1. Introduction

Approximately one in a thousand European citizens suffers from end-stage renal disease [1]. For suitable transplant candidates, living donor kidney transplantation (LDKT) offers better outcomes in terms of patient and graft survival, compared with deceased donor kidney transplantation. On average, around 40% of all kidney transplants worldwide are now performed using an organ from a living donor [2]. Living donor programmes therefore contribute substantially to the expansion of the supply of donor organs. For this reason, many countries are encouraging the development of living donor programmes to compensate the limited availability of organs from deceased donors; in some countries, living donation is the only available source of organs for kidney transplantation. This, together with the ability to plan a transplant before dialysis is necessary, means that LDKT has become increasingly accepted as the treatment of choice for patients with end-stage renal disease.

However, in many European countries the percentage of living donor transplants is still considerably low. In 2016, the annual rate of LDKT in the EU varied from 0 to 33.2 pmp [1]. These data suggest that by optimising the use of living kidney donors, overall kidney transplantation rates could be substantially increased in many European countries, yielding improved access to transplantation and better transplant outcomes. Another benefit is the reduction in dialysis costs.

Historically, LDKT was only an option between genetically related donor-recipient pairs (blood relatives). In the mid-1990s, evidence showed that kidneys from non-genetically related donors achieved comparable outcomes [3]. As a consequence, transplant programme providers started to consider a wider set of donors, with the aim of helping patients who lacked a compatible genetically related donor.

Donation between living donors and their intended recipient was originally only possible if the pairs were compatible; this occurs in approximately 60% of cases. Compatibility is defined on the basis of blood group (ABO) and human leukocyte antigen (HLA) type. Certain donor-recipient combinations of blood and HLA types will cause rejection of the transplanted organ by the recipient. In such cases, the donor-recipient pair is ‘incompatible’. Hence, even when a patient finds a (genetically) related
donor, incompatibility may still prevent LDKT. The introduction of kidney exchange programmes (KEPs) was an important next step to increase LDKT rates. ABO-incompatible and/or HLA-incompatible donor-recipient pairs, for whom direct donation to the intended recipient is not possible, benefit from such programmes by forming new donor-recipient combinations through a special matching programme. KEPs match donors to recipients in optimal combinations for kidney exchange within the pool of available incompatible pairs.

This paper covers three key areas: first, an overview of the development and features of KEPs – including ethical and legal conditions – is given; this is followed by a discussion of general organisational aspects and the final sections detail challenges and conclusions. Some of the information described in this paper was collected from a survey to members of the Committee of Transplantation of the Council of Europe (CD-P-TO), a further survey carried out by the European Cooperation in Science & Technology (COST) European Network for Collaboration on Kidney Exchange Programmes (ENCKEP) and from the outcomes summarised in the first ENCKEP Handbook [4].

2. Kidney Exchange Programmes

In 2004, the first national KEP in Europe was established in the Netherlands [5]. Several European countries have since independently developed KEPs to address incompatibility issues (see Figure 1) [6]. The survey among CD-P-TO members showed that 10 European countries are currently operating KEPs (Austria, Belgium, Czech Republic, France, Italy, Poland and Portugal, Spain, The Netherlands, United Kingdom) and a further 4 countries [Greece, Slovakia, Sweden, (along with Denmark and Norway under the Scandiatransplant Kidney Exchange Program, or STEP) and Switzerland] were interested in launching programmes. This information was corroborated by a second, more extensive survey by the ENCKEP [4].

Established KEPs aim to increase the possibilities for LDKT between incompatible pairs and offer an alternative to antibody removal for immunologically complex patients (i.e., HLA and/or ABO incompatible patients) [5,7]. While KEPs have contributed significantly to LDKT rates, they often struggle to become and stay effective in countries where the pool sizes are small and hence exchange options are limited. Small population size, legal constraints, ethical concerns and fragmentation of KEP pools within a country are the main barriers to be overcome. As a result, potential recipients may be disadvantaged.

In practice, this means that programmes differ in their organisation [6]. Some countries have scaled up to a national programme, while others retain a regional or single-centre approach. In most countries, the organs travel from the donor’s to the recipient’s centre, but in others the donor
travels. Moreover, there is variation in the organisation of matching with regard to selection and inclusion of donor-recipient pairs, the frequency of the matching runs and the optimisation criteria. The proportion of transplants achieved as a result of KEPs accounts for between 0 and more than 20% of overall LDKT activity per country.

Legal and Ethical Considerations

As with the practice of living donation in general, safeguarding the interests of the individual who wishes to donate is a fundamental aspect of KEPs [8]. The risk-benefit analysis for the healthy donor and the patient in need of a transplant should take into account the direct benefit (or lack of it) to the donor compared with the potential benefit for the transplanted recipient. This includes the likely benefit for donors concerned for the wellbeing of their intended recipients derived from the close relationship between the two of them.

KEPs facilitate a form of indirect donation in which the relationship between donor and recipient is reciprocal, i.e. all donors donate a kidney and all of their intended recipients receive a transplant. However, the transaction is not directly between the donor and their intended recipient, which may be an additional barrier to success. This process requires even more stringent donor (and recipient) assessment than direct living donation. A KEP is only possible if the national legislation allows living
organ donation between non-blood- or emotionally related donor-recipient pairs, or if the legislation explicitly allows for cross-donation through a KEP.

LDKT offers the recipient the best chance of a successful transplant outcome. However, there is always a risk that a donor withdraws his/her consent or is unable to proceed to donation for a medical reason at a late stage – or, rarely, even on the day of surgery itself – leaving the recipient without the anticipated transplant. To reduce this risk, the majority of KEPs conduct simultaneous procedures to avoid the possibility that a recipient does not receive a kidney once his/her intended donor has already donated to the other pair.

Anonymity between recipients and their new donors is also considered essential in most European KEPs before the transplant procedure and is recommended afterwards. Anonymity between the members of the new pairs diminishes the risk of potential coercion (or the seeking of payback/profit). Furthermore, it reduces the possibility of donation refusal in cases where the donor does not like the potential exchange recipient.

In the context of KEPs, this risk is increased by involving multiple donors and recipients in any one exchange. Donor-recipient pairs may be reluctant to participate in a KEP because of emotional anxieties about the donation not being made directly to the intended recipient and logistical concerns (e.g. the donor travelling to another centre for surgery; impact of cold ischaemia if the kidney travels between centres; lack of confidence in the system). Policies to minimise distress (e.g. when an exchange collapses) and to give priority for transplantation to recipients who miss out during the course of an exchange (i.e. once donor and recipient surgery is underway), as well as specific informed consent for kidney paired exchange could help to motivate pairs to participate in the programme.

There is ethical consensus that donations of organs by living donors are to be voluntary and unpaid. However, the principle of non-payment does not prevent living donors from receiving reimbursement for legitimate expenses and loss of income related to the donation [8].

**Conditions for a Successful Kidney Exchange Programme**

Taking into account the legal and ethical principles, current practice and experience shows that there are certain prerequisites for establishing a successful KEP [9].

The first condition is that there is a legal framework in place that permits non-direct donation. Subsequently, a transparent structure should be created that includes standard operational procedures. This can be achieved if KEPs are organised based on protocols, clinical standards and operating procedures agreed by the stakeholders involved. Among these stakeholders are participating transplant centres, histocompatibility and immunogenetics laboratories, a central/regional/local coordination team and donor-recipient pairs. Central coordination to oversee
identified pairs, perform matching runs, collect follow-up data and ensure mechanisms are in place to minimise the risk of identified transplants not proceeding due to the collapse of an exchange are essential. Hence, much attention has been focused on evidence-based, complete and up-to-date screening of both donors and recipients to establish their clinical, immunological and psychosocial status. Since confidence in the system is fundamental, it helps when all professional partners in the system know each other and are familiar with each other’s working methods.

In contrast to direct living kidney donation, the behaviour of participating donors and recipients affects not only their individual interests but also those of other donor-recipient pairs in the KEP, especially if they decide not to proceed after an exchange has been identified. Whilst it is impossible to predict every eventuality (e.g. change of donor circumstances or unforeseen recipient illness), KEPs should aim to be able to address reasons for non-proceeding transplants that could have been foreseen by anticipating possible solutions. The impact of a high non-procedure rate may be significant: distress to donors and recipients, loss of confidence in the KEP and reduced participation.

3. Organisational Aspects

A KEP requires a multidisciplinary and, in most cases, a multi-centre approach. Therefore, KEPs must define a structure to coordinate and monitor all activities which can be national, regional or centre-based. The key components of effective KEPs are [4]:

a) Medical, psychological, social, legal and ethical frameworks for donor and recipient care – to ensure consistent, high quality, safe clinical practice in line with international standards and best practice guidelines. Special considerations include anonymity requirements, indirect donation and reciprocity, management of identified transplant procedures that cannot proceed, and management/listing of recipients for transplantation who may miss out within the KEP. Organisation of donor and recipient follow-up should also be carefully considered.

b) Information for patients – the options for LDKT, individual donor and recipient risks and benefits should be presented clearly and at an early stage to maximise opportunities for timely, successful transplantation/re-transplantation.

c) Technical standards for living kidney transplantation – equitable clinical and surgical expertise to ensure consistent quality of care for all donor and recipient pairs must be guaranteed.

d) Capacity and capability – a sufficient and appropriately trained multidisciplinary workforce should be established. In particular, clinical and scientific expertise, and central coordination are needed. Immunological testing is central to successful KEPs and must be performed by accredited histocompatibility and immunogenetics laboratories using standardised testing and reference criteria.
in every laboratory for every donor and recipient pair. Central coordination by dedicated living donor coordinators in nephrology and transplant centres is effective in supporting donors, recipients and family members throughout the process of donation and transplantation.

e) FINANCIAL INFRASTRUCTURE – LDKT is a cost-effective treatment for ESRD compared with dialysis, offering significant financial savings to the health economy. Sustainable funding through state or privately funded insurance arrangements is necessary to support national LDKT and KEPs. Clinical and personnel costs associated with the coordination and management of national programmes, together with the reimbursement of out-of-pocket expenses and loss of earnings of the living donor, are the responsibility of the respective governments in participating countries.

f) TRUST – Trust is fundamental to a successful KEP; trust between the partners who have to work within the framework and between the donor-recipient pairs in the system.

4. Challenges for Kidney Exchange Programmes

KEPs are acknowledged as an effective solution to overcome immunological incompatibility and, in some countries, they offer opportunities to improve HLA- or age-matching between compatible donor-recipient pairs. However, the main challenges to maintaining and extending programmes are the limited pool of donor-recipient pairs at the start of a scheme, a decreasing pool in terms of quantity or diversity of pairs (e.g. increased numbers of blood group O and/or highly HLA-sensitised recipients) and the availability of other (competitive) options for incompatible pairs, such as antibody removal for both ABO and HLA incompatibility, despite poorer outcomes.

Effective KEPs increase the opportunities for patients, particularly those with immunological complexity, to receive a compatible transplant, which is almost always the preferred option. In countries with permissive legal frameworks, supportive policies and established KEPs, the patient benefits – especially for those who are very difficult to match – of the KEP can be further enhanced by the inclusion of donor-recipient compatible pairs (e.g. for improved HLA- or age-matching, or for the greater good) and unspecified (non-directed altruistic) living kidney donors to augment the pool. Experience suggests that such a strategy maximises the benefit for all donors and recipients involved, including recipients on the national transplant list with no living donor of their own. As well as utilising unspecified living donors to initiate a chain of transplants within their KEPs, a few countries are considering using deceased donor kidneys to achieve a similar outcome (as reported by national representatives in response to the COST survey). Extending the KEP pool by allowing international exchange is another very practical and obvious solution. However, this would require fine-tuning of protocols and extra attention to donor-recipient pair screening to avoid any possibility of enhancing medical tourism or even organ trafficking.
5. **Conclusions**

Due to organ shortages, many countries are investing in living donor programmes, which are often the best option for patients in need of a kidney transplant. Since around 40% of living donors are incompatible with their intended recipient, KEPs offer an alternative to help overcome HLA- and ABO-incompatibilities. To achieve this goal, pools of donor-recipient pairs are created to generate alternative pairs of possible matches. KEPs provide an excellent opportunity to extend existing living donor programmes. However, since KEPs are a form of indirect donation, conditions to develop and maintain effective and safe programmes must be implemented. A KEP should include a sound and transparent (nation/regional) organisation which takes care of the needs of the recipient and donor, taking into account all ethical and legal considerations. The organisation of a KEP requires transparent protocols and efficient and trust-based cooperation between the multidisciplinary teams of professionals. Within Europe, the further development of KEPs should take place within the framework of the Council of Europe resolutions on living donation [10,11] and the EU legal framework [12].

6. **References**

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