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EDITORIAL

Live liver donors: Are they at a higher risk for post-operative thrombotic complications?

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Abstract

Live liver donor transplantation to adult recipients is becoming a common practice, increasing the organ pool and providing an alternative to whole cadaveric liver transplantation. These patients are healthy adults without serious medical conditions and typically have normal coagulation profiles preoperatively. Right hepatic lobectomy is usually performed for adult recipients, while left hepatic lobectomy is performed for pediatric recipients. Removal of the whole right lobe from the donors may expose theses patients to multiple intraoperative and postoperative complications. Hypercoagulability has been identified as a serious complication which leads to thromboembolic phenomena with potential fatal consequences. The primary aim of this review is to look at possible changes in post-operative coagulation dynamics that may increase the risk for development of thromboembolic complications in live liver donors. In this article, we stress the importance of addressing the issue that conventional clotting tests (PT, INR, PTT) are unable to detect a hypercoagulable state, and therefore, we should examining alternative laboratory tests to improve diagnosis and early detection of thrombotic complications. Measurement of natural anticoagulant/procoagulant biomarkers combined with conventional coagulation studies and thromboelastography offers a more accurate assessment of coagulation disorders. This allows earlier diagnosis, permitting appropriate intervention sooner, hence avoiding potential morbidity and mortality. Biomarkers that may be evaluated include, but are not limited to: protein C, soluble P-selectin, antithrombin Ⅲ, thrombin-antithrombin complex, and thrombin generation complex.

Key words: Live liver donors; Hypercoagulability; Post-operative thrombotic complications

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LIVE LIVER DONORS: ARE THEY AT A HIGHER RISK FOR POST-OPERATIVE THROMBOTIC COMPLICATIONS?

As the result of an increasing number of patients with end-stage liver disease awaiting liver transplantation, an increased number of centers performing liver transplantations and due to the encouraging results from living-related pediatric transplantation, adult to adult living donor liver transplantation is becoming an increasingly popular option. However, in pediatric live-donor liver transplantation typically uses the donor liver's left lobe or fewer segments resulting in less dramatic effects on the post-resection donor's hepatic functions. The overall immediate postoperative complications which are related to the

surgery (bleeding, bile leak) are very low and mostly have been encountered in centers that perform few of these procedures[1]. However, as documented by recent review of donor's data the overall morbidity rate was 31% for the first year after surgery[2]. Critical analysis of surgical outcomes would suggest that there is under-reporting and under-estimation of the frequency and severity of such complications[3-5].

The lack of standardization of the surgical techniques and variation in surgical skill and experience can greatly affect the perioperative course of live liver donors[6-8]. In most transplant centers right-lobe hepatectomy is performed for adult-to-adult live donor liver transplantation by removal of 60%-70% of the hepatic mass (right lobe) including middle hepatic vein[9-11].

Post-operative complications, especially during the first few months, include pulmonary embolism with an incidence of 7%, so of which were fatal[12]. Deep venous thrombosis, spleen and portal vein thrombosis have been reported as part of the serious thrombotic complications[12]. Overall, there is underestimation and underappreciation of the thromboembolic risks in the living donors, a fact that possibly reflects a lack of appreciation of changes in the post-liver resection coagulation profile.

Most of the natural procoagulants and anticoagulants are manufactured in the liver. In addition, other important functions of the liver include removal of activated clotting factors from the blood and thus keeping and maintaining a balance between anticoagulant/procaogulant mediators[13]. Although, during surgery, bleeding is a major concern for both the surgical and anesthesiology teams, the results from recent study showed that living donors progressively developing hypercoagulable state as shown by thromboelastograph (TEG) even in the presence of anti-thrombotic prophylaxis[14].

In spite of the fact that post-operative coagulopathy in living donors can be easily diagnosed by conventional clotting tests (PTT, PT, INR), the incidence of post-surgical bleeding is extremely low. This is true regardless of whether coagulopathy is surgical or medical in origin. In the contrary, the diagnosis of a hypercoagulable state is not a routine part of post-operative care in spite of the several reports of serious thromboembolic complications in this group. The establishment of reliable laboratory tests to diagnose hypercoagulability is urgently needed to predict and diagnose the hypercoagulability in living donors in order to avoid serious thromboembolic complications.

TEG has been used to evaluate acquired and congenital/genetic induced clotting-related problems when compared to healthy reference subjects[14,15]. TEG can demonstrate hypercoagulability by a short R-time, an increased MA and accelerated K-value (Figures 1 and 2). The problem with TEG testing is considerable variability in its accuracy for predicting thromboembolic events[16]. From a review study where TEG was used to monitor coagulation, the conclusion reached was that the TEG, when used alone, did not significantly change the post-from pre-test probabilities of predicting thrombotic complications or its ability to impact decision-making[16]. TEG may have some value when combines with other lab tests. TEG is a global, dynamic test for whole hemostasis, while differential lab assays are more useful in attempting to understand the underlying mechanisms involved and the pathways that are affected.

Such lab tests are protein C (PC), soluble P-selectin (SPS) and antithrombin Ⅲ (ANTⅢ), thrombin-antithrombin complex (TAT) and thrombin generation complex (TGC) which are either the natural anticoagulants or indicators for *in vivo* clotting activation. Protein S is another vitamin-K dependent anticoagulant that is produced in the liver but with a substantial extra-hepatic production and may not be affected that much by hepatic surgery like the rest of anticoagulants[17].

PC is a vitamin k-dependent plasma serine protease zymogen that upon activation by thrombin-thrombomodulin complex, down-regulates the clotting cascades by a feedback loop inhibition mechanism[18]. PC and S will act together to deactivate FⅤa and FⅧa, this will shut down the process of thrombin generation through both intrinsic and extrinsic pathways[18]. In addition to the anticoagulant functions of PC, it has anti-inflammatory and cytoprotective functions[19]. In animal experiments, blocking the activation of PC has been shown to convert non-lethal dose of *Escherichia coli* to lethal phenotype which resulted in multi-organ failure[20]. The clinical application of recombinant human activated PC therapy in sepsis has been recently approved by the Food and Drugs Agency (FDA), however, the scope of anti-inflammatory action of PC is beyond the scope of this review[21].

Inadequate activation or inadequate hepatic production of PC, as in sepsis may play a pivotal role in not only multi-organ failure but in production of pro-thrombotic states as in the initiation of disseminated intravascular coagulation (DIC) in septic patients[22]. Accordingly, we can speculate that patients who are subjected to liver resection as in live donors; PC production may be seriously compromised. This may put patients in real danger of not only thromboembolic complications, but of an increased susceptibility to sepsis, a speculation that needs to be proved by further studies in this patient population.

Another naturally liver-produced anticoagulant which may suffer during hepatic resection is ANTⅢ. Recombinant human ANTⅢ has been used to reverse the coagulation abnormalities in sepsis, DIC and hepatic failure. Recent studies have shown that ANTⅢ may have powerful anti-inflammatory effects. ANTⅢ has inhibitory effects on endotoxin-induced neutrophil activation and it down-regulates the expression of certain proinflammatory cytokines (TNF-α, IL-6)[23]. It has been used in some of European ICU patients to teat sepsis, but in the USA, it is only FDA approved to treat certain coagulation abnormalities. Low levels of ANTⅢ may have potential effects on susceptibility to gram-negative infections and/or endotoxemia, not only in critically ill patients, but also in postoperative liver resection patients. The questionable

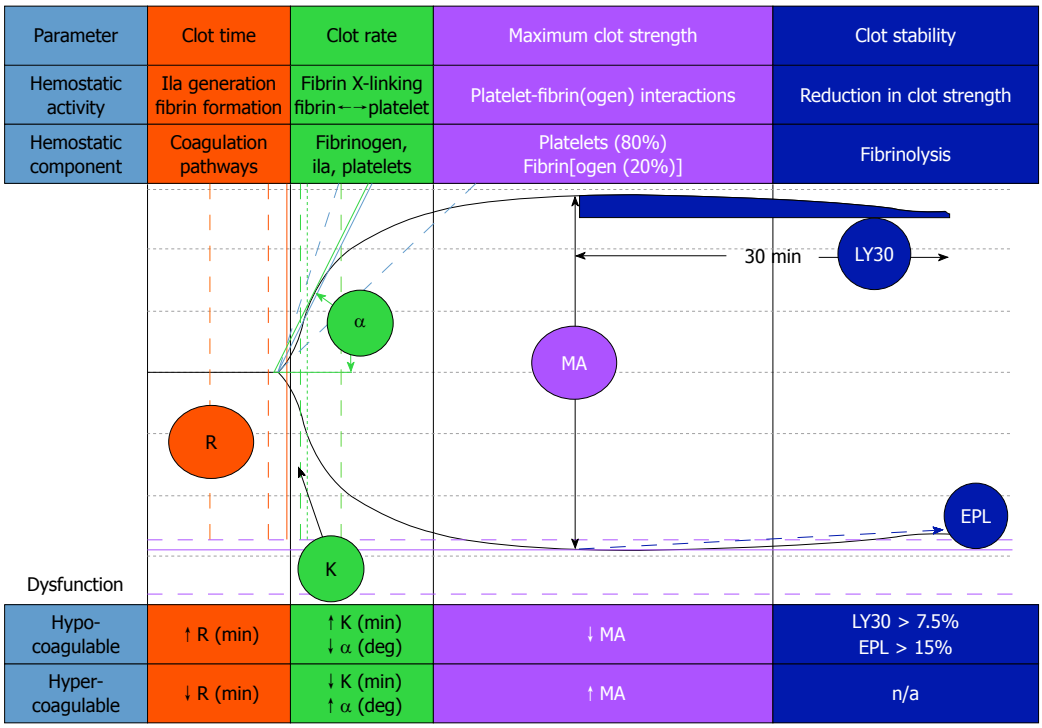

Figure 1 Thromboelastogram parameters.

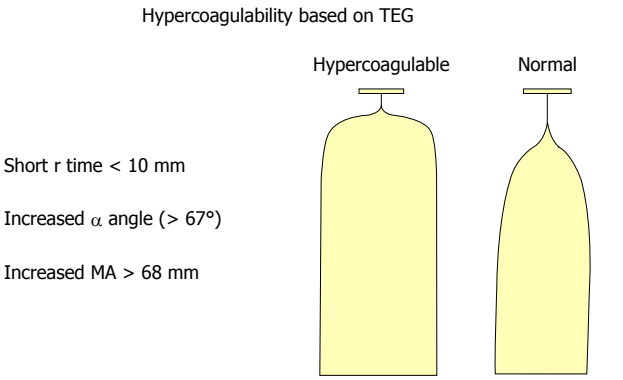

Figure 2 Normal thromboelastogram and hypercoagulable thromboelastogram. TEG: Thromboelastograph.

role of ANTⅢ in postoperative hypercoagulation and sepsis in live liver donors requires serious investigation by all surgical centers that practice this surgical procedure[24].

SPS protein is an adhesive molecule that has a peculiar expression under certain condition by both platelet and vascular endothelium. SPS has been shown to play an essential role in vascular inflammation and injury and links inflammation to thrombosis[25]. Conventional platelet count and platelet activation tests have received major criticism due to the fact that *ex vivo* studies a part from being operator-dependent might not actually reflect the occurrence of *in vivo* platelet activation[26]. SPS can be a useful as a specific biomarker for *in vivo* platelet activation. The mechanisms of SPS expression and cleavage after platelet activation makes this molecule very resistant to *ex vivo* activation provided that plasma is immediately separated from the cellular elements[27]. Overall, SPS may represent a useful and unique test for *in vivo* platelet activation and which may be of valuable in understanding changes in coagulation dynamics after major liver resection[28].

TGC, thrombin, the primary enzyme found in the coagulation cascade, plays a pivotal in hemostasis. The measurement of the formation and inhibition of thrombin in plasma relates directly to the patient's coagulation status. The plasma levels of TGC may give us an excellent picture of what is going *in vivo* as far as activation of coagulation and it can be very useful tool in monitoring of postoperative changes in coagulation in liver resection patients.

The TAT results when thrombin cleaves a scissile bond near the C-terminal of ANTⅢ forming a covalent, TAT complex is relatively stable. An elevated levels of TAT indicate ongoing clot activation and can be easily measured by Sandwich-style ELISA test which makes this biomarker a useful in monitoring *in vivo* changes in coagulation status.

CONCLUSION

In conclusion, having these natural anticoagulants/procoagulants biomarkers evaluated and combined with the conventional clotting tests and TEG may help in better understanding the pathophysiological changes in coagulation after major liver resection. In live liver donors, monitoring coagulation profiles by this approach may greatly reduce or eliminate the risk of serious thrombotic complications[29]. There are still many questions that need to be answered as far as changes in coagulation and immunological response to stress and sepsis in live liver

donors. Further studies are required to better understand this problem and decrease the risk of exposing otherwise healthy patients who do not require surgery to possible life-threatening thrombotic complications. The issues that need to be addressed in any investigations in this group of patients include: what biomarker/biomarkers to monitor, for how long, how frequently, are conventional clotting tests non-diagnostic in this regard, and is use of the TEG enough to monitor the changes in clotting? When we are better able to understand these important changes which occur in these patients, we will be better able to access the risk/benefit ratio with respect to outcomes.

For the time being, the best clinical practice is to fully investigate the potential live liver donors for the possibility of acquired or inherited/congenital coagulation abnormality before considering them as live liver donors. 2nd careful monitoring of their post-surgical coagulation functions with conventional clotting tests, TEG and considering the evaluation of natural anticoagulant biomarkers is vital part of postoperative care. Early postoperative mobilization and anti-thrombotic prophylaxis forms an integral part in the prevention of thrombo-embolic complications.

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OBSERVATION

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Long-term renal function, complications and life expectancy in living kidney donors

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Abstract

Living kidney transplantation is now a widely accepted treatment for end stage renal disease (ESRD) because it provides excellent outcomes for recipients. However, long-term outcomes of living kidney donors have not been well understood. Because securing the safety of the donor is essential to the continued success of this procedure, we reviewed articles discussing long-term outcomes of living kidney donors. Most studies found no decrease in long-term survival or progressive renal dysfunction in previous kidney donors. Moreover, the prevalence of hypertension was comparable to that expected in the general population, although some did report otherwise. Urinary protein showed small increases in this population and was associated with hypertension and a lower glomerular filtration rate. Quality of life following living kidney donation seems to be better than the national norm. We also encountered several reports of ESRD in previous living kidney donors. Regular follow-up of kidney donors is recommended and future controlled, prospective studies will better delineate risk factors which cause health problems following living kidney donation.

Key words: Living kidney donor; Long-term survival; Hypertension; Proteinuria; Renal function; Quality of life

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INTRODUCTION

Although securing the long-term safety of living kidney donors is essential to the continued success of this procedure, the long-term consequences after kidney donation are not fully understood. There have been several studies of living kidney donors which found no decrease in long-term survival. Most of the data suggests that the donors had normal renal function, with an incidence of hypertension comparable to that expected in the age-matched general population, while others demonstrated that donor nephrectomy is associated with mild proteinuria and hypertension. In this editorial, we will review the articles which focused on the outcome of living kidney donors to clarify the current status in this field.

LIFE EXPECTANCY FOLLOWING LIVING KIDNEY DONATION

Most long-term follow up studies of living kidney donors

find no decrease in long-term survival. According to the analysis of 430 previous living kidney donors in a Swedish single center, the survival rate of 20 years was 29% better than the expected survival rate calculated by using national registers[1]. Moreover, the analysis of 481 previous Japanese living kidney donors also showed that the survival rate of kidney donors was better than the age- and gender-matched cohort from the general population and the patterns and causes of death were similar to the general population[2]. The study of larger numbers of donors, as many as 3698, who donated kidneys during the period from 1963 to 2007 for a longer follow-up period in a US single institute, also ascertained that the survival of kidney donors was similar to that of controls that were matched for age, sex and race or ethnic group[3]. Thus, the overall evidence suggests that living kidney donors have a survival better than or similar to that of non-donors. These results might be attributed to the fact that only healthy persons are accepted for living kidney donation.

HYPERTENSION FOLLOWING LIVING KIDNEY DONATION

Hypertension is thought to be one of the major concerns following living kidney donation. However, a couple of studies demonstrated no increase of hypertension after living donor nephrectomy. A 15-year experience of 162 living donors in Italy showed that the long-term incidence of hypertension in living donors was similar to the general population[4]. Furthermore, the analysis of 402 donor nephrectomies in Sweden showed that, although hypertension was present in 38% of the donors, the age-adjusted prevalence of hypertension among donors was not higher than in the general population[5].

On the other hand, some studies demonstrated an increase of hypertension after living donor nephrectomy. Analysis of 75 donors in a US single center showed that the prevalence of hypertension was significantly increased when compared with age/sex matched data from epidemiological studies of the general population, especially in those over the age of 55 years[6]. Also, in a live kidney donor cohort with a 93% retrieval rate of the 152 donors, mean blood pressure had significantly increased by 9 mmHg in systolic and by 2 mmHg in diastolic pressure, which remained significantly below normal[7]. One meta-analysis showed that kidney donors may have a 5 mmHg increase in blood pressure within 5 to 10 years after donation, over that anticipated with normal aging[8]. Future controlled, prospective studies with long periods of follow-up will better delineate the risk of hypertension following living kidney donation.

PROTEINURIA FOLLOWING LIVING KIDNEY DONATION

Most reported data suggests that proteinuria increased in the living kidney donor population, although the follow-up period and measurement of proteinuria and/or microalbuminuria differed by report. German experience at a single center of 102 living kidney donors for 35 years showed that microalbuminuria was found in 22.6% of the donors[9]. Another study showed that 56% of 152 donors developed proteinuria (> 150 mg/d) but only 10% had albuminuria[7]. In an analysis of 402 outcomes after donor nephrectomy in Sweden, significant proteinuria (> or = 1.0 g/L) was found in 3% and slight proteinuria (< 1.0 g/L) in 9% of the donors and proteinuria was associated with hypertension and a lower glomerular filtration rate (GFR)[5].

One meta-analysis, which analyzed a total of 5048 donors from 48 studies with an average follow-up of 7 years after donation (range 1-25 years), demonstrated that the average 24 h urine protein was 154 mg/d and concluded that kidney donation results in small increases in urinary protein[10].

RENAL FUNCTION FOLLOWING LIVING KIDNEY DONATION

Renal function is the greatest long-term concern after living kidney donation. In a report analyzing 25 living kidney donors, total kidney function measured as creatinine clearance (CCr) showed a significant drop of 36% of the pre donated value. However, remaining kidney clearance increased by an average of 34% as measured by Tc 99m DTPA renography. Compensatory hypertrophy of the remaining kidney measured by ultrasound attributed to an increase in the renal volume of 15%[11]. Other investigations show a 25% decrease of GFR with mean time after uninephrectomy of 11 years[7] and a 27% decrease with mean patient follow-up of 25 years[12].

In a Swedish study, the average estimated GFR (12 years after donation) was 72% ± 18% of the age-predicted value. The ratio of the estimated to the predicted GFR showed no correlation to the time since donation, indicating that there is no accelerated loss of renal function after donation[5]. These results demonstrated that, although living kidney donors lose GFR by 15%-25%, they usually do not show the accelerated loss of renal function if they do not have risk factors for chronic renal disease (CKD). One unique study examined renal function more than 20 years after donation by comparing that with siblings. They showed no significant difference in serum creatinine, blood urea nitrogen and CCr between donors and their siblings[13].

END STAGE RENAL DISEASE IN PREVIOUS DONORS

There were considerable reports of end stage renal disease (ESRD) of previous kidney donors. In a survey which used the Organ Procurement and Transplantation Network (OPTN) database, a total of 56 previous living

donors were identified as having been listed for deceased donor kidney transplantation. They concluded that living renal donation has long-term risks that may not be apparent in the short-term and that the numbers reported underestimate the actual number of living donors with renal failure because they include only patients listed for a kidney transplant[14]. In the latest survey of OPTN and the Center for Medicare and Medicaid Services databases, 126 cases of ESRD among 56 458 living kidney donors (0.22%) were found. The ESRD rate was nearly five times higher for blacks than for whites and two times higher for males than females, which were similar to those previously reported for ESRD in the general population[15].

In an analysis of 402 donor nephrectomies in Sweden, no donor died with uremia or had dialysis treatment before death. However, three donors developed renal disease and one was in dialysis treatment. In two of these cases, hereditary factors were possibly involved[5]. In a Mexican experience, four kidney donors developed ESRD thereafter, three becoming kidney recipients[16]. Another two case reports described kidney donors who developed ESRD[17,18]. Analysis of 464 outcomes after donor nephrectomies at the University of Minnesota showed that 84 had died and 380 were alive. Of the 84 donors who had died, three were known to have had kidney failure. Of the 380 still alive, three had abnormal kidney function and two had undergone transplantation[19].

One Japanese study carefully investigated the association between postoperative clinical courses and changes in renal function in eight donors who developed ESRD. According to their findings, except for one donor who developed ESRD, none of the donors developed progressive renal dysfunction immediately after donation. Their renal functions remained stable for a long period but started to decline after developing new comorbidities, especially risk factors known as progression factors (proteinuria or hypertension) or accelerating factors (cardiovascular event or infection) of CKD[20]. However, the overall evidence suggests that their risk of ESRD is not increased.

QUALITY OF LIFE IN LIVING KIDNEY DONORS

As in medical issues, quality of life (QOL) in living kidney donors is crucial to be able to continue this procedure. According to the experience in a German single institute of 102 living kidney donors, everyday life was managed as well as before surgery after 2-4 wk by the highest percentage (42%) of patients, but working capacity was only regained after 1-3 mo by a comparable percentage (44%). Ninety-one percent would again decide in favor of a donation[9]. In another survey, the majority of living kidney donors had an excellent QOL. As a group, they scored higher than the national norm on the SF-36. However, 4% were dissatisfied and regretted the decision to donate. Furthermore, 4% found the experience extremely stressful and 8% very stressful. Multivariate analysis found that relatives other than first degree and donors whose recipient died within 1 year of transplant were more likely to say they would not donate again if it were possible. Furthermore, donors who had perioperative complications and female donors were more likely to find the overall experience more stressful[21].

Women considering kidney donation are frequently anxious about their ability to have children after nephrectomy[22]. There is a single center survey which described 490 pregnancies in 239 donors after donation. Compared to pregnancies before donation, pregnancies after donation had increased rates of gestational diabetes, gestational hypertension, preeclampsia, prematurity and fetal loss. The authors reported that these incidences of adverse events observed in donors were similar or better than expected levels for the general population[23]. Therefore, pregnancy after kidney donation is not necessarily a contraindication, although it is better to be avoided.

CONCLUSION

We have reviewed long-term outcomes in living kidney donation. As the background differs by region, it is difficult to build an international standard. Regular follow-up of kidney donors is recommended in order to manage complications effectively and to detect health problems early in those who may develop them. A national registry is necessary to enable data collection so that long-term risk can be accurately assessed.

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REVIEW

Key issues in transplant tourism

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Abstract

Access to organ transplantation depends on national circumstances, and is partly determined by the cost of health care, availability of transplant services, the level of technical capacity and the availability of organs. Commercial transplantation is estimated to account for 5%-10% (3500-7000) of kidney transplants performed annually throughout the world. This review is to determine the state and outcome of renal transplantation associated with transplant tourism (TT) and the key challenges with such transplantation. The stakeholders of commercial transplantation include: patients on the waiting lists in developed countries or not on any list in developing countries; dialysis funding bodies; middlemen, hosting transplant centres; organ-exporting countries; and organ vendors. TT and commercial kidney transplants are associated with a high incidence of surgical complications, acute rejection and invasive infection which cause major morbidity and mortality. There are ethical and medical concerns regarding the management of recipients of organs from vendors. The growing demand for transplantation, the perceived failure of altruistic donation in providing enough organs has led to calls for a legalised market in organ procurement or regulated trial in incentives for donation. Developing transplant services worldwide has many benefits - improving results of transplantation as they would be performed legally, increasing the donor pool and making TT unnecessary. Meanwhile there is a need to re-examine intrinsic attitudes to TT bearing in mind the cultural and economic realities of globalisation. Perhaps the World Health Organization in conjunction with The Transplantation Society would set up a working party of stakeholders to study this matter in greater detail and make recommendations.

Key words: Living unrelated donor; Organ trafficking; Transplant commercialism; Infection; Graft survival; Patient survival; Complication

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INTRODUCTION

Medical tourism refers to patients travelling across national borders for healthcare elsewhere. People tend to travel for care that either is not available in their home country or perceived to be superior (better quality and delivered in a more timely fashion) to where they live. Medical tourism has emerged as a global health care phenomenon, valued at $60 billion worldwide in 2006[1]. With insurance companies in the US beginning to integrate foreign care into their coverage by offering discounts to patients agreeing to overseas travel, medical tourism is projected to become a $21 billion a year industry in the US by 2011[2]. Transplant tourism (TT) has been used to indicate travel outside of one's country of residence for the principal purpose of obtaining organ transplantation services[3-5]. TT unlike general medical tourism, has always been surrounded with controversy regarding the

source of organs, donor's care after transplantation, and recipient outcome[4]. Though instances of organ buying, selling and/or trafficking occur, emotionally and/or biologically related living donor transplants are also achieved by transplant tourists[3]. Despite objections to TT by the transplant community and efforts to boost altruistic organ donation, many patients continue to travel to other countries to receive commercial transplants[3,6] - confirmed by WHO statistics: Saudi Arabia (700 in 2005), Taiwan (450 in 2005), Malaysia (131 in 2004) and South Korea (124 in the first 8 mo of 2004)[7].

Access to organ transplantation varies according to national circumstances, and is partly determined by the cost of health care, availability of transplant services, the level of technical expertise and the availability of organs. The extent of organ sales from commercial living donors (CLD) was estimated in 2007 to account for 5%-10% of kidney transplants performed annually throughout the world[7]. If the 69 400 renal transplants performed worldwide in 2008[8] is an indication of annual transplant activity, then between 3500 and 7000 commercial renal transplants are performed per year. The stakeholders of commercial transplantation include: patients on the waiting lists in developed countries or not on any list in developing countries; dialysis funding bodies (states, insurers, and providers); middlemen (brokers, officials, and doctors), hosting transplant centres; organ-exporting or selling countries; travel and tourism industries; and organ vendors[9]. Patients refused entry on the waiting list for medical reasons may sometimes seek commercial transplantation.

The worldwide escalation in the number of patients with kidney failure, increasing demand for transplantation, shortage in the supply of organs and deaths on the transplant waiting list continue to fuel TT[10-13]. Only about 10% of the approximately 12 000 patients on a waiting list for a transplant in Japan are transplanted per year[14]. TT is facilitated by several factors including the ease of travel as the world has become a global village; difficulty in ensuring compliance with international law; and the widening gap between the rich and the poor[15]. The aim of this review is to determine the state and outcome of renal transplantation associated with TT and the key challenges with such transplantation.

TYPES OF TOURISM

According to Shimazono[7], TT takes various forms as depicted in Figure 1. In the traditional model, patients generally travel from less developed nations (country A, Figure 1) to transplant centres in relatively more highly developed countries (B and C, Figure 1) to receive services that are not typically available in their own countries. However, TT can occur when donor and recipients living in the same country travel to another country with less stringent requirements or better transplant facilities (model Ⅱ, Figure 1).

TT has become tarnished by organ trafficking and commercialisation and is often thought to be illegal. However, not all medical tourism that entails the travel of transplant recipients or donors across national borders is associated with unethical behaviour. Examples include, when travel of a related donor and recipient pair is from countries without transplant services to countries where organ transplantation is performed or if an individual travels across borders to donate or receive a transplant from a relative. Any official regulated bilateral or multilateral organ sharing program is not considered TT if it is based on a reciprocated organ sharing program among jurisdictions[16]. The Declaration of Istanbul has clarified the terms "organ trafficking", "transplant commercialisation" and particularly "transplant tourism", by introducing the term, "travel for transplantation"[17]. Organ trafficking entails the "recruitment, transport, transfer, harbouring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power, of a position of vulnerability, of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation by the removal of organs, tissues or cells for transplantation". Travel for transplantation becomes TT when it involves commercialisation or organ trafficking or deprives the local population of their services. Whether this new definition would make a difference is difficult to judge as travel for transplantation would also be shrouded with suspicion and requiring proof that nothing untoward is associated with it. In TT, patients travel on their own to obtain organs through the organ trade or through other means that contravene the regulatory framework of their countries of origin[7]. Many clinical and bioethical concerns surround this trade, and the unavailability of sufficient amounts of verifiable data to inform discussion of this exceedingly complex issue has led to divergent views across the world[1,18]. There is need for cultural awareness and sensitivity in deliberating TT and its role in transplantation in certain parts of the world. The issue of TT is far from being settled and in the meantime, patients on waiting lists exploit the cultural

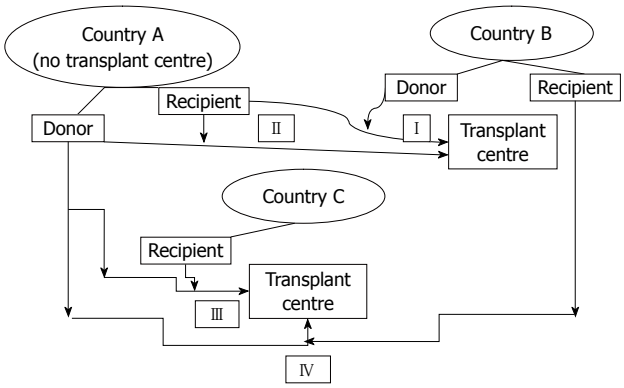

Figure 1 Types of transplant tourism. Model Ⅰ: Recipient (R) travels to country B where donor (D) and transplant centre (TC) are; Model Ⅱ: R and D travel to another country for transplantation; Model Ⅲ: D travels to country C where R and TC are; Model Ⅳ: D and R residing in different countries travel to another country (C) for transplantation.

and economic differences between regions of the world to their own advantage[19].

FACTORS DRIVING TT

Need for transplantation

There is a significant emerging burden of chronic kidney disease in developing countries, due to the ageing population and a high incidence of type 2 diabetes mellitus and hypertension. The majority of those with established renal failure (ERF) die because of lack of funds as few can afford regular maintenance dialysis or renal transplantation which is often not available[20]. Unavailable or underdeveloped organ donor and transplant services coupled with poor dialysis facilities pose significant barriers to the delivery of efficient and cost-effective renal replacement therapy. Rich patients living in such economies would be tempted to seek help elsewhere. It is thought that the lack of provision of transplant services in developing countries has made TT inevitable[21].

In countries with developed transplant services, lengthy waiting times can contribute to increased risk for clinical deterioration, reduced quality of life, and in many cases, removal from the list if their clinical picture significantly deteriorates. Some patients with monetary means have responded to this dilemma by placing themselves on waiting lists at multiple hospitals in the US (where the system allows), thereby increasing their chances of receiving a transplant. Review of TT in British Columbia showed that it mainly involved ethnic minorities (90%) who traveled to their country of origin for transplantation after waiting a median of 2 years[22]. Some patients from developed countries with established transplant programmes whose immediate prospects of being transplanted are low, travel to other countries where they can acquire kidneys either from executed prisoners or live unrelated donors (LURD)[23,24]. According to the Korean Network for Organ Sharing, 7641 patients were on the waiting list for kidney transplantation by 2008 with only 481 (one in 15) receiving a deceased donor transplant[25]. Recently, active and proposed US medical insurance programs are taking steps to address the problems of organ availability, long waiting times, and high medical and surgical costs by promoting TT. Such programs are created explicitly to encourage policy holders to travel to foreign countries for the purpose of obtaining transplants[26,27]. So unlike many illegal markets, this one is driven by the need of patients with irreversible kidney failure at risk of increased morbidity and mortality[28]. The longer the wait for a transplant, the higher is the risk of a poor outcome.

Organ donation

The lack of legislation and infrastructure has prevented growth of deceased donor programmes in developing countries so living donors have continued to be the major source of transplantable kidneys[29]. Even the most well-developed deceased-donor programs (e.g., the Spanish program) can barely cover 50% of its waiting list because the demand for deceased-donor organs far exceeds supply. LURD transplantation (Table 1)[30,31] is amenable to donor recruitment by undesirable or illegal practices such as coercion or commercialisation[32-34]. Commercial LURD transplantation is made possible because a high proportion of the population in developing countries live below the poverty line and some believe that selling an organ can positively change their circumstances[28,35].

Table 1 Types of living donation

Genetically related	
1st degree relative	Parent, sibling, offspring
2nd degree relative	Grandparent, grandchild, aunt, uncle, niece, nephew
Other	Cousin
Emotionally related	Spouse, in-laws, adopted, friend
Unrelated (not genetically or emotionally related)	Directed (possibility of donor-recipient financial arrangement)
	Non directed (altruistic)
	Paired exchange
	Living-deceased exchange

Bribery and corruption

Though commercial transplantation is prohibited in most countries[23,35], the practice of organ sales is common in some parts of the world and drives TT[16]. The countries where such practices are common score poorly on the corruption perception index compiled by Transparency International[36]. The declaration of Istanbul[17] on organ trafficking and TT provides clear strategies for stopping these practices but no sanctions for those states failing to comply. It is suspected that in some countries like India, sale of organs might still be going on due to bribery and corruption[37].

Cultural issues and disregard to the rule of law

Between 2002 and 2008, the Philippine government, through the Department of Health, administered a program called the Philippine Organ Donation Program that allowed prospective kidney donors to sign up, be allocated to prospective recipients and receive gratuities for their kidney. TT flourished during this period because of rampant disregard for the regulation limiting foreign recipients to 10% of total kidney transplants[38].

TT is perceived in certain cultures and developing economies as a human right that meets the demands of all stakeholders and should therefore be organised rather than declined in the interest of Western countries[39]. As such, the merits of culturally insensitive policy statements issued by otherwise well-intended transplant professionals/organisations must be evaluated within the broader context of foreign relations and diplomacy, as well as cultural and ethical relativity. Some have called for caution in imposing beliefs and values on others, given the differing cultural and socio-political circumstances in a global economy. Policies or position statements emanating from a relatively superficial assessment of an exceedingly complex issue fail from a multi-cultural perspective[1]. Critics

state that the primary issues to which position statements on TT are directed concern the source and circumstances surrounding the procurement of donor organs - confusing the donor organ acquisition process with the receipt of a transplant surgical procedure in a foreign country. The situation in China where executed prisoners are used as a source of donor organs directly and indirectly raises many questions about the role of capital punishment, religion, informed consent, financial incentives in relation to organ donation. Capital punishment has in the past been practiced in virtually every society, although currently only 58 nations actively practice it. Whereas in the US, both the ethical justification and the legal basis for capital punishment remain open to debate, it has been abolished in the European Union, Australia, New Zealand and Canada[40].

TRANSPLANT OUTCOME

In addition to ethical reasons, concern about paid unregulated renal transplantation is due to the associated excessive morbidity and mortality, for example, in one study seven of 36 commercial transplants performed in India and Pakistan during 2006-2007 died within 2 mo of transplantation[41]. It is important that accurate data on outcomes of transplants carried out abroad are known so that patients can be counselled about such activity[24,42]. The outcome of recipients of organs through TT is reported to be inferior to those transplanted under ethically more acceptable conditions (Table 2)[5,6,23,25,41-54].

Reported outcomes of commercial kidney transplantation may not be reliable for the reasons that: commercial transplantation is illegal; recipients of such transplants return to their native countries soon after the operation and may not return for follow up; and it may not be in the interest of practitioners to publish poor results[37]. Furthermore, data on such activity is often based on reports by returning patients to home transplant centres or units for continuing care[25]. Peri-operative deaths and defaults from treatment may not be included in published results. Transplants performed in less than ideal circumstances are characterised by inadequate pre-transplant evaluation, general lack of information about peri-operative issues, immunosuppression and long term outcome. Despite these factors, there are numerous reports indicating that TT is associated with a high incidence of surgical complications, acute rejection and invasive infection which cause major morbidity and mortality[5,23,25,29,43,44,46,49,50,51,55-58].

Transplant tourists have a more complex post-transplantation course with higher infectious complications including the transmission of HIV and hepatitis B and C viruses[5,23,25,41,46,53,55]. The Dubai experience with 45 paediatric renal allograft transplantations performed outside the United Arab Emirates between 1993 and 2009 is sown in Table 2. Major viral infections (Epstein-Barr virus, cytomegalovirus, varicella zoster) were four-times more common in patients that had received LURD grafts than in those that had received living related donor grafts[48]. Infectious complications with unusual pathogens and contraction of illnesses because of unsafe blood-banking processes have been reported[18]. Nineteen cases of invasive fungal infections occurring in 17 patients resulting in graft loss or death in 13/17 (76%) of patients and overall mortality of 59% (10/17) have been described[59]. Invasive fungal infections, frequently originating at the graft site, have emerged as a serious complication of commercial renal transplantation and are associated with high rates of graft loss and death.

One study from the United Kingdom reported that patients who had been suspended from the local transplant list for medical reasons were operated on abroad indicating the existence of substandard medical practices[60]. Furthermore, transplantation of LURD kidneys is associated with a high complication rate affecting graft and patient survival[48]. A comprehensive review of commercial kidney transplantation performed in several developing countries showed patient and graft survival were generally inferior to internationally accepted standards[61]. Some studies report survival figures comparable to local standards[5,47,58]. Analysis of 16 renal patients from the Ivory Coast transplanted abroad between 1995 and 2009 showed an overall graft survival was 93% at 1 year and 80% at 5 years. Not only did five of their 16 patients die during the study period but the remaining had inadequate follow up because they were unable to afford it[45].

EFFECT OF TT ON TRANSPLANT SERVICES

TT may result in a significant proportion of donor-recipient couples undergoing assessment with no favourable end point. Between January 2006 and June 2008, 69 potential renal transplant recipient and 99 donors were investigated but transplants could be performed only in 35 patients (51%) as 11 opted for TT and 23 others withdrew for different reasons[62]. However, Israeli experience shows the beneficial effect of TT. An analysis of waiting time and mortality among patients placed on the kidney transplant waiting list at the Rabin Medical Centre in Israel, between 2001-2005 shows that the annual rate of transplants of newly listed candidates increased from 13.6% in 2001 to 30% in 2005, mainly because of the growth in the number of patients transplanted abroad. In the same time period, the mean waiting time for kidney transplantation in Israel fell from 705 to 509 d. The death rate for newly listed patients has remained low at a mean of 3% per year[63].

Large transplant centres with long waiting times are increasingly likely to see patients return newly transplanted from overseas requiring urgent attention, with particular consideration to infectious complications[4]. Biggins *et al*[64] conducted an anonymous internet administered case-based questionnaire survey of healthcare professionals with affiliations to hepatology and transplantation. Of 674 completed surveys, the majority stated they would provide

Table 2 Outcome of living donor renal transplantation performed outside recipient countries

Study (country), period	*n*	Graft survival (%)		Patient survival (%)		Type	Comments
		1-yr	5-yr	1-yr	5-yr		
Tsai *et al*[6] (United Arab Emirates), 1987-2006	215T 321H	55.0 60.0		81.5 89.3		Both LRD and LURD	China; 10-yr survival figures; Higher risk of cancer in T group
Kennedy *et al*[23] (Australia), 1990-2004	16	66.0		85.0		LURD	Commercial transplants in India and China. Aspergillosis in one patient
Kwon *et al*[25] (South Korea), 1999-2005	462T	96.8 (death censored)		96.5		LURD	All transplants performed in China. Fifteen patients died; 42.5% complication rate. Results based on returning patients' accounts
Ivanovski *et al*[41] (Macedonia), 2006-2007	36T H	60.0 100.0		78.0 100.0			Transplants in India and Pakistan; 16/36 wound infections; active HCV+ in 9; seven died; 3 MI; TN in 3; 56% developed complication in early post op period. Acute rejection in 9/36. Poor communication
Krishnan *et al*[42] (UK), 1996-2006	36T 40H	87.0 97.5		83.0 97.5		Commercial Living donor in UK	Indonesians in the UK. Poor clinical outcome in tourists - 42% had major infections
Rizvi *et al*[43] (Pakistan), 1997-2007	180 126	94.0 86.0	80.0 45.0			LRD LURD	Mortality 16 (6%) for LRD and 34 (27%) for LURD
Sever *et al*[44] (Turkey), 1992-1999	115		66.0		80.0		Commercial transplants in India, Iran, Iraq. Significant medical complications
Ackoundou-N'Guessan *et al*[45] (Ivory Coast), 1995-2009	16T	93.0	80.0	93.0	53.0	Both	Patients from Ivory Coast; two losses from AR; 5/16 died during period; death-censored graft survival
Gill *et al*[46] (US), 1995-2007	33 UCLA	89.0 98.0				UCLA - University of California Los Angeles	Transplants in China, Iran, Philippines, *etc.*; three graft losses; 17/33 (52%) had infections; one death; AR 30% *vs* 12% in home transplants; survival figures inferior to cohort of 66 matched local patients
Geddes *et al*[47] (Scotland), 2000-2007	18						Travel from Scotland to Pakistan for transplants. No deaths; Malaria in one; acute rejection rate 11.1%; eGFR at 1 yr 51.8 mL/min every BSA1.73 m^2
Majid *et al*[48] (United Arab Emirates), 1993-2009	45	100.0 87.8	100.0 43.4	100.0 91.2		LRD (10) LURD (33)	Paediatric; DBD 2; three death within 4 mo of transplantation; 10-yr survival
Ghods[49] (Iran), 1986-2006	1995	90.5	74.4	93.9	87.1	496 LRD; 1499 LURD	Kaplan-Meier estimates; rates for LURD. 10-yr graft and patient survival rates were 49% and 72% respectively. Paid and regulated system in Iran
Rizvi *et al*[50] (Pakistan), 1990-2002	1000	90.0	75.0	95.0	85.0		Private-public partnership model
Salahudeen *et al*[51] (United Arab Emirates/Oman), 1984-1988	131			81.5			Transplants performed in India. 25 deaths in first year; HIV = 5; HBV = 3; Septicaemia in 4. Insufficient information to patients
Morad *et al*[52] (Malaysia), 1990-1996	289 126 258	90.0 90.0 91.0		93.0 92.0 96.0		India China Local (Malaysia)	Comparable results to local transplants
LURD Transplant Study Group 1997[53], 1978-1993	540 75	90.0 90.0	72.0 83.0	97.0 95.0	92.0 91.0	Commercial Emotionaly related	22 centres in India; Higher infection risk amongst commercial transplants: Hep B infection 8.1 v 1.4 in commercial renal transplantation
UK Transplant[54], 2002-2004	1000	95.0	90.0	98.0	96.0	Both	First transplants only

LRD: Living related donor; LURD: Living unrelated donor; T: Tourism; H: Home country.

post-transplantation care for patients who underwent liver transplantation at another domestic centre, but respondents who suspected unethical procurement practices in China were more reluctant to do so. Their choice of travelling to China for an organ leaves transplant centres with decisions about how to respond to the needs of patients who return after transplantation. Rhodes *et al*[12] discussed two cases that raised this dilemma, and argued for upholding commitments to traditional principles of beneficence and non-judgmental regard in sorting out the policies that a transplant centre should adopt. Adopting positions based solely on high moral grounds without consideration of the plight of the affected patients might not be appropriate[65]. Most professional societies do not condone TT but this should not abrogate a physician's right to care for such patients. It is thought that ethical principles mandate transplant physicians to provide adequate care for returning transplant tourists[66].

The rate of organ donation in Israel has remained stagnant over the last 10 years, while in the same period many other countries (for example, Spain, Italy and the USA) have made significant progress in improving their donation rates. It is not unreasonable to conclude that TT is directly responsible for the low deceased donation

rate in Israel. Furthermore, it would appear as if unrelated donors are instead being used as alternatives to related donors. Shroff[67] opined that in many affording middle class or upper class families, even when there are relatives in good health who can donate, the general argument that is often presented is "why donate and take any risks when you can buy a kidney?" In Korea where there was a rapid increase in TT between 2001 and 2005, the number of deceased donors stagnated during the same period[25].

The indirect effects of TT on transplantation in Israel are significant. For example, the population of patients who do remain on the waiting list for kidney transplantation at home now consist mainly of high-risk patients. Furthermore, admitting patients transplanted elsewhere early after their transplant (5 d to 1 mo) with severe complications such as humoral rejection, severe infectious complications or urinary leak or even with a failed graft frustrates the team and adds extra work and significant costs for local hospitals[21].

EFFECT ON VENDORS

The risks associated with living kidney donation such as surgical complications, death and deterioration of remaining kidney function which may result in the need for dialysis or transplantation[68] also apply to CLDs as well. Kidney vendors are reluctant to reveal their identity[69]. This culture of secrecy means that it is impossible to fully understand the full effects of their donation. Unlike other similar exploitative social situations, organ donation requires an invasive surgical procedure that has both physical and psychological implications[67]. Detailed longitudinal interviews conducted by Budiani[69] revealed that 78% of 50 CLD reported deterioration in their health condition. This is likely a result of factors such as insufficient donor assessment, pre-existing compromised health conditions. Naqvi *et al*[70] conducted a cross sectional survey of 104 kidney vendors in Pakistan concentrating on their general health status and post-operative renal function. They compared this group to 184 matched living related kidney donors from their centre. They found a higher rate of hypertension (17% *vs* 9.2%, $P = 0.04$); lower Cockcroft-Gault glomerular filtration rate (mL/min) of 70.94 ± 14.2 *vs* 95.4 ± 20.44 ($P = 0.0001$); hepatitis C positivity in 27% *vs* 1.0% ($P = 0.0001$); and hepatitis B positivity 5.7% *vs* 0.5% ($P = 0.04$), respectively in vendors compared to matched controls. They concluded that vendors had compromised renal function suggesting inferior selection and high risk for developing chronic kidney disease in long term. Ninety one percent expressed social isolation about their donation and 94% regretted donating[69]. The studies in Pakistan and Egypt are consistent with findings in India[71], Iran[72] and the Philippines[38] that revealed deterioration in the health condition of CLD.

A kidney sale does not solve the most frequently given reason for being a CLD as 81% spent the income from donation within 5 mo, mostly to pay off financial debts rather than investing in quality of life enhancements[69]. A socioeconomic and health survey of 239 kidney vendors from Punjab in eastern Pakistan showed that while 93% vended kidneys for debt repayment, after the event 88% had no economic improvement in their lives and 98% reported deterioration in general health status[73]. Goyal *et al*[71] studied 305 commercial kidney donors in India and reported that the average family income declined by 33% after nephrectomy and 86% reported worse health status. In a study of 300 commercial live donors, Zargooshi[72] showed that poverty prevented 79% from attending follow up care. A long-term financial disadvantage is reported following nephrectomy from a compromised ability to generate a prior income level.

LEGALISED MARKET IN ORGAN PROCUREMENT

The current reality is that demand for transplantation far outstrips supply of organs throughout the world. ERF patients are desperate for transplantation and some die on the waiting list. In many developing countries, there are no deceased donor programmes and no dialysis facilities. It is thought that TT functions according to market laws and is profit-driven, as opposed to the legal organ exchange programs in Europe and the US, which are non-profit and patient-oriented[21]. The data on TT is sketchy and probably unreliable but it is estimated to represent about 10% of world transplant activity[7]. There is evidence of unrelenting increase in commercial transplantation and the failure of legislation to eliminate this practice[74]. Several countries have laws prohibiting the practice of TT and consequently, where this practice takes place illegally, it is unregulated. Given the desperate desire of patients to undergo organ transplantation, their risk of being exploited should not be underestimated[7]. Comparing CLD to people being sold as slaves, Demme opined that buying and selling under conditions of severe inequality amounted to coercion[75].

The arguments against TT are that it encourages CLD, which is immoral because it treats the human body as a commodity and exploits the poor. It also undermines altruistic donation of cadaveric organs, encourages exploitation of kidney donors by unscrupulous middlemen and endangers the lives of donors undergoing nephrectomy in poor, unregulated conditions[74,76,77]. Rothman *et al*[78] speculate that the introduction of cash payments may weaken the moral obligation to donate. There are concerns about justice and fairness as well as it is felt that a market system rewards the better-off[75]. It is also argued that commercialisation of living kidney donation does not serve the interests of the donors, endangers the health of recipients, and undermines the healthy development of the international transplantation[76].

On the other hand, some believe that those against a market system may indirectly be supporting TT because refusal to allow organ sales also does not allow for proper regulation of sales. Many places where organ sales cur-

rently take place do not share Western views of informed consent. Those in favour of a regulated market argue that vendors ought to be allowed respect of their autonomy to do as they wish with their own organs.

The current system of organ procurement which relies on altruistic donation is inadequate to meet the current and future need for transplantable kidneys[11]. Hippen[79] argues that a regulated market in organs from living vendors is the only plausible solution arguing that such a market would ensure: safety for both vendors and recipients; transparency regarding the risks to vendors and recipients; institutional integrity regarding guidelines for cooperating with kidney vendors; and operation under the rule of law. Clemmons[80] advocates a legalised organ market as a way of curtailing the black market in organ procurement. Some of the arguments labelled against CLD are in fact against the effects of an unregulated market - "exploitation" of "vulnerable" vendors[9,17]. There are those who feel that equating transplant commercialism to "violating human dignity"[17] must be counterbalanced by holding a society that forces many of its members to consider transplant commercialism accountable[81]. Despite much discussion about its ethical problems[82], some individuals have advocated a regulated program of financial incentives for kidney donation[83,84]. Certainly, the high mortality rate and frequency of serious complications seem not to justify such unregulated commercial transplantation.

Iranian model

The Iranian model provides a useful example of a regulated system of paid donation. Some experts believe that the use of financial incentives to shape human behaviour is much better understood than the use of altruism[85]. The Iranian government pays all of the hospital expenses of renal transplantation; provides essential immunosuppressive drugs; and gives an award and health insurance to the LURD. The majority of LURD also receive a rewarding gift (arranged and defined by the Dialysis and Transplant Patients Association before transplantation) from the recipient or one of the charitable organisations. The program is under the close scrutiny of the transplant teams and the Iranian Society for Organ Transplantation regarding all ethical issues. To prevent TT, foreigners are neither allowed to undergo renal transplantation from Iranian LURD nor permitted to volunteer as kidney donors to Iranian patients[85]. The Iranian model had no role for a broker or an agency in this transplantation program. As a result, the number of renal transplant centres and renal transplantations that were performed rapidly increased such that by 1999, the renal transplant waiting lists in the country were eliminated[85].

The elimination of renal transplant waiting lists would indicate that all patients with ERF have equal access to renal transplant facilities, provided there is equity of access to the transplant waiting list. A study of 500 renal transplant recipients and their LURD to determine which socioeconomic classes received transplants more from paid kidney donors showed no significant differences. The results showed that 84% of paid kidney donors were poor and 16% were middle class, and of their recipients, 50.4% were poor, 36.2% were middle class, and 13.4% were rich meaning that > 50% of kidneys from paid donors were transplanted into patients from a low socioeconomic class[86]. However, Harmon *et al*[87] argue that a government regulated system is not ethically achievable, that the elimination of the waiting list in Iran might have to do with the limitations imposed on listing.

The Iranian experience suggests that a regulated market will reduce harm by opening it to scrutiny, enforce compliance with standards to protect donors, recipients and society, remove middlemen, and enable the poor to receive transplants on an equal footing with the rich[74]. Even though strongly opposed to TT and the associated unregulated black-market trafficking of organs, Starzl *et al*[88] recognise that simply making organ trafficking illegal will not make it go away. In addition to efforts to increase voluntary donation from deceased and conventional living donors, they called for a regulated trial of incentives for donation, to determine whether such incentives would increase the number of available organs while preserving the health, well being and dignity of donors and their families. This view is in consonance with an earlier call for a change in the law so that trials of financial incentives to promote organ donation can be done[89].

Healthcare authorities and professional transplantation organisations have to tackle the continuing donor crisis by designing legally acceptable utilitarian solutions, for instance, through the establishment of a regulated compensated donation system[21]. Epstein[9] states that the recent achievements in the struggle against international organ trafficking do not seem to herald the abolition of transplant commercialism but rather presage its reconfiguration in deglobalised forms. The main argument in favour of compensation is simple-financial incentives will increase donation, so fewer transplant candidates will suffer and die while waiting. In addition, development of a regulated system of compensation is the most effective means of crippling the core economic support for TT. Because dialysis is so much more expensive than a transplant, compensated donation could be cost-neutral to the healthcare system in developed countries. Despite this, the warning that a regulated market could be counterproductive to efforts to increase altruistic donation[78] must be considered carefully. The reported decrease in the proportion of living donor transplants in Hong Kong following the transfer of sovereignty from Britain to China may support this contention[77].

RECOMMENDATIONS

There is need for international cooperation aimed at supporting the development of organ donation and transplantation programs, within an effective ethical and regulatory framework, while taking into account the public health context of each country. Concerted efforts must

be made to curtail commercial organ transplantation by: (1) Expanding living donations by ensuring long-term safety of donors and removing disincentives to organ donation; (2) Maximising deceased donation by ensuring adequate infrastructure, trained personnel, effective coordination and supportive government policy; (3) Improving provision of renal care to all developing nations by forging adequate co-operation between nephrologists, patients, governments, charitable organisations and industry; and (4) Improving transplantation services and curtailing TT by collecting information on transplantation; expanding education in transplantation; and developing professional guidelines for organ donation and transplantation.

CONCLUSION

The lack of objective verifiable data regarding TT means that the true size of the problem is unknown. Data on outcome of transplantation is mainly based on the accounts of returning patients and there is not much information about peri-operative deaths. Despite these facts, most people in the medical profession and governments accept that trade in human organs for transplantation is illegal and should be stopped. However, legislation does not address the root cause and altruism has proved inadequate in ensuring an adequate supply of organs for transplantation. As attempts to increase donation have not been universally successful and TT seems to be growing, alternative options are now required. The big choice is between a regulated compensation programme and a regulated market. Not long ago, only genetically related living donation was allowed. The increasing demand for transplantation forced professionals to explore other ways of increasing donation and emotionally related donation was approved. The ensuing excellent results of non genetically related donors and the continuing increase in demand led to modification of regulatory laws and the introduction and subsequent growth of LURD. It is now time to re-examine intrinsic attitudes to TT bearing in mind the cultural and economic realities of globalisation. Perhaps the WHO in conjunction with The Transplantation Society would set up a working party of stakeholders to study this matter in greater detail and make recommendations.

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Innsbruck, Austria

February 1 - 5, 2012
2012 BMT Tandem Meetings
American Society for Blood and Marrow Transplantation
Manchester Grand Hyatt,
San Diego, CA, United States

February 22 - 24, 2012
British Transplantation Society 15th Annual Congress
Glasgow, Scotland

February 23 - 25, 2012
2012 Canadian Society of Transplantation Annual Scientific Conference
Fairmont Château Frontenac,
Québec, Canada

March 8 - 10, 2012
3rd International Conference on Transplantomics and Biomarkers in Organ Transplantation
La Jolla/San Diego,
CA, United States

April 18 - 21, 2012
The International Society for Heart and Lung Transplantation (ISHLT), 32nd Annual Meeting and Scientific Sessions
Prague, Czech Republic

April 25 - 27, 2012
United Network for Organ Sharing's 20th Annual Transplant Management Forum
Wyndham Rio Mar Beach Resort,
Puerto Rico

June 2 - 6, 2012
2012 American Transplant Congress
John B. Hynes Convention Center,
Boston, MA, United States

July 15 - 19, 2011
24th International Congress of the Transplantation Society
Berlin, Germany

September 13 - 15, 2012
ELITA - LICAGE LIVER MEETING and 4th ELITA Split-Liver Course
Ghent, Belgium

September 29 - 30, 2012
Advances in nephrology, dialysis, Kidney Transplantation
Odessa, Ukraine

October 5 - 7, 2012
V Congress of Transplantologists
Kharkiv, Ukraine

October 5 - 7, 2012
2012 European Organ Donation Congress, 24th ETCO-EDC
Dubrovnik, Croatia
October 12 - 14, 2012
ESOT and AST Joint Meeting - Transformational therapies and diagnostics in transplantation
Nice, France

November 2 - 4, 2012
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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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