deceased donor organ transplantation program and economic constrains. The organ trafficking is regularly reported in media in underdeveloped World. There is no other outcome for these patients other than death if they did not undergo organ transplantation. The life of these patients can be saved by exchanging liver of patient with end stage kidney disease with kidney of patient with end stage liver disease with optimum patient care before organ harvesting. There is no better solution for such kind of patients other than exchange of organs (liver *vs* kidney). The patient who participate in such exchange should be medically, psychosocially suitable, fully informed of the risks and benefits as a donor, competent, willing to donate and free of coercion. Let us be clear: The intention of such kind of exchange is to save human life and without exchange of organs (liver *vs* kidney) such patients will never going to receive organ transplantation. No alternative existed for such patients and millions more like them. Such organ exchange even if inequitable would able to add years of life to patients who would have died without it.

The mortality rate is at least 10 times higher in living donor liver donation with mortality rate of 0.5% than living donor kidney donation with mortality rate of 0.03%[57-59]. The morbidity rate of 20% is also higher in living donor liver donation. There is regeneration of liver and not kidney in short period. The health care providers from developing and developed World including policy makers should come together to discuss challenges and solution to solve the disparity in access to organ transplantation in developing and developed World. This will be great service to mankind who are in real need. More discussion and studies are required for patient/donor selection, professional /public acceptance, legislation, logistics, exploitations, equity and ethical issues for such kind of organ exchanges in near future to solve the global problem of organ shortage especially in developing world on the International platform such as the World Health Organization and The Transplantation Society. This could be an alternative to xenotransplantation and may serve as Nobel service to Mankind.

CONCLUSION

Kidney exchange transplantation has increased living donor kidney transplantation for end stage renal disease patients with chronological incompatibility and financial incompatibility. The participating transplant teams and donor-recipient pairs should make the decision by consensus about kidney donor travel *vs* kidney transport and anonymity *vs* non-anonymity in allocation as per local resources and logistics. There is need of uniform algorithm for management of incompatible donor-recipient pairs.

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MINIREVIEWS

Utility of central venous pressure measurement in renal transplantation: Is it evidence based?

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Abstract

Adequate intravenous fluid therapy is essential in renal transplant recipients to ensure a good allograft perfusion. Central venous pressure (CVP) has been considered the cornerstone to guide the fluid therapy for decades; it was the only available simple tool worldwide. However, the revolutionary advances in assessing the dynamic preload variables together with the availability of new equipment to precisely measure the effect of intravenous fluids on the cardiac output had created a question mark on the future role of CVP. Despite the critical role of fluid therapy in the field of transplantation. There are only a few clinical studies that compared the CVP guided fluid therapy with the other modern techniques and their relation to the outcome in renal transplantation. Our work sheds some light on the available published data in renal transplantation, together with data from other disciplines evaluating the utility of central venous pressure measurement. Although lager well-designed studies are still required to consolidate the role of new techniques in the field of renal transplantation, we can confidently declare that the new techniques have the advantages of providing more accurate haemodynamic assessment, which results in a better patient outcome.

Key words: Fluid monitoring; Central venous pressure; Renal transplantation

Core tip: We suggest that central venous pressure (CVP) measurement should be abandoned in renal transplantation since it may be misleading. We recommend using intra-operative and post-operative cardiac output monitoring devices for guiding fluid therapy in renal transplant recipients. Although lager well-designed studies are still required to consolidate the role of new techniques in comparison to CVP monitoring in the field of renal transplantation. We Suggest that the new methods have the advantage of providing a more accurate haemodynamic assessment in renal transplant cases.

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INTRODUCTION

Central venous pressure (CVP) measurement have been in use for more than half a century to assess intravascular fluid status of renal transplant recipients and, thereby, be used as a guide for intravenous fluid therapy in renal transplantation. With the current advances in the diagnostic tools, the value of CVP is a point of debate. Several studies proved that CVP measurements are neither correlated to cardiac output nor have a precise correlation with intravascular volume status, therefore it's value in fluid management of renal transplant recipient is at the best speculative. On the other hand, the traditionalists continue to believe that CVP values are of sufficiently good enough as a benchmark in determining resuscitation goals for a given patient.

It is well recognised that optimum fluid resuscitation is essential to maximise the outcomes in critically ill patients. However, only a few studies have reliably endeavoured to assess the role of CVP in comparison to other modern techniques in the field of renal transplantation. We aim to answer this question in regards to clinical application of CVP and objectively review from the point of view of its benefits and inherent limitations.

HISTORICAL USE OF CVP

The clinical correlation between CVP and the intravascular fluid volume were established more than 50 years ago[1]. Theoretical basis of CVP is to measure the pressure in the superior vena cava (SVC) or right atrium pressure, which reflects the right ventricle preload[2]. Indeed, several textbooks have dogmatically stated that CVP provides a clinically relevant and reliable information in regards to circulatory and volume status of patients[3].

Marik *et al*[3] published a systematic review article that evaluated the relationship between CVP and the fluid status of the patients and concluded that CVP is an unreliable indicator of the fluid status and should not be used as a guide to fluid management. Furthermore, Marik *et al*[4] as per updated meta-analysis for evaluation of CVP reliability in clinical practice, reiterated abandoning the use of CVP as a guide in fluid management.

Cecconi *et al*[5] pointed that commonly used preload measurements such as CVP or end diastolic volume, when used in isolation, cannot be used reliably as a guide to fluid resuscitation. They rather recommend using more than one hemodynamic variable for patient evaluation and management. Nonetheless, the study validated the role of CVP in certain situations as severe congestive heart failure or hypovolemia, where the use of CVP is valuable in guiding fluid management[5].

CVP IN THE CURRENT PRACTICE

CVP measurement continues to be a pedestal in day to day clinical practice. A survey studying the resuscitation practices of Canadian physicians have shown that 89.2% of them would use CVP as a monitoring parameter in septic shock as shown in Figure 1[6]. Additionally, CVP-determined endpoints were considered the end-point of volume resuscitation in the early phases of septic shock by 78.7% of the Canadian clinicians as illustrated in Figure 2[6].

Bignami *et al*[7] addressed the current clinical practice in hemodynamic monitoring after cardiac surgery in Italy. They analysed data collected from 71 centres using a 33-item questionnaire from. For monitoring intravascular volume status, CVP was used most frequently (26.7%), followed by arterial BP (19.7%) and echocardiography (5.6%)[7]. Sondergaard *et al*[8] reported that CVP, though not a direct measure of preload, can be used to assess volume status, heart performance and systemic vascular resistance.

DRAWBACKS AND LIMITATIONS OF CVP IN RELATION TO RENAL TRANSPLANTATION

Recent medical advances in understanding haemodynamic of the vascular system together with the availability of new technology have changed the scope of diagnostic approaches. We strongly feel that CVP is not the right tool in assessing the fluid balance and guide fluid therapy in renal transplantation. CVP reading is affected by several physical and anatomical factors as illustrated in Table 1[9].

During kidney transplant operation, the recipient is exposed to many intraoperative factors which may alter the CVP reading, hence, can be misleading in decision

Table 1 Factors affecting the measured central venous pressure reading[9]

Central venous blood volume	Venous return/cardiac output
	Total blood volume
	Regional vascular tone
Compliance of central compartment	Vascular tone
	Right ventricular compliance:
	Myocardial disease
	Pericardial disease
	Tamponade
Tricuspid valve disease	Stenosis
	Regurgitation
Cardiac rhythm	Junctional rhythm
	Atrial fibrillation
	Atrio-ventricular dissociation
Reference level of transducer	Positioning of patient
Intrathoracic pressure	Respiration
	Intermittent positive pressure ventilation
	Positive end-expiratory pressure
	Tension pneumothorax

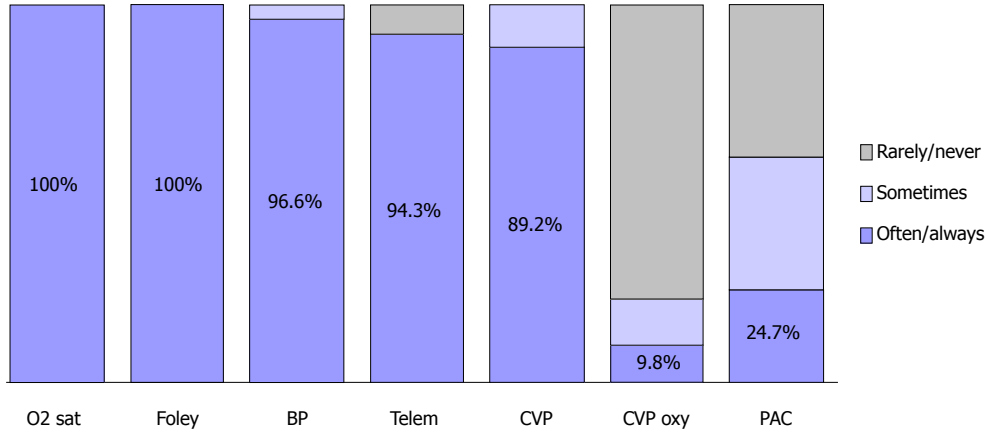

Figure 1 Monitoring parameters used by intensive care unit physicians[6]. BP: Intra-arterial blood pressure; CVP: Central venous pressure; CVP oxy: Continuous monitoring of central venous oxygen saturation; Foley: Foley catheter; O2 sat: Oxygen saturation; PAC: Pulmonary artery catheter; Telem: Telemetry.

making. These factors can be summarised in the following points: (1) During the operation, the position of the patient is not always in flat supine position. The surgeon may be tilting the table in a different direction, commonly head down while elevating the left or the right side to improve the access to the iliac vessels. The effect of posture changes on CVP reading was documented since a long time[10]; (2) transplant surgery always entails the use of abdominal retractors. These retractors must have a pressure effect on the viscera and subsequently affect the venous return. Moreover, the tension created by the retractors will resist movement of the diaphragm and will eventually affect the intrathoracic pressure. These mechanical factors again will give a false CVP reading[11]; (3) there is positive pressure ventilation (PPV) during the transplant operation will affect the CVP reading as mentioned in Table 1[9]. There is no convincing evidence demonstrating to how much the CVP is affected by PPV; (4) the target intra-operative CVP remains elusive. While aggressive hydration ensures good allograft perfusion. On the other hand, overhydration carries the risk of pulmonary congestion, pulmonary oedema, and prolonged intubation especially in patients with pre-existing cardiac conditions[12]; (5) CKD patients on dialysis fluctuate between the volume overload state and the dry state during the post-dialysis period, which makes it difficult to declare which CVP reading should be considered as a normal reading. Additionally, the effect of ageing, long-standing hypertension and the use of various medications affecting the peripheral vascular resistance (alpha blockers, beta blockers and calcium channel blockers) would be further confounding parameters[9]; and (6) we should not forget that placement of central venous catheters and other devices may result in central vein stenosis. Central vein stenosis can jeopardise the future of arteriovenous fistula and arteriovenous graft in the ipsilateral extremity when the renal graft fails, and the patient returns to dialysis[13-15].

Table 2 Advantages and limitations of some commercially available (minimally invasive) cardiac output monitoring[19,20]

Modality	Examples	Advantages	Limitations
Pulse wave analysis	LiDCO*rapid*™ and FloTrac/Vigileo™	Requires only arterial line; Beat-by-beat CO monitoring (this may help to evaluate response to IV fluids). - Validated by clinical studies in different medical and surgical conditions	Presence of arterial line with optimum waveform signal is a prerequisite; Accuracy may be reduced by sever arrhythmia; Needs frequent recalibration during periods of hemodynamic Instability
Lithium dilution	LiDCO*plus*™	Simple technique (can use peripheral arterial line); Continuous CO monitoring	Arterial line required; Accuracy affected by some neuromuscular blocking drugs; Lithium chloride is contraindicated in patients undergoing treatment with lithium salts
Electrical bioimpedance	BioZ®	Completely non-invasive	Numerous mathematical assumptions; Limited validity in patients with dysrhythmias
Partial CO2 rebreathing	NICO™	Easy to set up	Requires intubation and mechanical ventilation with minimal gas exchange abnormalities and fixed ventilator settings; Accuracy decreased with haemodynamic instability
Pulsed dye densitometry	DDG-330®	Non-invasive	Intermittent assessment; Accuracy may be affected by vasoconstriction, movement of the sensor and interstitial oedema

CO: Cardiac output; OR: Operating room.

POSSIBLE ALTERNATIVES FOR FLUID STATUS MONITORING

The introduction of commercially available equipment for assessing dynamic preload variables [*e.g.,* stroke volume variation (SVV)] considered a revolutionary advance in peri-operative fluid management. Srivastava *et al*[16] evaluated the use of intraoperative transesophageal Doppler (TED) to estimate the corrected flow time and variation in stroke volume values. TED was used to guide intraoperative fluid management in 110 living donor renal transplant recipients, and the outcome was compared with the historical records of 104 control recipients who received CVP guided fluid management over the previous year. They concluded that TED was associated with a similar rate of immediate graft function. Moreover, it was associated with a significantly less amount of intra-operative intravenous (IV) fluids, and reduced incidence of postoperative fluid overload[16].

Similarly, Kumar *et al*[17] studied the use of SVV (obtained from minimally invasive cardiac output monitor) to guide the perioperative fluid therapy in major abdominal surgery. The study documented a significantly lower amount of IV fluids used with the new technique, not only that but also there was a significantly shorter ICU stay, and a non-significant shorter hospital stay[17]. These non-invasive tools were used successfully as a part of enhanced recovery programs in kidney transplantation to improve patient outcomes and speed up patient's recovery after surgery[18].

Furthermore, several other non-invasive techniques are utilised for cardiac output assessment and IV fluid guidance like lithium dilution technology (*e.g.,* LiDCOplus™ machine) and arterial pulse wave analysis (*e.g.,* FloTrac/Vigileo™)[19,20]. However, each one of these novel, non-invasive techniques has its own limitations. Clinicians should be aware of the underlying principles and limitations of each technique to choose the best modality for each clinical scenario individually[19,20]. Advantages and limitations of some of the currently available non-invasive approaches are summarised in Table 2[19,20].

The reliability of these new techniques to guide fluid therapy in surgical cases has been investigated in several clinical trials. The conclusion of these trials is summarized in Table 3.

CONCLUSION

Although CVP measurement continues to be popular, yet it is not ideal for guiding and monitoring of fluid management in renal transplantation. It is noteworthy that there may be large variations in intravascular volume status and the patients have limited range of intravascular volume that can be called euvolemia (because of co-morbidities, vascular complications, drugs and the effects of disease on the autonomic nervous system). Therefore, the volume that is infused in a patient whose fluid balance status is doubtful is going to be imprecise if CVP is to be relied upon to appreciate their baseline value. Pulmonary oedema could be the first sign of fluid overload. Other variables such as the patient position, the use of abdominal retractors, and the positive pressure ventilation make any CVP reading meaningless. As clearly evident from the data presented in Tables 1-3, we suggest that CVP measurement be abandoned in renal transplantation since it may be misleading. Alternative to CVP, we recommend using intra-operative and post-operative cardiac output monitoring devices for guiding fluid therapy in renal transplant recipients. Understanding their limitations helps to provide more robust monitoring of fluid therapy. Giving that these novel tools are only

Table 3 Dynamic evaluation of fluid status in comparison to conventional approach

Author	Patients No.	Study group	Conclusion
Berkenstadt *et al*[21], 2001	15	Patients undergoing brain surgery	SVV could predict fluid responsiveness to even a small volume loading of 100 mL of 6% hydroxyethyl starch given for two minutes; There was no correlation between the changes in SV and the values of the CVP and heart rate before or after loading
Rex *et al*[22], 2004	14	Coronary artery bypass grafting (CABG) patients	The dynamic index SVV allowed real-time monitoring of left ventricular preload. Moreover, it allowed assessing the haemodynamic effect of a fluid challenge; Other preload variables (*i.e.*, PAOP, CVP, LVEDAI and ITBI) failed to predict fluid responsiveness
Preisman *et al*[23], 2005	18	Coronary artery bypass grafting (CABG) patients	Functional haemodynamic indices were superior to static indicators of cardiac preload in predicting fluid responsiveness; Use of CVP for the evaluation of intravascular volume status, have been found to lack any predictive value
Hofer *et al*[24], 2005	40	CABG patients	Stroke volume index was significantly correlated with SVV ($P < 0.001$) and PPV ($P < 0.001$) only; While CVP failed to have a significant correlation ($P = 0.235$)
Wiesenack *et al*[25], 2005	20	CABG patients	Stroke volume index correlated significantly with SVV and PPV derived from pulse contour analysis ($P < 0.05$) but not with CVP or pulmonary artery wedge pressure
Cannesson *et al*[26], 2006	18	CABG patients	Left ventricular stroke area measured by transoesophageal echocardiographic automated border detection is not only sensitive to changes in preload but also, can quantify the effects of volume expansion on cardiac output; The difference in CVP reading did not reach statistical significance in the study groups
Lee *et al*[27], 2007	20	Neurosurgical patients	Corrected flow time by oesophageal Doppler and PPV are better than CVP and LVEDAI in predicting fluid responsiveness
Cannesson *et al*[28], 2007	25	CABG patients	ΔPOP can predict response to volume expansion as well as quantify the effects of volume expansion on hemodynamic parameters during cardiac surgery; There was no statistically significant relation between CVP and increase in cardiac index after volume expansion
Belloni *et al*[29], 2008	19	CABG patients	Their results confirm the ability of SVV ($P = 0.0005$) and PPV ($P = 0.001$) to predict fluid responsiveness in ventilated patients during cardiac surgery No significant differences were found in mean LVEDA and CVP before and after fluid administration
Biais *et al*[30], 2008	35	Postoperative period of liver transplantation	SVV and PPV measurement by arterial waveform analysis can be used to predict the effects of volume expansion in mechanically ventilated patients after liver transplantation; The failure of CVP and PAOP to predict fluid responsiveness agrees with increasing evidence that static preload indicators are not suitable for functional haemodynamic monitoring
Hofer *et al*[31], 2008	40	CABG patients	Conventional static preload parameters failed to reflect the fluid status or to predict fluid responsiveness. CVP is therefore unsuitable for predicting ventricular response to fluid loading; SVV measured by the FloTrac™/Vigileo™ and the PiCCOplus™ systems exhibited similar performances regarding predicting fluid responsiveness
de Waal *et al*[32], 2009	18	CABG patients	SVV of > 8% can predict fluid responsiveness with 100% sensitivity and 78% specificity, while PPV ⩾ 10% can identify fluid-responders with 64% sensitivity and 100% specificity; CVP readings were not better in predicting fluid responsiveness than random chance
Cannesson *et al*[33], 2009	25	CABG patients	SVV of 10% helped in discrimination of responders to volume expansion with an 82% sensitivity and 88% specificity; SVV may be a potential alternative to DeltaPP which is an accurate predictor of fluid responsiveness in ventilated patients; SVV was significantly a better predictor of fluid responsiveness than CVP and PCWP in this study
Zimmermann *et al*[34], 2010	20	Elective major abdominal surgery	Both SVV and PVI are valid indicators of fluid responsiveness in ventilated patients during major abdominal surgery; CVP did not adequately reflect circulating blood volume and failed to predict fluid responsiveness in this study
Desgranges *et al*[35], 2011	28	CABG patients	PVI can predict fluid responsiveness during general anaesthesia whatever the site of measurement in the operating room (the finger, the ear, and the forehead); PCWP and CVP showed no significant difference between responders and non-responders
Shin *et al*[36], 2011	33	Elective living donor liver transplantation	Femoral SVV > 8% can predict responders to fluid loading with a specificity of 80% and a sensitivity of 89%; CVP and PAOP did not correlate with the changes in the cardiac index that occurred with a fluid challenge

Broch *et al*[37], 2011	81	CABG patients	SVV (P = 0.002) and PPV (P < 0.0001) were found to be reliable indicators for fluid responsiveness unlike CVP (P = 0.13) that failed to predict it; PVI ability to predict fluid responsiveness is limited in the presence of low perfusion indices
Cannesson *et al*[38], 2011	413	Multicentre study of different abdominal and cardiac surgeries	PPV [AUC 0.89 (0.86; 0.92)] is superior to CVP [AUC 0.57 (0.54; 0.59)] in prediction of fluid responsiveness (P < 0.001)
Yazigi *et al*[39], 2012	60	CABG patients older than 70 yr	PPV is a reliable predictor of fluid responsiveness while CVP and PAOP were not better than a random chance in predicting the response to fluid; PPV reliability was not affected by the decreased arterial compliance and increased arterial stiffness related to aging
Bogović *et al*[40], 2017	24	Major (abdominal or trauma) surgery	The study stressed on the inability of CVP to provide a valid evaluation of the preload; SVV and PPV monitored by LiDCO™ were better alternatives for preload assessment

AUC: Area under the receiver operator characteristic curve; CVP: Central venous pressure; DeltaPP: Respiratory variations in arterial pulse pressure; ITBI: Intrathoracic blood volume index; LVEDA: Left ventricular end-diastolic area; LVEDAI: Left ventricular end-diastolic area index; PAOP: Pulmonary artery occlusion pressure; PCWP: Pulmonary capillary wedge pressure; PPV: Pulse pressure variation; PVI: Pleth variability index; SV: Stroke volume; SVV: Stroke volume variation; ΔPOP: Respiratory variations in the pulse oximetry plethysmographic waveform amplitude.

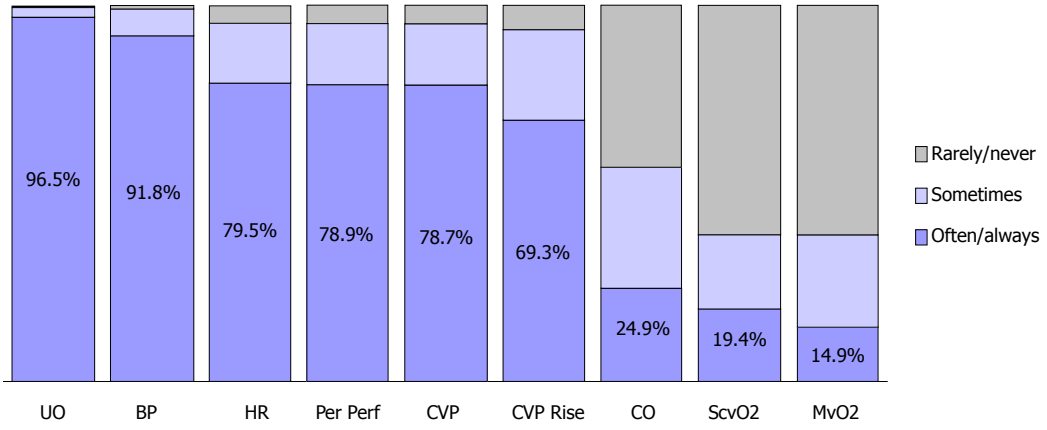

Figure 2 Volume resuscitation end-points[6]. BP: Blood pressure; CO: Cardiac output; CVP: Central venous pressure; CVP rise: Sustained rise in central venous pressure; HR: Heart rate; MvO2: Mixed venous oxygen saturation; Per Perf: Peripheral perfusion; ScvO2: Central venous oxygen saturation; UO: Urine output.

used in the ITU/HDU and operating theatre settings, management of these patients on the ward relies mainly on regular vital signs monitoring including daily body weight rather than being misled by erroneous CVP reading.

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MINIREVIEWS

Vaccination practices in End Stage Renal Failure and Renal Transplantation; Review of current guidelines and recommendations

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Abstract

Due to the increased burden of infectious complications following solid organ transplantation, vaccination against common pathogens is a hugely important area of discussion and application in clinical practice. Reduction in infectious complications will help to reduce morbidity and mortality post-transplantation. Immunisation history is invaluable in the work-up of potential recipients. Knowledge of the available vaccines and their use in transplant recipients, donors and healthcare providers is vital in the delivery of quality care to transplant recipients. This article will serve as an aide-memoire to transplant physicians and health care professionals involved in managing transplant recipients as it provides an overview of different types of vaccines, timing of vaccination, vaccines contraindicated post solid organ transplantation and travel vaccines.

Key words: Immunization; Travel vaccines; Infection; Immunosuppression; Inactivated vaccines; Vaccination post-transplant

Core tip: Patients in end-stage renal failure and those after renal transplantation have a higher risk of opportunistic infections with catastrophic complications and poor response to standard vaccines. Special individualized consideration is needed to immunize these

patients within the existing vaccination protocols.

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INTRODUCTION

End stage renal disease (ESRD) and long-term haemodialysis results in a state of immune compromise with increased risk of systemic infections. Similarly, Renal transplant (RT) recipients on maintenance immunosuppression, also have an increased life-time risk of opportunistic infections. Post-transplant infectious complications are one of the leading causes of morbidity and mortality in these patients. Although immunization against common pathogens can avoid potentially catastrophic complications, questions remain regarding safety, optimal timing and efficacy in these patients.

Transplant recipients are usually excluded from vaccine trials, leading to a scarcity of data regarding their safety and efficacy in these patients[1,2]. However, several guidelines have emerged based on individual case series and experience with other immunocompromised patients[3]. Nevertheless, there exists a clinical hiatus between published guidelines and routine clinical practice, due to safety concerns and fears of increased graft rejection after immunization[4].

IMMUNE STATUS AND IMMUNIZATION

Post-transplant immunosuppression has a cumulative effect on the immune system, including suppression of antigen presentation, T and B-cell proliferation and antibody production. Therefore, the host serological response to vaccination is suppressed and variable compared to the non-transplant individual[5]. Furthermore, transplant recipients have a state of hypogammaglobulinaemia, contributing to the low sero-conversion rates[6]. Therefore, patients with ESRD require a detailed and careful immunization history before enlisting for RT.

TYPE OF VACCINATION: LIVE, KILLED OR INACTIVATED

The place of live attenuated vaccines in transplant recipients remains an area of significant concern. Active viral replication following live vaccines has been demonstrated in immunocompromised hosts, leading to systemic infection. Viral replication can persist for several weeks after vaccination and such vaccines are recommended at least 6 wk prior to the planned transplant[7].

Killed and inactivated vaccines are safe in the transplant recipient. These can be administered in line with the immunization schedule for general population. Nevertheless, vaccination in general, is best avoided in the initial 6 mo after RT, where the immunosuppression is maximal. An exception is the influenza vaccine, which is safe as early as 4 wk after RT, to coincide with seasonal outbreaks[8,9].

TIMING OF VACCINATION

The optimum time for primary vaccination is the pre-transplant phase (Tables 1 and 2). Primary immunization should be carried out early after enlisting for RT due to the variable serological response rates[10]. This allows use of all types of vaccines including live vaccines, achieving adeqaute antibody titres and managing possible vaccine related reactions without compromising graft outcome. Live vaccination may interfere with the reading of Tuberculin skin test (TST) which is commonly done in most transplant cenetrs for all potential recipients. Therefore, the TST should be performed simultaneously with live vaccination or delayed by at least 28 d[11]. Similar difficulties with interpretation have also been reported with the newer interferon gamma release assay (IGRA)[12].

DOSING

Crespo *et al*[13] observed that following influenza vaccination, seroconversion rates were 33%, 42% and 82% in ESRD, post-RT and healthy controls respectively. A similar trend of poor sero-conversion is noted with other standard vaccinations among patients with ESRD and after RT. Furthermore, antibody titres tend to decline faster in these patients compared to healthy adults, requiring frequent monitoring of titres and booster vaccination in those who remain sero-negative or have suboptimal antibody levels.

VACCINATION OF HEALTH CARE PERSONNEL AND CARE GIVERS

Certain vaccines such as hepatitis-B are mandatory for all health care workers prior to assuming duties. Other vaccines (*e.g.*, Varicella, influenza) are recommended in most centers and have shown to minimize hospital-acquired infection. All killed or inactivated vaccines are safe in health care workers and close contacts of RT patients. However, live vaccines should be avoided as it can lead to viral shedding and active infection in the transplant recipient[14].

VACCINATION IN LIVING DONORS

In live donor RT, all donors need to be comprehensively

Table 1 Vaccination in end stage renal disease and pre-transplant

Vaccine	Live/inactivated	Comments
Hepatitis B	Inactivated	Higher concentration in 3-4 divided doses Check seroconversion after 6-12 wk Repeat dosing if HBsAb titre < 10 IU/L
Pneumococcal	Inactivated	(1) Adults (≥ 19 yr), previously unvaccinated; PCV-13 followed 8 wk later by PPSV-23 (2) Previously vaccinated; Single dose of PCV-13, one year after the last PPSV-23
HPV	Inactivated	All patients aged 9-26 yr
Influenza	Live (LAV)	Contra-indicated
	Inactivated (TIV)	Recommended annually
MMR	Live	Mandatory for all paediatric patients; 2 doses given 4 wk apart
		Single dose booster for all sero-negative adult patients
Rubella		For all seronegative female patients of child-bearing age
Varicella	Live attenuated	For all paediatric and adolescent patients, completed 6 wk before transplant
HZV	Live	Recommended for all elderly (> 60 yr) patients
		Optional for those 50-60 yr with a history of varicella or zoster
		No evidence of benefit in those < 50 yr
DTP	Inactivated	For all paediatric patients
Td/ Tdap	Inactivated	Td; Formerly (before 2005) recommended to all adult patients as a booster
		Tdap to all as a one-time dose followed by Td booster every 10 yr
BCG	Live	Routine neonatal vaccination done in Asia, Eastern Europe, Middle East, Africa and South America
		Elsewhere, recommended children < 5 yr deemed to be at high risk (see text)

HPV: Human papilloma virus; MMR: Mumps and rubella; DTP: Diptheria, tetanus and pertussis; BCG: Bacille Calmette-Guérin; LAV: Live attenuated vaccine; TIV: Trivalent inactivated vaccine.

checked for their immunization history. Potential donors should be up-to-date in their age appropriate immunization schedule. Live vaccinations should be avoided within 4 wk of a planned organ donation[7].

COMMON VACCINES IN THE TRANSPLANT PATIENT

Hepatitis B vaccine

Patients on long-term haemodialysis and after RT have a higher risk of hepatitis-B infection. It may manifest as an aggressive primary infection or reactivation of latent infection, requiring mandatory vaccination of all patients with ESRD, ideally before initiating dialysis. In case it had been missed, it is safe to be given while on dialysis or after RT. However, these patients have poor seroconversion rates (67%-86%), and require higher dosing, given as 20 or 40 (instead of the usual 10) micrograms of recombinant hepatitis-B in 3-4 doses at 0, 1, 2 and 6 mo[9,10,15].

Hepatitis-B surface antibody (HBsAb) titre should be checked 6-12 wk after completing the vaccination schedule and annually thereafter continuing beyond the transplantation. Those who fail to achieve desired titres (10 IU/L) are recommended a second course of vaccination. Those who fail to achieve the desired titres after two courses should be tested for active infection[3]. Booster dosing is also recommended for those with suboptimal HBsAg titres at annual monitoring after RT.

Pneumococcal vaccine

Streptococcus pneumoniae infection can lead to severe and life-threatening pneumonia in ESRD and following RT. Furthermore, the incidence of invasive pneumococcal infection is also significantly higher in patients after RT compared to the general population. Therefore, routine vaccination is recommended in all patients with chronic kidney disease[15]. There are two common vaccine variants; the polysaccharide 23-valent (PPSV-23) and conjugated 13-valent (PCV-13), effective against different serotypes of the pathogen[16]. Both are inactivated vaccines and safe in the immunosuppressed host. Adult (≥ 19 years) patients with chronic kidney disease who have not been previously vaccinated should receive a single dose each of PCV-13 followed 8 wk later by PPSV-23[15]. If previously vaccinated with PPSV-23, they should receive a single dose of PCV-13 after 1 year from the last dose of PPSV-23[17]. In immunocompromised hosts including those after RT, a second dose of PPSV-23 is recommended 5 years after the initial dose.

Human papilloma virus vaccine

Human papilloma virus (HPV) infection is one of the commonest prevalent infections among female transplant recipients. In the immunosuppressed host, specific strains of human papilloma virus may result in an increased risk of cervical, vulval or anal carcinoma[18]. The available trivalent and quadrivalent vaccines are both inactivated and safe in the immunocompromised host. It is recommended for all prospective male and female recipients aged 9-26 years, given prior to RT[4,15].

Influenza vaccine

Influenza infection can have devastating consequences in the immunosuppressed host. Early studies described prolonged viral shedding and risk of allograft rejection

Table 2 Common vaccinations contra-indicated post-transplant

Vaccine	Remarks
Influenza-Live attenuated	Inactivated is recommended annually
MMR	Recommended pre-transplant to all paediatric patients and sero-negative adult patients
Varicella	Recommended pre-transplant to all paediatric and adolescent recipients
HZV	Recommended pre-transplant to all those > 60 yr and those with a history of varicella or zoster infection (50-60 yr)
BCG	Trials under way for inactivated vaccine-currently not in routine clinical use post-RT
Oral polio vaccine	Inactivated injectable vaccine recommended when indicated
Typhoid	Travel vaccine, not routinely recommended
	Inactivated variant available for emergency travel

MMR: Mumps and rubella; BCG: Bacille Calmette-Guérin.

with influenza infection, leading to reservations regarding vaccination[19]. However, a direct causal effect of the vaccine on graft rejection has not been substantiated[20,21].

Two common vaccine variants exist; the live attenuated vaccine (LAV) and the trivalent inactivated vaccine (TIV). LAV and its intra-nasal variant are contraindicated after RT. The newer adjuvant vaccine is also contra-indicated as it has been shown to induce *de novo* anti-HLA donor specific antibodies, although with no proven clinical implications on the allograft[3].

Safety and efficacy of TIV is well documented and is recommended annually to all patients with ESRD and post-RT. It has been shown to be safe as early as one month after RT in line with seasonal influenza outbreaks. This current trend has led to a significant shift in practice pertaining to influenza vaccination after RT. A survey by Chon *et al*[22] covering 239 transplant centers across United States found that 95% of centers recommended influenza vaccine to their recipients compared to 84% in 1999.

Measles, mumps and rubella vaccine

Mumps and rubella (MMR) vaccine is a live attenuated vaccine and is contraindicated after RT. It is mandatory in all prospective paediatric recipients, recommended as a two-dose regimen approximately 4 wk apart after enlisting for RT[23]. In adults, serological testing is recommended and a single dose vaccination is undertaken for those who are seronegative.

Testing of rubella antibodies is recommended for all prospective female recipients of child-bearing age and vaccination performed if seronegative. Although adult rubella infection is self-limiting, immunization provides protection against congenital rubella syndrome in the event of post-RT pregnancy.

Varicella vaccine

Varicella can cause overwhelming disseminated disease in the immunosuppressed host. The varicella vaccine is live-attenuated and is contra-indicated after RT. It is recommended in all prospective paediatric and adolescent transplant recipients, completed at least 6 wk prior to transplantation[7,23]. If a deceased donor offer is received before completing 6 wk, RT can still proceed with a prophylactic regimen of acyclovir. In a study by Broyer *et al*[24], pre-transplant vaccination showed a dramatic reduction in post-RT varicella from 45% to 12%. Furthermore, the rate of late reactivation as zoster following vaccination (7%) was significantly lower than following primary infection (38%). In the event of a post-RT exposure in seronegative patients, prophylaxis is recommended with acyclovir, valacyclovir or intravenous immunoglobulins[25].

Herpes zoster virus vaccine

Herpes zoster reactivation (shingles) after transplant can lead to disseminated infection or troublesome herpetic neuralgia. Therefore, vaccination is recommended for all prospective elderly recipients (⩾ 60 years) at least 1 mo before RT. In those aged 50-60 years, vaccination is optional and can be considered in those who have a history of varicella or zoster infection[11]. There is no clear evidence for its benefit in recipients younger than 50 years.

Polio vaccine

The live oral polio vaccine is contra-indicated in transplant recipients and their contacts. Hence, paediatric transplant recipients and their household contacts are excluded from routine polio vaccination programs[3]. Instead, they are given the inactivated injectable vaccine in-line with the normal immunization schedule.

Diptheria, tetanus and pertussis vaccine

Diptheria, tetanus and pertussis (DTP) is an inactivated vaccine and is recommended to all prospective paediatric RT recipients. Until 2005, all prospective adult recipients were recommended a booster dose of tetanus-diphtheria (Td) only. However, a resurgence of pertussis related respiratory illness prompted the inclusion of pertussis vaccine to this schedule. The currently available tetanus toxoid-diphtheria-acellular pertussis (Tdap) vaccine is inactivated and safe in ESRD and after RT. Hence the current recommendation for both groups is a one-time dose of Tdap followed by Td boosters every 10 years[3,23].

Tuberculosis vaccine

The frequency of post-transplant active tuberculosis is

estimated to be 20-74 times higher than the general population, with a mortality rate reaching 30%[26]. Immunosuppressive medication may interfere with TST and IGRA used in diagnosis. Despite active disease, sputum smears may remain negative while the clinical manifestations are often atypical, leading to significant diagnostic delays. Furthermore, the disease may actively contribute to allograft dysfunction, resulting in the high morbidity and mortality[27].

The Bacille Calmette-Guérin (BCG) vaccine is a live vaccine and is contra-indicated after RT. Attempts at producing an effective inactivated vaccine have been largely unsuccessful. The only human trials to show efficacy of an inactivated vaccine was the Dar-Dar and DAR-901 trials conducted in Tanzania for patients with human immunodeficiency virus who were previously vaccinated with BCG at birth. The DAR-901 phase Ⅲ study showed the inactivated vaccine was well tolerated and did not cause post-vaccination tuberculosis[28].

Countries in Asia, Eastern Europe, Middle East, Africa and South America have universal neonatal BCG vaccination. In contrast, North America, United Kingdom, Australasia and Western Europe do not practice routine BCG vaccination due to low prevalence of TB, recommending it only to those neonates and children considered to be at a higher risk than the general population. This includes children < 5 years who live in an area of high prevalence, who have parents or grandparents born in a country of high prevalence, who live 3 or more months per year in a country with high prevalence or who have a close contact with diagnosed pulmonary TB[29].

Meningococcal vaccine

Meningococcal vaccine is usually recommended for patients undergoing splenectomy, those with complement deficiency or with HIV infection. In the transplant patients, it is widely recommended for those intending to travel to endemic regions. More recently, the meningococcal vaccine has been recommended for selected transplant candidates who are likely to receive eculizumab as immunosuppression[15]. Eculizumab is a complement inhibitor and has been linked to an increased incidence of meningococcal infection[30]. Accordingly, highly sensitized recipients who are likely to be given eculizumab post-transplant are recommended a two-dose regimen given 8 wk apart in the lead up to RT.

TRAVEL VACCINATION

Vaccinations of transplant recipients who intend to travel overseas to areas where certain infections are endemic, need special consideration. Preplanning allows serological testing before the intended travel to ensure protective serological status. In emergency travel circumstances, passive immunization with immunoglobulins can be considered[31].

Hepatitis-A vaccine

Transplant recipients have a poor seroconversion rate to hepatitis-A vaccination and show rapid decline in antibody titres[32]. For those travelling to endemic regions, the vaccine is recommended in two divided doses given six to twelve months apart. In addition to being a travel vaccine, hepatitis A vaccination is also recommended to RT recipients who are male homosexuals, recreational drug users, receive platelet regular concentrates and those who also have concomitant chronic liver disease[23].

Typhoid vaccine

The oral live attenuated vaccine is contraindicated after RT. If it is to be given, it must be done prior to transplant for those who reside in or travel to endemic areas. If emergency travel is needed, the inactivated injectable vaccine is recommended[33].

Polio vaccine

The live oral vaccine is contraindicated after transplant. Any transplant recipient travelling to endemic regions should receive a booster dose of the inactivated injectable vaccine[7].

Meningitis vaccine

The meningococcal vaccine is inactivated and is recommended to all travelers to endemic areas. This becomes especially important for transplant recipients who travel to regions such as Sub-Saharan Africa and Saudi Arabia, where it is a pre-requisite for travel[34].

Yellow fever vaccine

Yellow fever becomes endemic in peak seasons in Sub-Saharan Africa and certain regions of South America. The vaccine is a live attenuated and is contraindicated after RT. Hence, those who live or intend to travel to these regions need to be vaccinated before the transplant[35].

Rabies vaccine

Transplant recipients who are at constant risk of animal exposure such as veterinarians, should be considered for pre-transplant pre-exposure prophylaxis[15]. In all other transplant recipients, rabies vaccination becomes relevant only after possible rabid exposure. Such patients require comprehensive post-exposure prophylaxis. This comprises of injectable intramuscular vaccines in divided doses coupled with human rabies immunoglobulin[36].

Japanese encephalitis vaccine

Transplant recipients travelling to endemic East Asia and South-East Asia are recommended Japanese encephalitis vaccination. The newer killed inactivated vaccine is safe and recommended in two doses given 4

wk apart prior to intended travel[37].

CONCLUSION

Patients with ESRD and after RT are a distinct cohort that carry an increased risk of common infections, potentially catastrophic complications of such infections as well as reduced immunogenicity following immunization. In general, all immunization related details should be obtained prior to enlisting for RT. Any planned vaccines should be administered early in the pre-transplant phase at least 4 wk before the RT. While inactivated vaccines are considered safe beyond the first 6 mo after RT, live vaccines are contra-indicated throughout the post-transplant period. The reduced seroconversion rates and faster antibody clearance in these patients mandates regular screening for antibody titres and administration of booster doses when necessary.

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SYSTEMATIC REVIEWS

Perioperative glucose management and outcomes in liver transplant recipients: A qualitative systematic review

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Abstract

AIM

To investigate the relationship between post-liver transplantation (LT) glycemic control and LT outcomes.

METHODS

A qualitative systematic review on relevant prospective interventions designed to control glucose levels including insulin protocols. Studies investigating an association between glycemic control and post-LT outcomes such as mortality, graft rejection, and infection rate were reviewed. PubMed, EMBASE, and other databases were searched through October 2016.

RESULTS

Three thousands, six hundreds and ninety-two patients from 14 studies were included. Higher mortality rate was seen when blood glucose (BG) $\geqslant$ 150 mg/dL (P = 0.05). BG $\geqslant$ 150 mg/dL also led to higher rates of infection. Higher rates of graft rejection were seen at BG > 200 mg/dL (P < 0.001). Mean BG $\geqslant$ 200 mg/dL was associated with more infections (P = 0.002).

Nurse-initiated protocols and early screening strategies have shown a reduction in negative post-LT outcomes.

CONCLUSION

Hyperglycemia in the perioperative period is associated with poor post-LT outcomes. Only a few prospective studies have designed interventions aimed at managing post-LT hyperglycemia, post-transplant diabetes mellitus (PTDM) and their impact on post-LT outcomes.

Key words: Diabetes; Liver transplant; Non-alcoholic steatohepatitis; Outcomes; Non-alcoholic fatty liver disease

Core tip: Despite the importance of post-liver transplantation (LT) glycemic control, there are no evidence-based guidelines on how to manage hyperglycemia in the post-LT period. The aim of this qualitative systematic review is to determine potential associations between glucose levels post-LT and outcomes such as mortality, graft rejection, infection rate, and other related post-LT outcomes. In addition, we analyzed methods for targeting glycemic control including specific therapeutic regimens or insulin protocols utilized in LT recipients.

Paka P, Lieber SR, Lee RA, Desai CS, Dupuis RE, Barritt AS. Perioperative glucose management and outcomes in liver transplant recipients: A qualitative systematic review. *World J Transplant* 2018; 8(3): 75-83 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i3/75.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i3.75

INTRODUCTION

Hyperglycemia after liver transplantation (LT) is a common phenomenon associated with increased risk of allograft rejection[1,2]. Poor glycemic control is also implicated in other post-LT complications including infection[3-5], acute kidney injury[6], new onset diabetes after transplantation (NODAT)[7,8], and malignancy, in addition to complications related to the metabolic syndrome including increased cardiovascular risk[9]. Despite the importance of post-LT glycemic control, there are no evidence-based guidelines on how to manage hyperglycemia in the post-LT period. Moreover, it is unclear what degree of glycemic control is associated with graft failure and complications such as infections. Similarly, predictors for poor glycemic control and NODAT in LT recipients have not been identified, apart from donor graft steatosis[9], post-LT immunosuppression[10-12], steroid use, and hepatitis C virus (HCV) infection[13]. These gaps in our existing knowledge necessitate a review of the literature on glycemic control and perioperative outcomes in LT recipients.

Given the increasing prevalence of non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome, many patients will arrive at transplant with some degree of insulin resistance. Post-LT hyperglycemic management will be essential to improving patient care and outcomes. The incidence of NODAT ranges from 20% to 44% among LT recipients, with rates varying depending on methodology used[8,9,11,14]. The aim of this qualitative systematic review is to analyze methods for targeting glycemic control including specific therapeutic regimens or insulin protocols utilized in LT recipients, and to determine associations between glycemic control and post-LT outcomes such as mortality, graft rejection, or infection rate. To achieve this goal, we reviewed prospective interventions targeting glucose control, as well as retrospective studies that examined the association between glucose control and relevant perioperative transplant outcomes.

MATERIALS AND METHODS

Overview

Our qualitative systematic review included *a priori* search criteria of journal articles and conference abstracts among adult (age ⩾ 18 years) human orthotopic or living donor LT recipients. Studies were limited to the English language and had to include at least one relevant outcome of interest such as patient survival, graft rejection, infection rate, acute kidney injury, and graft survival. Given the focus on perioperative glucose control, study outcomes were limited to glucose control during the first year post-LT.

Databases and search terms

A health sciences librarian with clinical input from our study team designed the *apriori* search strategy. PubMed (https://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.elsevier.com/solutions/embase-biomedical-research), SCOPUS (https://www.scopus.com), Clinical trials.gov (https://clinicaltrials.gov), and WHO ICTRP (http://www.who.int/ictrp/en) using the search terms outlined in Supplementary Table 1. Searches were performed on October 18, 2016 and updated in December 2017. All studies prior to this date were included.

Study selection

Using the various databases outlined above, our search yielded a total of 1624 results after removing duplicate results. Four reviewers (PP, SRL, RAL, and ASB) independently screened the titles and abstracts of 406 search results each for potential eligibility and a consensus was reached to include a total of 14 studies in the final analysis (Figure 1). Although the search strategy was designed to exclude patients receiving other transplants from this review, some of these studies included patients that received combined liver-

Table 1 Characteristics of retrospective studies

Ref.	Country	Year	*n*	Group 1	Group 2	Study outcome(s)	Comments
Ammori *et al*[5]	United States	2007	184	Strict glucose control (BG < 150 mg/dL)	Poor Glucose control (BG ⩾ 150 mg/dL)	Mortality Infection rate	
Chung *et al*[25]	South Korea	2014	211	BG decline during the Neohepatic Phase (Yes)	BG decline during the Neohepatic Phase (No)	Mortality, length of ICU stay, early allograft dysfunction, MELD Score recovery	Outcomes were assessed relative to the drop in hyperglycemia after the neohepatic phase
Gelley *et al*[21]	Hungary	2011	310	*De novo* diabetes	Control	HepC recurrence and association with NODAT	
Hartog *et al*[23]	United Kingdom	2014	430	DBD	DCD	NODAT	
Keegan *et al*[17]	United States	2010	161 (158 were available for analysis)	Pre-protocol	Protocol	Mortality Morbidity Graft function	
Linder *et al*[18]	United States	2016	114	PTDM	Non-PTDM	PTDM	BPAR, allograft failure, death, CMV infection are additional endpoints
Park *et al*[4]	United States/ Taiwan	2009	680	SSI (Yes)	SSI (No)	SSI	
Trail *et al*[20]	United States	1996	497	PTDM	Case-control	PTDM morbidity	PTDM leading to infections and graft rejection
Wallia *et al*[1]	United States	2010	144	BG > 200 mg/dL	BG < 200 mg/dL	Graft rejection, infection, and re-hospitalization	Graft survival and prolonged ventilation
Wallia *et al*[19]	United States	2011	73	Glucose management service	Non-Glucose Management Service	Graft rejection, infection, and re-hospitalization	Graft survival and prolonged ventilation
Yoo *et al*[6]	South Korea	2016	304	Normoglycemia (BG: 80-200 mg/dL)	Mild hyperglycemia (BG: 200-250 mg/dL)	AKI	Group 3: Moderate hyperglycemia (250-300 mg/dL) Group 4: Severe hyperglycemia (> 300 mg/dL)

DBD: Donated after brain death; PTDM: Post-transplant diabetes mellitus; Non-PTDM: Transplant diabetes mellitus free; DCD: Donated after circulatory death; NODAT: New onset diabetes after transplantation; AKI: Acute kidney injury.

kidney transplantation. These patients were included since the results were reported in a composite manner (*i.e.*, data for liver transplantation alone patients *vs* combined liver-kidney transplantation patients were not reported separately). Overall, the number of liver-kidney transplantation patients was relatively small, and the results were predominantly driven by LT recipients alone.

Quality assessment

Four reviewers independently assessed the risk of bias in each study. Selected studies were reviewed based on representativeness of study population, comparability of cohorts, adequate assessment of outcomes, sufficient length of follow-up, adequacy of follow-up, and source of study funding. The prospective randomized study was assessed using the Cochrane risk of bias tool and the Newcastle-Ottawa Scale (NOS) was used for the cohort/case-control studies[15,16].

RESULTS

This qualitative systematic review includes results from 14 full text articles. Of the 1624 records identified electronically, 780 were duplicates and 109 were eligible after abstract review. Of the 109, there were 22 articles that were reviewed and retrieved in full-text form. Of these, 8 were excluded and data from 14 full text articles (11 retrospective studies, 2 prospective studies and 1 cross-sectional study) were found to be eligible and included in this review (Figure 1).

Characteristics of included studies

The characteristics of the included studies are shown in Tables 1 and 2. A total of 3692 patients (3077 patients were retrospectively studied; 615 patients were prospectively studied) from 14 studies were included. The studies spanned 20 years from 1996 to 2016 with most occurring in the past decade and included transplants pe-

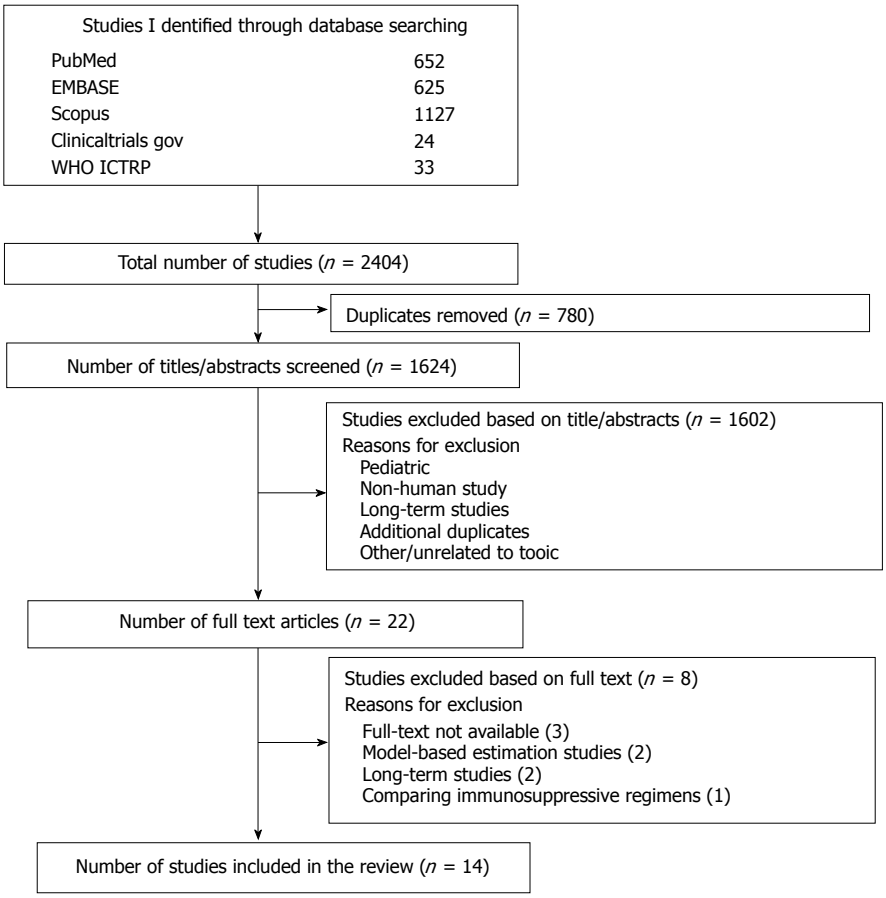

Figure 1 Consort diagram.

rformed in the United States, United Kingdom, Taiwan, Spain, South Korea, and Hungary.

Risk of bias in included trials

Supplementary Table 2 shows the risk of bias assessment of all the included trials. Of the 14 studies that were included, 11 were retrospective in nature and carry a potential to be inherently biased. NOS was used to assess risk of bias for the cohort/case-control studies and a modified version of the NOS was used for the single cross-sectional study. The single randomized prospective study, for the most part was deemed to have minimal bias utilizing the Cochrane risk of bias tool[15,16].

Study outcomes

Clinical outcomes for each trial are summarized in Table 3. Major outcomes of interest in relation to blood glucose (BG) level include mortality, graft rejection, infection rate, acute kidney injury (AKI), graft survival, post-transplant diabetes mellitus (PTDM), and NODAT.

Mortality

Three studies evaluated the relation between glycemic control and mortality in orthotopic liver transplantation (OLT) patients. Ammori *et al*[5] found a statistically significant association between glycemic control and mortality. The retrospective review compared patients with strict glycemic control (mean blood glucose < 150 mg/dL) *vs* those with poor control (mean blood glucose ⩾ 150 mg/dL). A total of 184 patients were analyzed (n = 60 for strict control, n = 124 for poorly controlled). The strict control group had a mean glucose of 135 mg/dL while the poorly controlled group had a mean glucose level of 184 mg/dL. Baseline donor and recipient characteristics for both groups were similar with the exception of recipient age (47 ± 2 years *vs* 53 ± 1 year; strict *vs* poor control, respectively). The Kaplan Meier survival analysis showed a significantly improved one-year survival rate in the strict glucose control group (91.2%) as compared to that in the poorly controlled group (78.1%). The one-year mortality rate was found to be 8.8% and 21.9% (P = 0.05) for patients in the strict controlled group and poorly glucose control group respectively.

Keegan *et al*[17] also evaluated the impact of perioperative glycemic control in OLT patients. This retrospective analysis studied the impact of the initiation of a nurse-initiated protocol for glycemic management (protocol group) *vs* glycemic management prior to the initiation of the protocol (pre-protocol group). Prior to the implementation of the protocol, a variety of insulin infusion protocols and ad hoc sliding scales were used at the discretion of the physician for glycemic control.

Table 2 Characteristics of prospective studies and the cross-sectional study

Ref.	Country	Year	*n*	Group 1	Group 2	Outcome	Comment
Alvarez-Sotomayor *et al*[24]	Spain	2016	344	Diabetes before transplantation	No diabetes before transplantation	PTDM	Cross-sectional study
Villanueva *et al*[22]	United States	2005	107	Rosiglitazone	-	PTDM	
Welsh *et al*[28]	United States	2016	164	Intensive glycemic control	Moderate glycemic control	Hypoglycemia	Insulin requirements

PTDM: Transplant diabetes mellitus.

Table 3 Summary of important findings of perioperative glucose control on liver transplant outcomes

Outcome of interest	Important findings	Data sources
Mortality	Mean BG ⩾ 150 mg/dL increases mortality	Ammori *et al*[5] (retrospective study)
	Nurse initiated insulin protocol did not impact mortality	Keegan *et al*[17] (retrospective study
	PTDM influenced glucose levels but did not change mortality	Linder *et al*[18] (retrospective study)
Graft rejection	Mean BG > 200 mg/dL increases risk of rejection	Wallia *et al*[1] (retrospective study)
	Although, mean BG were lower with the use of GMS, it did not lead to lower rate of rejection	Wallia *et al*[19] (retrospective study)
		Linder *et al*[18] and Trail *et al*[20] (retrospective studies)
	Conflicting evidence exists relating to the development of PTDM and its relation to rejection	
Infection rate	BG ⩾ 150 mg/dL is associated with higher infection rate	Ammori *et al*[5] (retrospective study)
	BG ⩾ 200 mg/dL increases risk of SSIs	Park *et al*[27] (retrospective study)
	Use of GMS led to lower rate of infection	Wallia *et al*[1] (retrospective study)
	Higher BG levels post-LT also led to increased incidence of HCV recurrence	Gelley *et al*[21] (retrospective study)
		Linder *et al*[18] (retrospective study)
	No association between BG levels and post-LT CMV infection	Trail *et al*[20] (retrospective study)
	Development of PTDM did not lead to higher infection rate	
Post-transplant diabetes mellitus/new onset diabetes mellitus	Rosiglitazone ± sulfonylurea is a potential option for the management of PTDM	Villanueva *et al*[22] (prospective study)
		Linder *et al*[18] (retrospective study)
	Post-LT hyperglycemia is associated with the development of PTDM	Alvarez-Sotomayor *et al*[24] (retrospective study)
	Insulin use was significantly higher in PTDM patients with inadequate BG	
Acute kidney injury and graft survival	High glucose variability is associated with post-LT acute kidney injury	Yoo *et al*[6] (retrospective study)
		Wallia *et al*[1] and Trail *et al*[20] (retrospective studies)
	No association between post-LT BG levels and graft survival	

BG: Blood glucose; PTDM: Post-transplant diabetes mellitus; GMS: Glucose management service; HCV: Hepatitis C virus; LT: Liver transplantation.

Under the protocol, a nurse would initiate a continuous intravenous (Ⅳ) insulin infusion within 48 h post-OLT if a patient's BG was greater than 130 mg/dL. The insulin infusion would be titrated as necessary (based on hourly readings) to reach a target BG goal of 80-130 mg/dL. The primary purpose of this quality improvement study was to identify the percentage of all measurements that were in the hypoglycemic (BG < 60 mg/dL) or severely hyperglycemia (BG > 250 mg/dL) range. These measurements were compared between pre-protocol and protocol groups. A total of 158 patients were available for analysis (n = 84 in the pre-protocol group; n = 77 in protocol group). Severe hyperglycemia was observed in 90 of the 581 measurements (15.5%) in the pre-protocol group and 15 of the 539 (2.8%) in the protocol group (OR for protocol group 0.16; CI: 0.09-0.28). Statistical significance, however, was not seen in one-year mortality between the protocol group and the pre-protocol group. Four out of 75 patients (5.3%) died in the protocol group, compared with 5 out of 83 patients (6.0%) in the pre-protocol group (OR for death in the protocol group, 0.89; 95%CI: 0.23-3.42; P = 0.86).

Linder *et al*[18] evaluated the insulin burden between liver transplant patients that developed PTDM *vs* patients that did not. BG levels between these two groups were reported as well as mortality rates. A total of 114 patients were retrospectively analyzed and while postoperative BG levels were similar in the ICU setting between the two groups, a statistically significant difference in floor (non-ICU) average BG levels (mg/dL) was seen between patients that developed PTDM and those that did not (184.7 ± 31.5 and 169.3 ± 31.4 respectively, P = 0.013). Statistically significant differences in one-month average BG levels were also seen-176.0 ± 31.1 for the PTDM group and 160.6 ± 28.0 for the non-PTDM group (P = 0.007). However, there was no significant difference in one-year mortality in the PTDM and non-PTDM groups.

Graft rejection

Four studies examined the association between glycemic

levels and graft rejection in liver transplant recipients. In a retrospective analysis conducted by Wallia *et al*[1] (n = 144), there was a statistically significant association between glucose level and graft rejection. Higher rates of rejection were seen in patients with a mean BG level > 200 mg/dL compared to those that had a mean BG level < 200 mg/dL (76.7% and 35.1% respectively; P < 0.001). A retrospective subgroup analysis by Wallia *et al*[19] (n = 73) studied the effect of a glucose management service (GMS) on blood glucose levels and its impact on clinical outcomes including graft rejection. The GMS consisted of a group of nurse practitioners supervised by an endocrinologist responsible for managing BG. The BG levels were managed by the primary transplant team in the non-GMS group. The mean inpatient BG level during the peri-transplant period was 189.0 ± 45.0 in the non-GMS group and 157.9 ± 32.3 in the GMS group (statistical significance data not provided). Although, patients in the non-GMS group had higher BG levels, hyperglycemia did not lead to higher rates of graft rejection (45% in the non-GMS group *vs* 29% in the GMS group, P = 0.156).

In the previously described retrospective analysis by Linder *et al*[18], biopsy-proven acute rejection (BPAR) was also studied as an outcome and there was a statistically higher incidence in PTDM *vs* non-PTDM patients (41.7% *vs* 24.2% respectively, P = 0.048). Similarly, a retrospective study by Trail *et al*[20] (n = 497), studied morbidity, including graft rejection, in DM patients after LT compared with matched control patients. Mean fasting blood glucose for patients with PTDM was 122.3 ± 5.0 mg/dL compared to 101.9 ± 3.9 mg/dL for the matched control patients (P < 0.01). Despite the statistically significant difference in glycemic levels between the PTDM group and matched control group, the number of rejection episodes was similar between the two groups, *i.e.*, rates of rejection were not significantly different between groups.

Infection

Six retrospective studies evaluated the association between glucose levels and infection. Park *et al*[4] studied the association between intraoperative hyperglycemia and surgical site infection (SSI) postoperatively in a retrospective study (n = 680). Of the 680 patients, 76 (11.2%) experienced SSI after LT. Severe hyperglycemia (defined as mean BG ⩾ 200 mg/dL) was seen in 37.8% of the 76 patients with SSIs compared to only 21.9% of the 604 non-SSI patients (P = 0.002) suggesting an association between the occurrence of SSIs and mean BG levels ⩾ 200 mg/dL. Similarly, In the study by Ammori *et al*[5], infectious complications when assessed 30 d post-LT were significantly associated with worse glucose control-among the strict glucose control group (mean BG < 150 mg/dL), there were 60 (30%) post-LT infections, compared to 124 (48%) infections in the poor glucose control group (mean BG ⩾ 150 mg/dL) (P = 0.02). The retrospective subgroup analysis by Wallia *et al*[19] found that the patients in the non-GMS group with higher BG levels exhibited higher rate of infection compared to the patients in the GMS group at one-year post-LT follow up (79% *vs* 51% respectively, P = 0.015). Gelley *at al*[21] found that higher early postoperative fasting plasma glucose led to higher incidence of HCV recurrence (diagnosed with histology criteria of the Knodell score), although no data was shown with regards to BG levels.

In contrast to the above studies, Linder *et al*[18] showed no association between glycemic level and post-LT CMV infection (patients with PTDM had higher BG levels compared to non-PTDM patients). Similarly, Trail *et al*[20] also showed no significant difference in infectious rates between patients with PTDM and those without PTDM. This study also evaluated the severity of infection as well as the type of infection and no differences were seen between the two groups.

Post-transplant diabetes mellitus and new-onset diabetes after transplantation

Villanueva and Baldwin evaluated the use of Rosiglitazone (ROSI) therapy for patients with PTDM. DM was diagnosed according to the American Diabetes Association (ADA) criteria (symptoms of hyperglycemia with post-prandial BG ⩾ 200 mg/dL, or fasting BG ⩾ 126 mg/dL on two separate occasions). The study followed 40 patients that developed PTDM that were initially stabilized by twice-daily NPH and regular insulin. These patients were subsequently started on ROSI 4 mg/d with the treatment goal to discontinue insulin while maintaining a target goal of HBA1c ⩽ 6.5%. Thirty of the patients that were initially treated with insulin were able to discontinue insulin within 3-4 mo. Three patients required chronic insulin therapy despite ROSI ± a sulfonylurea, and were considered insulin dependent. ROSI monotherapy was sufficient in 12 patients (30%), whereas 25 patients (62.5%) required ROSI + sulfonylurea to maintain insulin independence and normoglycemia. ROSI was continued at 4 mg/d in 25 patients while 15 patients required an increase to 8 mg/d. PTDM patients treated with ROSI maintained a mean HBA1C of 5.6% ± 0.8 (target BG levels were < 100 mg/dL for fasting glucose and < 140 mg/dL for post prandial glucose). A commonly seen side effect among patients treated with ROSI was edema (13%). These data suggest ROSI ± sulfonylurea may be a potential intervention that can reduce insulin burden in patients with PTDM[22].

Linder *et al*[18] also showed that patients who developed PTDM had significantly higher BG levels (1-mo average BG) suggesting post-LT hyperglycemia could play a role in the development of PTDM. Multivariate analysis for predictors of PTDM showed the use of Basiliximab was a negative independent predictor [AOR 0.182 (0.040-0.836), P = 0.03] and rejection was a positive independent predictor [AOR 3.237 (1.214-8.633), P = 0.019] for the development of

PTDM. Hartog *et al*[23] demonstrated that pulse high-dose steroids was an independent predictor of NODAT [OR 3.1 (1.7-5.6), P = 0.001]. In addition, this study also demonstrated donor graft type was associated with early occurrence of NODAT (within 15 d post-LT). Multivariate analysis showed donation after cardiac death (DCD) graft type was associated with significantly early occurrence of NODAT compared to donation after brain death (DBD) graft type [OR 6.5 (2.3-18.4), P = 0.001].

In addition to the previously mentioned outcomes, PTDM has also been associated with higher insulin use in post-LT patients. A cross-sectional study by Alvarez-Sotomayor *et al*[24] evaluated 344 patients of whom 141 patients experienced PTDM (157 total but 16 patients did not have HbA1c readings prior to enrollment). Patients with PTDM who had adequate glycemic control (defined as HbA1c < 7%), were significantly less dependent on insulin (39.4%) compared to patients with inadequate glycemic control (80.8%) (OR 6.6, 95%CI: 1.8-24.6, P < 0.001). Finally, Chung *et al*[25] found male sex, emergency surgery, surgical time (⩽ 9 h), and serum lactate (> 5 mmol/L) to be independent predictors for refractive hyperglycemia (RH), however, most post-LT outcomes were not significant in relation to RH.

Acute kidney injury and graft survival

Other outcomes of interest including AKI, graft survival, and complications related to hospitalization were not studied extensively. Three studies evaluated graft survival and no statistically significant association was seen between post-LT glycemic control and graft survival[1,19,20]. Similarly, no association was seen between BG levels and re-hospitalizations[1,19]. A study by Yoo *et al*[6] demonstrated no association between hyperglycemia and AKI in LT recipients; however, patients with greater glucose variability, as defined by the SD of blood glucose levels, more commonly presented with AKI (P = 0.019). Using SD as a surrogate marker for glucose variability, patients were divided into quartiles according to the SD of intraoperative and postoperative (initial 48 h of ICU admission) blood glucose levels. Patients with the lowest SD were assigned to the first quartile, ranging to those with the highest SD who were assigned to the fourth quartile. Glucose variability was significantly associated with AKI among patients in the third quartile (23.3% of patients with no AKI *vs* 30.3% with AKI, OR 2.47, CI: 1.22-5.00, P = 0.012) and fourth quartile (22.1% with no AKI and 31.1% with AKI, OR 2.16, CI: 1.05-4.42, P = 0.035).

DISCUSSION

This qualitative systematic review of 14 studies examined post-LT glucose control, interventions designed to target glucose control, and associations with post-LT outcomes including infection rate, PTDM, AKI, graft survival and mortality. Ultimately, this review concludes that perioperative hyperglycemia leads to unfavorable post-LT outcomes; however, the degree to which it plays a role may depend on the specific outcome in question. There is strong evidence to support an association between perioperative hyperglycemia and post-LT outcomes such as high infection rate and graft rejection[1,4,5,18-20,26]. A review by Park *et al*[27] that focused specifically on intraoperative hyperglycemia found a similar association between hyperglycemia and infection rate. In contrast, the strength of the evidence that exists to support an association between perioperative hyperglycemia and outcomes such as mortality and graft survival is not as well founded[1,5,17-20]. High glucose variability may also be a factor with the development of certain complications such as AKI[6]. In addition, donor graft type (DCD *vs* DBD) may also play a role in the early occurrence of NODAT (within 15 d post-LT)[23].

What was difficult to discern from these studies was the target BG level associated with poor post-LT outcomes. The studies in this review used different target BG levels to evaluate different outcomes, thus making it difficult to associate the degree of glycemic control with certain outcomes and also limiting comparisons that could be made between studies. The studies also varied in their definition of PTDM, the timing of glucose monitoring (immediate post-operative to days post-LT), and the medications used to manage hyperglycemia (ranging from insulin infusion to oral meds). The variability in the studies is what limits the comparisons that can be made and is the reason we can only perform a qualitative review of the literature. Additionally, most of the studies were retrospective observational studies and were not designed to study the specific association between hyperglycemia and post-LT outcomes. Finally, there were some studies that included a small number of combined liver-kidney transplant recipients and the results were reported in a composite manner, thereby making it difficult to detect LT-specific associations between glucose control and post-LT outcomes.

In this review, all of the relevant literature regarding glucose control and post-LT outcomes was compiled systematically using an apriori search strategy of the major medical literature databases. The data were compiled in a qualitative, descriptive manner due to the heterogeneity among research strategies and outcomes that exist in published literature

The conclusions from this review have robust implications for clinical practice. It is imperative to monitor glucose control pre- and post-LT. Along with hyperglycemia, it is also important to consider complications associated with strict glycemic control such as hypoglycemia and high insulin burden when deciding specific BG levels to target. Welsh *et al*[28] demonstrated the impact of hypoglycemia (defined as glucose ⩽ 70 mg/dL) pertaining to intensive and moderate glycemic control

in post-LT patients. There were a higher number of hypoglycemic patients in the intensive group and these hypoglycemic patients had significantly higher peak insulin drip rates, higher peak insulin glargine, and more importantly had significantly longer hospital stay. Therefore, it is crucial to target perioperative BG levels within a range that would limit complications associated with both hyper- and hypoglycemia. A reasonable target, based on our findings would be a range between 120 mg/dL to 150 mg/dL, given that BG $\geqslant$ 150 mg/dL were associated with negative post-LT outcomes. In addition, interventions through nurse-initiated glucose management protocols to achieve specific target BG levels, early screening to identify patients at high-risk for PTDM, and use of oral agents for management of PTDM seem to be a promising approaches to minimize post-LT outcomes[17,22,24]. Although not discussed extensively in this review, optimizing immunosuppression regimens may also play an important role as noted by the potential association between basiliximab and pulse steroids with PTDM[18,23]. Song *et al*[29] conducted a retrospective study in China and demonstrated that lower exposure of tacrolimus (measured by mean tacrolimus concentration at 6 mo) was associated with less risk of developing NODAT and its related complications. This suggested that not only optimizing the regimen important but also the dosing of immunosuppressive drugs utilized in the regimen need to be optimized. Such recommendations would be strengthened by prospective randomized data and thus highlights the need for further study in this area.

The need for close monitoring of glucose levels post-LT will become even more important in the future. More patients with insulin resistance will come to transplant in the coming years. NAFLD is the fastest growing indication for transplant and will become the leading indication over the next decade[30,31]. The change in disease etiology may also be accompanied by donor grafts from older patients with DM and obesity that may be more susceptible to poor outcomes from hyperglycemic stressors[32]. As NAFLD increases prevalence, the transplant community will see more NAFLD among both living donors as well. A reliable assessment of hepatic steatosis is of paramount importance for living donor selection as significant steatosis can impact the postoperative outcomes of recipients and safety of the donor[33]. Because of these challenges, the focus could be on developing and establishing a standardized protocol for the monitoring of blood glucose levels. The frequency of test like hemoglobin A1c, glucose tolerance test, and use of tools such as continuous glucose monitoring should be further explored.

Prospective clinical studies need to further examine the impact of perioperative glycemic control in LT recipients with specific attention to the outcomes listed above. An ideal target range for BG levels needs to be determined and specifically investigated in terms of reducing negative outcomes associated with both hypo- and hyperglycemia, as well as adverse events related to post-LT complications due to impaired glucose control.

ARTICLE HIGHLIGHTS

Research background

There are no standard guidelines to properly manage hyperglycemia in the perioperative period of liver transplantation.

Research motivation

Understanding the importance of blood glucose level and proper strategies to manage post-liver transplantation hyperglycemia could help reduce adverse outcomes

Research objectives

The primary objective was to identify an ideal blood glucose level to achieve in the perioperative period for patients undergoing liver transplantation. In addition, exploring treatment regimens to achieve the target blood glucose can help identify better strategies for the management of these patients in the future.

Research methods

This is a qualitative systematic review that utilized key search terms to find studies on PubMed and other common databases. The search terms were in relation to liver transplantation and blood glucose level management in the perioperative period.

Research results

A total of 14 studies fit the criteria to properly study the objectives. The findings from this qualitative review suggests that blood glucose levels greater than or equal to 150 mg/dL in the perioperative period generally leads to negative post-liver transplantation outcomes. Specifically, there was an increased risk of infections, graft rejection, PTDM, and mortality. Graft survival was not impacted by hyperglycemia and there was an increased risk of acute kidney injury with high glucose variability in the perioperative period.

Research conclusions

The findings from the compiled studies in this review suggest a blood glucose level between 120 mg/dL and 150 mg/dL could potentially be an ideal target to manage hyperglycemia post-liver transplantation. In addition, early screening, use of oral agents, and utilizing resources such as a glucose management service could be potential strategies to limit adverse outcomes post-transplantation.

Research perspectives

Future studies can validate the findings from this review through a prospective study while implementing some of the strategies discussed in this review to minimize post-liver transplantation outcomes.

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