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Kidney transplantation: a road-map to improve access and overcome barriers

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M

2021

Tipo de trabalho: Artigo de Revisão Bibliográfica

Título: Kidney transplantation: a road-map to improve access and overcome barriers

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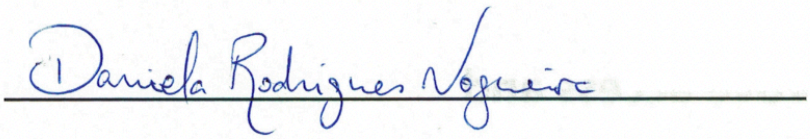

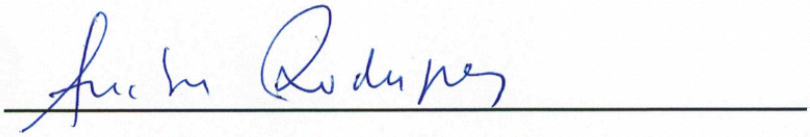

Porto, 2 de junho de 2021

I give thanks for arriving
Safely in a new dawn,
For the gift of eyes
To see the world,
The gift of mind
To feel at home
In my life.
The waves of possibility
Breaking on the shore of dawn,
The harvest of the past
That awaits my hunger,
And all the furtherings
This new day will bring.

- On Waking
by John O'Donohue

Agradecimentos

Aos meus pais, pelo apoio que - tal como o amor - foi constante e incondicional.

Aos meus amigos, pela companhia ao longo destes anos, que se revelaram infinitamente mais felizes do que era possível imaginá-los.

Ao Gonçalo, por atravessar comigo o limite da zona de conforto para ajudar a criar algo que durará para sempre.

À Dra. Manuela Almeida, pela disponibilidade inquestionável e por me levar a conhecer pessoas e histórias maravilhosas.

E à Doutora Anabela, pela boa disposição contínua, pelo sentido de humor e aventura, e por partilhar comigo um entusiasmo contagiante por este projeto, mas também, e acima de tudo, pelo futuro.

Resumo

A doença renal crónica é um problema de saúde prevalente a nível mundial e está estabelecido que o transplante renal, especificamente de dador vivo, constitui atualmente o método mais vantajoso, de entre os tratamentos disponíveis. Assim, é essencial investir intensamente no aperfeiçoamento desta estratégia terapêutica, que é a melhor opção para a maioria dos doentes elegíveis. Neste trabalho, foi elaborada uma coletânea sistematizada de barreiras existentes ao acesso e completamento do processo de transplante renal, seguida de uma série de recomendações contrastantes para as ultrapassar. Adicionalmente, foi criado um *website* neste contexto, com o objetivo de proporcionar à população geral, e particularmente a potenciais dadores e recetores de órgãos, acesso fácil a informação de confiança. Este recurso digital focado na comunicação pretende servir como um primeiro passo tangível para superar os obstáculos identificados criando, desta forma, um impacto positivo, significativo e duradouro.

Abstract

End stage kidney disease (ESKD) is a prevalent health issue across the world and it is well established that kidney transplantation, specifically from a living donor, currently constitutes the best value-based treatment method. Ergo, it is crucial to invest heavily on the heightening of this care strategy as the best possible option for the majority of eligible patients. A systematized compendium of existing barriers to access and completion of the kidney transplant (KT) process has been elaborated, followed by a series of contrasting recommendations to overcome them. Additionally, a website has been developed in this context, aiming to provide the general population, particularly potential organ receptors and donors, better access to trustworthy information and data. This communication-focused digital resource plans to serve as a tangible inaugural action to combat these hindrances and, thus, to create a long-lasting, positive and significant impact.

List of abbreviations

AA - African American

ABOi - ABO incompatible

BMI - body mass index

CHUP - Centro Hospitalar Universitário do Porto

CKD **-** chronic kidney disease

COPD - chronic obstructive pulmonary disease

eGFR - estimated glomerular filtration rate

ESKD - end stage kidney disease

GFR - glomerular filtration rate

HD - hemodialysis

HLAi - HLA incompatible

KDIGO - Kidney Disease: Improving Global Outcomes

KT - kidney transplant

LDKT - living donor kidney transplant

LTFU - lost to follow-up

pmp - per million population

RRT - renal replacement therapy

SPN – Sociedade Portuguesa de Nefrologia (Portuguese Society of Nephrology)

STR - standardized transplant ratio

Índice

Introduction

The relevance of chronic kidney disease (CKD) is increasing, with associated public health costs and a significant contribution to the population's morbidity and mortality.[1,2] There are five stages of kidney disease, with gradually worsening glomerular filtration rates (GFR). The progression rhythm varies greatly between individuals, and while some can maintain relatively steady GFR values for longer periods of time, others advance rapidly, predominantly in later stages. Patients with stage 1 CKD may be asymptomatic and need only observation and control of risk factors, such as hypertension. However, once they progress into stage 5 or ESKD, a kidney transplant or some type of dialysis treatment on a regular basis is required.[3] It is established that KT affords patients improved survival rates, better quality of life and higher cost-effectiveness than dialysis, regardless of the elected modality, even among resource-limited contexts.[3,4,5,6,7,8,9] Furthermore, the presence of comorbidities does not necessarily disaffirm the benefits of waitlisting and transplantation, when deemed suitable. Indeed, it is possible to achieve comparable survival gains as in older patients without comorbidities.[10]

To understand the value of kidney transplant, we must first understand the patient circuit. Multiple steps are required for a patient to receive a KT, such as transplant education, referral for a detailed evaluation process at a transplant center, completion of medical and psycho-social assessments, and securing a donor, be it a living one or a place on the waiting list for a deceased donor KT.[11] The time window between referral and waitlisting can vary greatly, which makes it an effective intervention point of the process with great potential to increase transplant access.[11]

There are four treatment modalities available to ESKD patients, namely: kidney transplant; hemodialysis; peritoneal dialysis; and conservative medical treatment.[12]

Although it is common that a transplanted patient has had a previous period of dialytic treatment, this is not always the case. In fact, a preemptive KT, or an earlier transplant, is associated with better overall outcomes and perceived quality of life when compared to a KT after longer periods of dialysis.[5,13]

When discussing this matter, there is a major division between living donor and deceased donor KT, which in turn can be from a cadaver donor or a non–heart beating donor. ABO or HLA incompatibilities are the main limitations to a living donor kidney transplant (LDKT), and cross

over KT, in which there is a kidney exchange between two pairs of donors and patients, can be an effective solution to this problem.

It bears clarifying that the role of KT on the patient circuit is not always a cure, as it can also act as an intermediate step of a more complex treatment strategy.

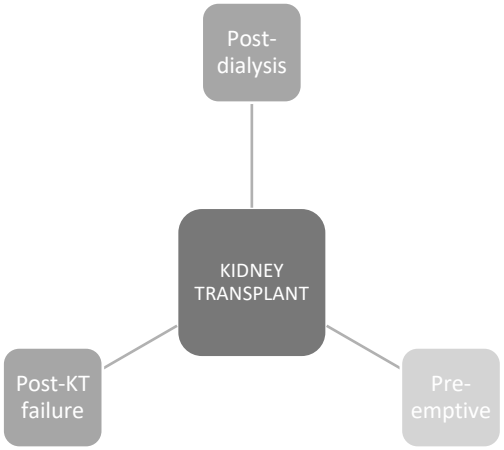

Figure 1

It is crucial to understand that this treatment modality represents the biggest value-based health care option to a patient with ESKD. As such, there must be a strong investment in its promotion, as well as in the eradication of existing barriers and amplification of access, focusing specifically on LDKT as the best possible route.

Objectives

With the present work, we seek to explore and understand the main barriers to kidney transplant, not only on a global basis, but also approaching Portugal's reality. Not only that, but we set to take a concrete step in the process of eliminating such barriers, particularly concerning the accessibility to LDKT, through the development of a website. Our prospect is that this digital instrument may contribute to facilitate communication and increase health literacy among the general population in a simple, easily accessible manner and potentially affect a rise in the statistics of LDKT in our context. Ultimately, the main goal of this work is to induce long-lasting changes in a short-term period, influencing the paradigm of KT in a positive and meaningful way.

Methodology

The approach presented in this work consists of a review of the existing literature from the last decade on the current state of KT and its role as the final step on the complex process inherent to a patient living with ESKD. In order to achieve this, we used data from the Portuguese Society of Nephrology (SPN) and the PubMed platform, exploring the following *MeSH* key-words: "kidney transplantation", "barriers", "patient-related outcomes" and "kidney failure, chronic". All articles included were in English language and review articles were excluded. Moreover, in close collaboration with the KT Unit at our hospital - *Centro Hospitalar Universitário do Porto* (CHUP) – we were able to shine a light on recent developments in our own center, which is one of the most prominent contributors for KT programs in Portugal.

Departing from this theoretical basis, a further analysis of the existing barriers to KT is exposed, followed by a collection of recommendations for potential improvements and ways to overcome the aforementioned obstacles. Finally, in partnership with the department of Technological Infrastructures of Porto University and Gonçalo Oliveira, a talented and proactive Multimedia student, we developed a website with the intention of better informing the general population about KT, namely using a living donor, as the best value choice of treatment for patients with terminal CKD.

Clinical aspects

To receive a KT, it is imperative that there is irreversible kidney failure. However, not every ESKD patient is an appropriate KT candidate and a thorough evaluation must be made.

Each patient must be subjected to a detailed assessment of medical and surgical issues, psychosocial factors, social support availability, financial viability and physical and cognitive abilities with the purpose of balancing the benefits and the risks of KT and long-term immunosuppression.[4,5,14,15] The criteria to be a candidate are still heterogeneous when comparing transplant centers around the world, and many patients fall into a gray area where they are neither definitively eligible nor ineligible.[16] On the other hand, there is the matter of potential donor evaluation, which in and of itself demands a whole other set of pre-requisites. With that in mind, the KDIGO (Kidney Disease: Improving Global Outcomes) work group has created guidelines with recommendations in order to establish a more uniform process leading

up to the actual KT procedure.[17] In this document, it is suggested that transplant programs should, whenever possible, provide customized quantitative estimates of short-term and long-term risks from donation; that each donor candidate should be submitted to a biopsychosocial evaluation and that it is essential to formulate a donor care plan that includes long-term follow-up.

A KT is not without some potential risks, which can be related to the procedure itself (such as infections or hemorrhages), to the immunosuppressants necessary after surgery or to difficulties related the transplanted organ. Among these complications, the most concerning of all is the rejection of the transplanted kidney.

It is known that LDKT is associated with superior patient and graft survival, earlier access to transplant, and improved quality of life when compared with deceased donor KT.[1,18,19,20] Furthermore, there is also confirmed benefits to preemptive transplantation, in which KT occurs before commencing dialysis.[21] As opposed to cadaver KT, preemptive KT leads to fewer pretransplant blood transfusions, increased rates of patient employment maintenance, improved long-term graft survival, lower rates of delayed graft function, and fewer episodes of acute rejection, besides allowing for greater flexibility in regards to timing.[22] In order to decrease patients' waitlist time and identify a living donor, transplant education should begin as early as CKD stage 3.[3] Notwithstanding, there appears to be a mismatch between the value of preemptive KT and its actual use and this corroborates the importance of creating task-forces with a goal to increase not only LDKT rates, but also preemptive KT rates.[21,23]

Patients and waitlist: national data

The latest available Portuguese data shows that there has been a steady increase in KT rates between 2012 and 2017, reaching a total of 529 transplants that year. Data from the European Renal Association from 2015 shows that Portugal performed 47 KT per million population (pmp), which is above the all countries average of 25 pmp. However, much like everywhere else, there is still a clear prevalence of deceased donor transplantation when compared with LDKT rates. Another interesting fact is that the patients' age is having less and less influence on graft survival rates, which in turn have been rising consistently over the decades, along with patient survival.[24]

In Portugal, the national healthcare system provides full access to renal replacement therapy (RRT), but there is still room to grow when it comes to increasing LDKT rates, with great

heterogeneity between national regions that causes significant disparities in access. Between 2015 and 2020, the median waiting time for a deceased donor transplant was 4.8 years. In contrast, the same statistic regarding living donor transplants was 0.8 years, which shows the importance of investing in LDKT so as to improve patients' outcomes. Globally, Portugal presents with some of the highest percentages of deceased donor transplants, but also of patients requiring RRT. In 2019, 514 kidney transplants were completed, translating to a total of 49,9 transplants pmp. However, among those, only 75 (14.6 %) were from living donors.[25] Over the last 10 years, CHUP performed close to 50% of all LDKTs in Portugal, with nearly one third of those being part of the living donor program. The COVID-19 pandemic has taken a toll on the transplant statistics, forcing the rearrangement of resources, the suspension of the programs from March up until May 2020 and causing an inevitable decrease in the numbers, having been performed by the end of the year only 41 LDKTs (4.02 pmp), indicating a drop of approximately 45%. So far, in 2021, CHUP has performed approximately 50 KTs, from which 11 were LDKT and 2 were kidney-pancreas transplants. (Data not published; Obtained through personal communication with Dra. Manuela Almeida, responsible for the LDKT Program at CHUP)

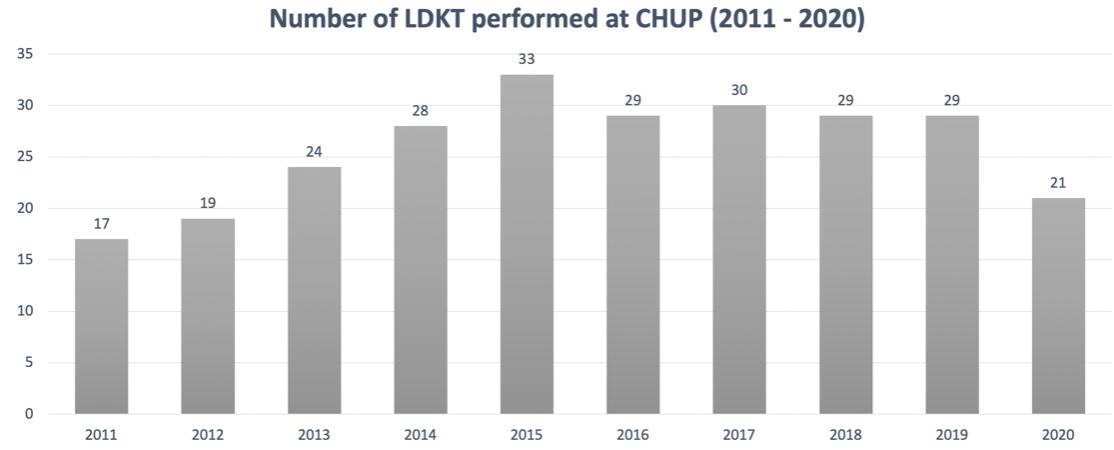

Figure 2: LDKT at CHUP

Furthermore, CHUP is also a reference center in Portugal for innovation in transplantation, rooted in well-developed scientific investigation teams and branding knowledge diffusion and clinical commitment as a mission. To our knowledge, CHUP is the only center in the country where it is possible to execute ABO incompatible (ABOi) KTs, and one of the most experienced with HLA incompatible (HLAi) renal transplantations. Between 2015 and 2020, 171 LDKTs were performed, from which 30% were preemptive, 9% were ABOi, 11% were HLAi and 15% were cross over KTs.

LDKT type	TOTAL: 171
Preemptive	**52** (30%)
ABOi	**16** (9%)
HLAi	**19** (11%)
Cross over	**26** (15%)

Figure 3: Innovative LDKT at CHUP

Barriers

We bring forward a breakdown of the main documented barriers to KT, from 3 different stand-points: the patient; the healthcare provider; and the system itself. It must be taken into account that the relative significance of the various perspectives fluctuates between regions.

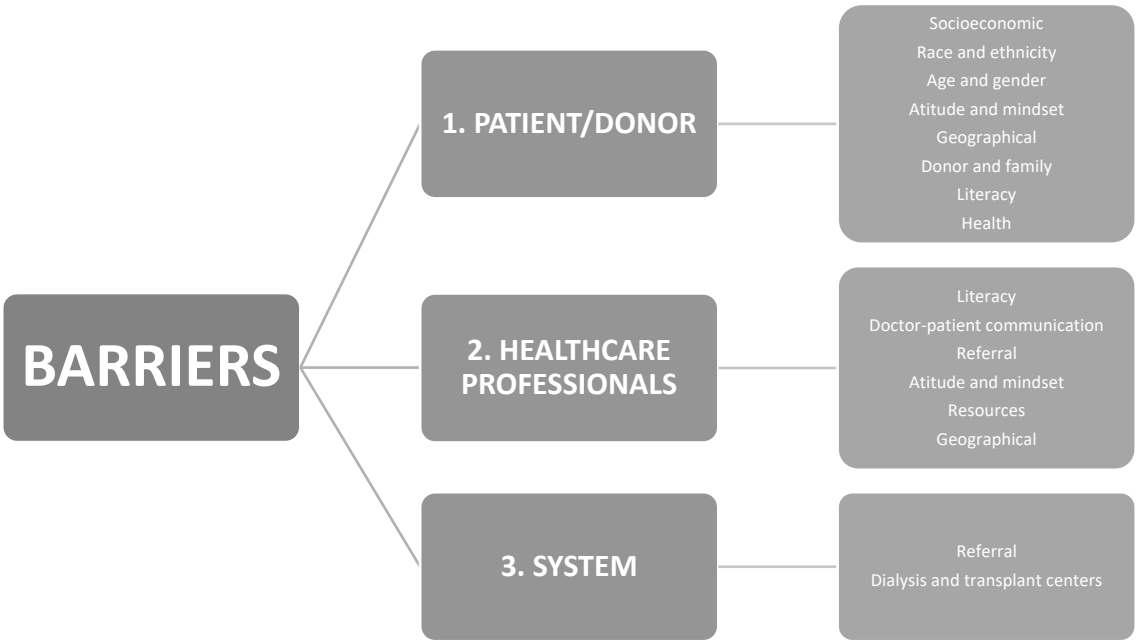

Figure 4: Identified Barriers to KT

1. Patient barriers

1.1. Socioeconomic

Financial difficulties and lower socioeconomical status seem to be amongst some of the most significant barriers to KT.[7, 15,26,27,28] In fact, a study by Ilori et al. concluded that financial concerns were reported by over half the individuals who declared not wanting a KT.[29] Another study discussed how these concerns outweighed fears about transplantation, scheduling, health, and transportation.[30]

Economical obstacles have been shown to delay transplant evaluation and cause loss of follow-up, resulting in higher mortality rates, especially in low and low-middle income countries.[4] Many times, the absence of health insurance, access to primary care physicians, as well as the potential costs associated with the transplant process can force patients and their families to face budget struggles and even debt, while also leading to a significantly higher probability of being unassessed.[4,16,31] Besides the KT itself, there are other financial-dependent factors to be accounted for, such as missed days of work, decreases of salary for inability, childcare or transportation expenses.[3,26,31] The same applies to many potential donors, the vast majority of which end up with out-of-pocket expenses at the end of the process, due, in part, to inadequate or insufficient reimbursement programs.[20,32,2] Additionally, the finding that most KT recipients have similar incomes to their related and unrelated donors implies a limited ability on their part to help mitigate the costs to said donors.[2]

Financial problems may arise due to other elements of the family needing expensive medical care, creating a need to prioritize health-related spending.[4] The absence of social security has also been demonstrated to be an obstacle to KT referral and completion.[26] Not having an occupation was another factor associated with a lower probability of referral to KT.[33,34]

1.2. Race and ethnicity

Patients' ethnicity has been shown to play a role, namely in the USA, as a barrier to the KT process, particularly concerning the referral steps.[35] Race-related disparities remain, in some countries, one of the key factors explaining delays and failure to complete steps toward receiving a transplant in this population.[15] A study by Patzer et al. has established African American (AA) race as a significant predictor of lower transplant rates at the dialysis facility level.[34] Another study explored the knowledge gaps between ethnicities (AA versus White) and found that although black patients who were KT candidates had been on dialysis for significantly longer than whites, they were given less information about KT as a treatment option and their families and friends were less included in discussions about this possibility.[36] Furthermore, it has been shown that black ESKD patients evaluated at a large transplant center in the Southeastern United States have reduced access to KT, being 59% less likely to receive a transplant at any given time compared to white patients.[37] AA patients reported experiencing more discrimination, perceptions of racism in healthcare, medical mistrust and religious objections to LDKT than did white patients, which is worrisome, as it may cause patients to disengage from the healthcare system and ultimately, to lose follow-up on the necessary steps to complete the KT process.[38] In Portugal, however, the racial disparities do not seem to represent a prominent

obstacle to KT, especially in the northern region, where the black population is significantly less numerous.

1.3. Age and gender

There are no absolute criteria concerning the age of patients, and KDIGO recommends that it is always considered in the context of additional comorbidities that may impact the outcome, never excluding patients based solely on their age.[17] With time, this matter should tend to lose influence when discussing access to KT, instead valuing functionality and clinical aptitude to the required treatments. Some studies affirm that young age is associated with higher referral and that these patients are usually more willing to consider living donation as a treatment option.[18,33,39] On the other hand, it has been proven that older patients, namely above the age of 65, were significantly more likely to be unassessed.[7,16] Not only that, but these patients have also shown to be more propense to refuse KT as a potential option.[40] Another study indicated that older age, being a woman, and less education were associated with high levels of health-related and psychosocial concerns, which can in turn lead to difficulties during the KT work-up.[41]

1.4. Attitude and mindset

Cultural and religious beliefs often times play a very significant part in patients' decision making when it comes to their health, especially among minorities.[20] A negative attitude towards organ transplantation, often associated with mistrust in the KT process itself, as well as incorrect beliefs or even certain established myths about this subject were described as encumbering factors.[4,9,29,31,40,42] The influence of family values and the cultural view of health can add to the already present stress and emotional distress and greatly influence the course of a patient's treatment.[4] Patients' beliefs may have such an impact that they alter whether they seek medical assistance or even whether they ask for a living donor volunteer from their family or friends.[38]

A study found that medical mistrust and specific concerns about risks for living donors were particularly prominent among Hispanic patients.[3] These concerns were also evident in the Asian community, with many patients having deep-seated beliefs in alternative and traditional therapy.[26] It's essential to address these matters, more so considering a study by Bartolomeo et al. in which it was concluded that patients frequently withdraw from the pre-KT process due to fear of the surgery itself and to pre-conceived beliefs that they will fail the work-up to achieve it.[7] Another study explored how religious beliefs are often dissociated from scientific facts and can ultimately lead to a false hope for an inexistent or unavailable cure.[4] A significant percentage

of patients interviewed in another study revealed not wanting to pursue KT because they were "happy with dialysis" (31.9%) or "unwilling to take [the necessary] risk" (26.5%).[26]

1.5. Geographical

It has been established by Pais et al. that a greater distance from transplant centers increases the risk of mortality and is a barrier to achieving transplantation in both children and adults.[4] Waterman et al. report that some of the main difficulties consisted of attending transplant education classes due to scheduling conflicts with work and challenges getting transportation to the class.[3]

Geographical barriers are a relevant variable to consider as well, in the sense that nephrologists practicing in rural settings were shown to be more likely to consider inadequate support and limited education of patients as reasons not to refer patients for KT.[7] Due to having more limited options in terms of transplant centers, dialysis units, and nephrologists, these factors may disproportionately impact rural communities.[7] A study using cohort data relative to Australian children with ESKD exhibited that geographical remoteness was associated with a substantially reduced probability of receiving a preemptive LDKT.[43]

Furthermore, the donors must not be overlooked when talking about this kind of obstacles, since it has been explained that many potential donors struggled with finding time to go through work-up investigations and even attend outpatient appointments.[26] Another study approached potential donors living abroad or in more remote areas within the UK as a significant barrier to donation on their part.[32]

1.6. Donor and family

A definite difficulty when discussing KT is navigating the patient's support network, be it their friends or families and potential donors. If these support networks lack the knowledge and understanding of what is needed of them, that can become a real barrier to the transplant process.[3] A fear commonly mentioned by patients is becoming a burden to their loved ones in any stage of the KT proceedings.[3]

However, one of the predominant concerns when discussing the patient-donor relationship is the apprehension to approach a potential donor and how to formulate such a request, leading, many times, to an unnecessary prolongment of dialysis treatment.[18,32,28,41] This barrier is corroborated when we observe study results in which the majority of patients that did not

choose KT as a possible treatment cited "lack of donor" as their main reason for doing so. Furthermore, 81.5% of this group were unmarried patients, suggesting the importance of a spouse as a potential organ donor.[26] It was very frequently observed how hesitant some families were about the whole process.[26] There were several reports of patients whose relatives had in fact offered to donate a kidney, which they were, however, reluctant to accept due to the concern that their loved one might develop kidney failure in the future.[3,9] In some situations, it was even possible to ascertain the weight of a health problem like CKD, particularly in cases of familial disease and hemodialysis, on the recipient and donor's shared quality of life.[32] Another problem identified by Pais et al. was that families without living donors seemed to lack timely access to deceased-donor organs, which ultimately perpetuates lower access to KT.[4]

1.7. Literacy

A finding transversal to all literature was that the patients' level of education and their understanding of their condition, the options available and the donation process itself was crucial to the success of the KT pursuit. Many patients presented with denial or poor awareness about their own health predicament as well as fears about the surgery and its possible risks, namely graft rejection or even death.[3,4,9,29,40] As such, low health literacy, denial of the ESKD diagnosis, and fear are recognized barriers to progressing towards transplant.[4,26,27,42] This lack of knowledge branches into other obstacles that can present as mistrust in the healthcare providers, lack of motivation to pursue this treatment, and perpetuation of myths.[4] It was evidenced that confusion about CKD, its short and long-term impact and the timing of the necessary steps to complete the transplant (like when to be evaluated or how to be waitlisted) were remarkable barriers in this context.[3] A study displayed the health providers' perception that patients did not comprehend the criteria to classify someone as a good living kidney donor.[3] Another study concluded that limited patient education might prevent consent by the patient for expanded criteria donor kidneys despite the patient benefiting from transplant.[7] It was observed that patients who had been on dialysis for under 5 years were less informed and showed less willingness to take risks when compared to patients who had been on dialysis for 5 years or more.[26] Illes et al explored this lack of knowledge and concluded that, of the group of patients included in the study, 21% thought only dialysis patients could be candidates to receive a cadaveric transplant, and 34% had the information that dialysis was a necessary precondition to being accepted to the waiting list. On top if that, 66% had never heard about living donor, kidney paired donation, or paired exchange as an option.[40]

A need for KT education in a clear, timely and consistent manner was identified as an essential factor to account for by both patients and healthcare providers, especially in the early stages of kidney disease, as well as guidance and support for those searching for a donor.[20] The lack of a reliable source of information delivered in a meaningful way was shown to lead to overwhelming feelings of hopelessness and, in the worse scenarios, actual disengagement from the process of exploring KT as a treatment of choice.[20,42] In another study, most participants reported a lack of information on the process of living donor evaluation, while also knowing that the risks of living donation were small.[32] Laouad et al. conducted a study at the end of which was exposed that 52.5% of the hemodialysis (HD) patients included had no information on KT, claiming this lack of understanding to be the main barrier that stopped them from pursuing it.[44] The same study has additionally brought to light that many patients incorrectly believe transplantation to be more expensive that HD even after it is well established that after 2 years, KT costs significantly less than any form of dialysis. Moreover, in this study, only 65.8% of subjects believed that renal transplantation offers a better quality of life than HD treatment.[44] This serves to show how a better comprehension of these matters could potentially improve the patients' interest in KT.

The shortcomings in patient education about KT have been suggested to lead to a certain attitude of passivity on the patient's part, who defers treatment choices entirely to the clinicians, often without challenging or even understanding their decisions. It was hypothesized that this could derive from a lack of long-term perspective, with patients reporting that their focus was on their immediate situation, without planning too far ahead, and thus, not believing they would ever need a transplant or that they could do anything about pursuing it at that point in the course of their disease.[32]

1.8. Health

Each patient has a unique set of health factors that must be accounted for when dealing with a potential KT. Patients with advanced CKD often have multiple simultaneous medical issues that can complicate the work-up leading to transplantation.[21] A study by Lockwood et al. suggested that a majority of the delayed or incomplete evaluations for KT were related to hospitalizations for concomitant illnesses. These complex scenarios can be the result of a combination of disease progression, effects of medications used to treat comorbidities, and the effects of renal replacement therapy.[31] In fact, all nephrologists interviewed in a study conducted by Ghahramani et al. considered comorbidities the most important criteria when deciding about their patients' candidacy for transplant.[27] Several factors were concluded to be linked to a lower likelihood of being referred for KT, namely smoking history/chronic obstructive pulmonary

disease (COPD), the presence of comorbidities, physical disabilities, low serum albumin level (<30 g/dL), high body mass index (BMI) value (>35kg/m^2), emergency first dialysis (vs planned one) and all primary renal diseases (compared with polycystic kidney disease).[33,39] Furthermore, it was explained that obese patients were significantly more likely to be unassessed.[16] On the other hand, hemoglobin levels above 12 g/dL were associated with higher referral rates for transplant.[33] On top of all this, it is important to address the discontinuation of treatment as a preponderant barrier in this context, since it was noted that almost half of the patients who continued treatment were successful in achieving a KT.[4] Additionally, it was mentioned that lower socioeconomic variables, late diagnosis, and poor access to care were all contributing factors to lost to follow-up (LTFU) among these patients.[4]

2. Healthcare professionals and providers barriers

2.1. Literacy

The level of knowledge presented by medical staff is key to the timely and adequate referral of patients to initiate the KT process. The lack of medical expertise in multiorgan transplantation was identified as a significant medical barrier in more than one study.[4,32] These shortcomings may present as not recognizing eligibility to KT or incorrectly considering a patient an inappropriate candidate for KT, for instance.[1] Another identified obstacle lies in the misconception that physicians are not responsible for transplant education, and as such, they may not effectively convey to the patients and their families all the necessary information to appropriately express the benefits of KT as a treatment option.[18] A study concluded that nephrologists may occasionally postpone important KT-related conversations with their patients due to a belief that kidney function still has enough stability, even in cases where it is severely diminished. This is often not the case, as kidney function may decline abruptly in the context of other underlying health problems.[21] Sandal et al. discussed the health professionals' lack of information and training as a crucial barrier to overcome and one that could potentially impact the communication between clinicians and patients about the risks and benefits of LDKT, to a point where there was admittedly some discomfort during these discussions, particularly surrounding the finding of a donor. The aforementioned lack of knowledge was aggravated by an absence of sufficient resources and up to date information. All of this led some participants to admit to feeling discomfort discussing LDKT with patients.[18]

2.2. Communication and doctor-patient relationship

A healthy doctor-patient relationship is one of the pillars for the success of any treatment strategy. One of the observed barriers in this context was the attribution of the onus of research and understanding about the transplant process solely to the patient, which was suggested to create feelings of loss and lack of support.[3] The importance of a functioning team was also noted in another study, in which dialysis and transplant teams were viewed as separate entities and, therefore, communication between the two was deemed as sporadic and insufficient, and to only occur during a crisis situation. On top of that, health professionals working in dialysis felt not being sufficiently updated on the progression of the recipient's and donor's evaluation.[18] Poor communication between patients and providers and among providers themselves was discussed as the most prominent barrier to successful completion of the pre-KT evaluation.[31] In another study, participants described clinician paternalism and even a lack of shared decision-making, describing that clinicians often failed to bring up KT as a viable option and to fully address this matter when asked about it.[32] A less than optimal relationship with the patients during the course of the KT work-up was perceived as a source of frustration to those patients, with some of them describing feelings of being "over-looked".[9] It was apparent between patients that there was a common wish that their doctor was an ally along the evaluation process, often seen as a difficult and scary journey.[9] In the same study, it was concluded that almost half of all participants did not understand their transplantation listing status correctly, which was attributed to potential flaws in the provider-patient communication.[9] Another study found that 78% of participants who agreed with the statement "No one has discussed KT with me" as a reason they would not pursue transplantation were in fact informed about kidney transplantation according to their provider, which corroborates the miscommunication and derived misunderstandings between the two parts.[41] If we take into account that patients who are well-informed about KT are more likely to be interested in pursuing it, it is fair to attribute some of the reluctance to choose this line of treatment not only to a lack of knowledge, but also to an ineffective doctor-patient communication.[9]

2.3. Referral

The referral process itself can be a source of difficulties to both preemptive kidney transplantation and successful waitlisting, so it is crucial to achieve the optimal timings.[1] According to KDIGO, the evaluation process for KT should commence at least 6 to 12 months prior to the projected start of kidney replacement therapy.[17] The reason for delays on this specific matter is often a lack of understanding by the health professional about how to refer a

patient to initiate the KT work-up.[1] A study by Bartolomeo et al. debated several practice-related reasons considered by nephrologists in transplant referral, such as the extent of the pre-transplant work-up, complexities of caring for the post-transplant patient, financial disincentive to provide care to transplanted patients, limited clinical and administrative support, and concern that the transplant center may take over their patients' care.[7] It is crucial to optimize these proceedings in order to potentially increase transplant rates, since data from the Australian ESKD registry revealed that patients who were referred later to a nephrologist were less likely to be put on the waiting list or given a KT.[1]

2.4. Attitude and mindset

Similarly to poor knowledge and discomfort discussing KT, health providers' personal biases can lead to inconsistent and inexplicit recommendations, which may intensify inequity to LDKT, chiefly in the disadvantaged demographic groups.[18,31] It was noted that academic affiliation and younger age were doctor-related factors associated with a more proactive attitude when it came to encouraging living donation, which corroborates that the clinician's mindset towards this treatment is a key element for the success of its implementation.[18,7,39] On the other hand, male nephrologists and more than 10 years from fellowship conclusion were factors associated with a lower likelihood of directing a patient for KT.[39] Browne et al. discussed that some dialysis professionals' behaviors were perceived as a discouragement in the context of KT pursuit.[42] As previously mentioned, a racism component may be present in some settings, with AA ESKD patients taking significantly longer than white patients in the same health status to complete their medical work up before being presented to the transplant team and to be accepted for KT.[38] Additionally, the same study showed that comorbidity, dialysis status, and availability of potential living donors were not associated with days to be accepted for transplant, which confirmed the proposed hypothesis that medical factors alone could not explain the racial disparities observed.[38] According to another study, women were more likely to be reported as unsuitable for KT due to age, medically unfit and having declined information when compared to men of similar age and comorbidities.[16]

2.5. Resources

It was frequently apparent that the management of time and resources is a hardship for healthcare providers. Nephrologists reported not having time to refer patients to KT clinics.[1] This issue of lack of available time was tackled in other studies, often more related to urban settings.[27] This problem affects not only the referral rates, as it also has demonstrated to have a

definite impact in patient education, with studies showing that a majority of providers both from for-profit and nonprofit dialysis centers reported spending less time than they personally believed to be ideal informing their patients and their respective families about the pertinent KT proceedings.[44,45]

2.6. Geographical

Some geographical barriers were noted by nephrologists as well as by patients. Rural settings were thought to be associated with a higher complexity in the decision process to refer patients for KT, namely due to potential obstacles in post-transplant care and scarcity of transplant centers in the area.[7] In multivariate analysis, clinicians with less than 3 transplant centers within a 50-mile radius were more likely to consider inadequate social support and age above 65 years as reasons not to refer patients for KT.[7] On the other hand, urban areas were associated with a higher chance of recommending KT as a treatment option.[39] Another study observed that the distance from transplant center to patients' residences was only remarked as a barrier to KT by rural nephrologists.[27]

3. System barriers

3.1. Referral

The referral process itself has been reported to represent a barrier to the transplantation proceedings, since it is a complex process which can cause difficulties to both healthcare professionals and patients.[1] It is an unanimously established opinion among healthcare providers that the work-up to KT is lengthy, which means there is a greater period over which the patient may become ill, and this may lead to a loss of eligibility to receive a KT. Furthermore, the long duration of this process can discourage patients and even potential donors to persist and reach the intended result, many times opting out of the evaluation due to frustration.[20] A study has shown that a possible flaw in the work-up can be the lack of contact to schedule an appointment after being referred to KT by their doctor.[1] An absence of referral guidelines, marked by a perceived disorganization of information, a high variability in the cutoff values and a myriad of time-consuming tests required prior to referral were some of the barriers pointed out by healthcare professionals, all of which were thought to contribute to confusion and decreased early discussion with patients about LDKT.[18,9] Another study noted that CKD clinics often had different policies and procedures than their partnering transplant units, which was a source of further confusion and errors. This absence of a collaborative kidney care continuum

with improved patient transitions between renal and transplant programs was considered an important barrier to tackle in this system.[20] Another study observed that the most frequently reported reason for not discussing KT with a patient was that they had often not completed the necessary assessment at the time.[16] All of these factors combined appear to ultimately lead to worse overall outcomes for these patients, after taking into consideration long waiting times and high death rates on dialysis, and that delays in KT education for appropriate KT candidates necessarily imply later referrals.[16]

3.2. Dialysis and transplant centers

As a key piece of the KT work-up, it is fundamental that dialysis centers are efficient and benefit the patients' health. However, it was apparent that other factors, namely of a financial capacity, are frequently very impactful in this continuum. It was observed on several studies that a lower percentage of patients treated at all for-profit facilities (vs all nonprofit facilities) received a LDKT or a deceased donor kidney transplant.[46,34] Additionally, when compared to nonprofit chain facilities, patients from for-profit chain facilities were 13% less likely to be waitlisted and large chains compared with mid and small chains were 8% less likely to place patients on the waiting list for KT.[47] The differences between for-profit and nonprofit dialysis centers were also evident when analyzing the time spent on KT education, having been shown that healthcare professionals working at for-profit centers were less likely to spend more than 20 minutes on KT education, involve the patient's family, educate patients about KT more than once, report that their patients initiated KT discussions, or consider their patients eligible for KT, in a way that patients at these types of centers were significantly more likely to be unassessed.[16,45] Moreover, a study found that an additional transplant center for every 10 000 ESKD patients increased the facility-level standardized transplant ratio (STR) by 5.3%, making the number of transplant centers in each region the most important network-level aspect associated with lower STR.[34]

How to overcome these barriers

1. Patient recommendations

1.1. Socioeconomic

There are numerous steps that can be taken to tackle the economic barriers to KT, like supplying more content concerning financial resources, namely about medication discount programs and

insurance options, providing and advocating for financial support with hospital financial assistance plans, non-governmental funding schemes for the communities, lobbying for universal healthcare coverage, which is essential for equitable access to transplant.[4,3] Additionally, being prepared can help to come up with solutions, so information regarding fund-raising and other financial preparedness mechanisms should be encouraged.[4] The aforementioned loss of incomes, be it relative to recipients or donors, can be attenuated by increasing the efficiency of clinic visits for ESKD care or living donor evaluation. For example, extending clinic schedules, investing in fast-track laboratory and pharmacy can help with this. Social workers can play an important part in creating a connection between caregiver and donor employers to potentially arrange paid medical leave agreements.[4] A study remarked on how several Asian countries have devised means to compensate live organ donors for the nonmedical expenses sustained.[26] Overall, there is consensus that the donor evaluation process should be financially neutral, and that there could be countless small changes easily implemented that would help progress in this path and turn it into a more manageable and less daunting endeavor.[20] As stated by Portuguese law, in accordance with the European directive n.º 2010/53/UE, the principle of financial neutrality applies to organ donation.[48] Thereby, there should not be economic losses to donors by the end of the KT process, which means providing potential donors with extra funds to cover travel costs or lost salaries.

1.2. Race and ethnicity

Although the Portuguese reality appears to escape this particular matter, the possibility of a yet unstudied referral partiality cannot be excluded. Moreover, it is important to recognize the potential weight of this issue in other regions of the world and to act accordingly in order to eliminate the preexisting racial bias. In a study by Patzer et al., the disparities observed in evaluation completion between white and black patients were lessened after educational intervention, which corroborates the importance of addressing these barriers.[49] The difficulties many communities face due to a lack of understanding of the language can be addressed by creating educational resources and classes taught in different idioms.[3] It is generally accepted that education must be provided based on the listener, which in these cases can mean taking into account their cultural individualities and beliefs and developing clear, appropriate and coordinated pathways to KT.[5,3] From a financial standpoint, creating uniform insurance programs may have the potential to ameliorate gaps in care between racial/ethnic groups in certain healthcare settings.[15]

1.3. Attitude and mindset

To remove the fear factor from the equation is to improve KT rates and ultimately the success of ESKD patients' outcomes, so stressing that organ donation surgery is safe is crucial. In order to achieve this, investing in patient literacy must be a priority and healthy and open communication amidst society is fundamental. Organ donation as a treatment possibility should be widespread and regarded as an invaluable act of generosity, while also encompassing extremely low individual-risk rates. On average, the risk of kidney failure 15 years after donation is less than 1%. Although risk among donors is higher than among healthy nondonors, it is still lower than among the general population. Regarding the surgery itself, the mortality rate within 90 days of donation is 0.03% and less than 3% of all donors experience major perioperative complications.[50] Besides that, qualms regarding long-term physical disability after organ donation need to be discussed with potential donors and their respective families, making sure all doubts are addressed.[4] It has been proven that the individuals who understood that KT improves quality of life were 5 times more likely to be willing to undergo a KT compared with those who answered incorrectly or did not know. This shines a light on the way individual perceptions on the quality of life this treatment can bring (compared with dialysis) may play a major role in patient's decision to pursue KT and why it is so important to clarify these benefits.[29] Clear discussions to quench concerns and misconceptions from an early stage of KT work-up are fundamental to strengthen patients' trust in the process and therefore, its success.[41]

1.4. Geographical

The advances of science and technology nowadays allow the offering of online learning options for those who have more difficulties getting to the centers.[3] Another strategy to overcome distance as a barrier consists on creating a contact system via telephone or email so as to maintain the patients' engagement in the proceedings. To this end, community healthcare providers must be actively involved in the monitorization of these patients' course and general well-being.[4] Nowadays, digital platforms have the potential to resolve a massive portion of inaccessibility related problems. It is critical to invest in innovative ways to enhance medicine through technology and to use it in favor of more equitable and smoother patient management strategies.

1.5. Donor and family

The support of the families and donors is key to the success of the KT treatment strategy. As such, providing general transplant education geared specifically toward families and friends, as well as delivering more living donor transplant information for patients and support persons can be a very impactful approach to this barrier.[3] Marlow et al. also explored the potential role of a patient navigator, as someone to accompany the potential KT recipient along the process and to support them every step of the way. Such a strategy could have a tremendous influence in promoting positive coping skills and even in facilitating behaviors for seeking living donors.[51]

1.6. Literacy

Considering that knowledge was unanimously presented as a fundamental pillar of the success of the KT work-up, investing in this aspect can have an immeasurable impact on the outcomes of these patients, particularly in minority groups.[49] An understanding of the process as a whole, from how to get waitlisted to post-transplant care, as well as the benefits it entails, could be extremely beneficial to all parties involved.[3,36,44] It has been witnessed with other chronic medical conditions that transplant education effectiveness declines over time, which can warrant the need to establish more frequent and structured educational sessions throughout evaluation, waitlist, and post-transplant periods, as well as continuously reviewing data, so as to reinforce the benefits of LDKT.[18,30] These discussions should always be started as early as possible, in a very direct manner, aiming to demystify the treatments while still tackling the consequences of failing to prepare well in advance.[36] Ultimately, these debates should be prioritizing the motto “transplant first”.[21] Educating young people and getting them engaged in these matters was understood as a way to enhance public awareness for LDKT. Targeting these demographics could mean starting to approach KT in elementary and secondary school curricula and encouraging workshops and other actions, thus raising innovative, forward-thinking individuals who will one day become potential organ donors and recipients.[20] When comparing urban versus rural groups, while the former discussed approaches to increase the donor pool, the latter suggested limiting the eligibility and thus decreasing the recipient pool as an additional scheme to improve transplant rates. Additionally, rural nephrologists mentioned the need for increased collaboration between nephrologists and the transplant center, as well as assistance with finances.[27]

Formulating culturally acceptable and personalized awareness programs within the community would lead to a greater acceptance of the diagnosis and willingness to receive ESKD treatment

among extended family members.[4,51,15,36] It has also been shown to be perceived as useful by both patients and healthcare workers to provide a support person who has gone through a similar experience, and who can be regarded as a peer mentor or navigator, as these individuals will more likely influence a potential kidney recipient and their family.[4,3,21,20,38] It was remarkable to observe how there was a general concordance about the need for the involvement of a multidisciplinary team, comprised of doctors, nurses, social workers, psychologists, nutritionists and pharmacists, to ensure the functioning of this complex journey.[3,18] A study dwelled on the difficulty reported by patients to ask someone to be a donor, and they expressed a wish to have formalized resources to more easily start this kind of discussions.[20] The advances of technology nowadays allow for new strategies to emerge, like using text message reminders, social media and/or patient portals, creating video classes instead of written materials to make it easier and more accessible to everyone, ultimately leading to a bigger interest in KT as a treatment choice.[3,21,29,31] As suggested by another study, current transplantation patients sharing their experiences with and information about the transplantation procedure via personal messages with the current potential organ recipients can significantly improve their interest in this treatment option.[40] It was advocated that it would be beneficial to have a centralized neutral source of information, so as to prevent data from being lost in the variety of resources and creating confusion and more stress.[20,49] This could be executed in the form of a website containing useful statistics and information, transplanted patients' testimonies, and contacts for transplant centers.

2. Healthcare professionals and providers recommendations

2.1. Literacy

Investing in educating all healthcare professionals in the context of KT is a key step to ensure the triumph of this treatment. Pais et al. debated the possibility of international transplant and nephrology organizations focusing on advocating for KT as a primary mission.[4] Besides the more technical aspects of this matter, it was suggested that transplant teams could enhance their own cultural competency to become better educated about the reasons why patients may take longer to complete the evaluation.[38] This could turn out to be extremely impactful in transplant rates.

2.2. Communication and doctor-patient relationship

There are a number of ways to improve doctor-patient communication. It is known that early referral has a positive impact on time allocated to look for potential donors and wait time acquisition for preemptive transplants, so an early introduction to transplant education with focus on prevention should be encouraged, along with access to information and support.[3,7,51,52] Stimulating discussions about KT among healthcare professionals is key to facilitating their own future contacts with patients.[18] Additionally, this investment in staff education should not be limited to doctors and nurses, having been proven that social worker interventions yielded higher rates of LDKT discussions and pursuit in patients with CKD compared to usual care.[52] The importance of having a "cheerleader", someone in the medical staff who advocates for and encourages KT and who communicates in an empathetic, open and informative way was deemed essential in navigating the pathway to this treatment.[42] In a study involving 906 nephrologists, the majority of providers spent less time on KT education than they believed to be ideal and those who spent more than 20 minutes on KT education covered more topics, had more one on one conversations, were more likely to involve the patient's family and were more likely to initiate KT education early during CKD stage 4.[45] These findings help to further elucidate to the potential impact of early and adequate debates about KT between patients and healthcare providers.

2.3. Attitude and mindset

Changing the biases and misconceptions about KT is intrinsically linked with appropriate and timely KT education, being important to target healthcare professionals involved in every step of the work-up. To put this into practice, transplant teams need to receive training in order to create more awareness of patients' cultural differences and to approach each individual with respect and care when it comes to helping them complete the evaluation process.[38]

2.4. Resources

Increasing support for patients after classes can be extremely helpful and a way of maximizing their time.[3] One of the main concerns mentioned by patients was the perceived lack of support during the work-up. In the same study, all providers agreed that it was essential to reduce the burden of learning and follow-up on patients who are overwhelmed and need additional support from their whole care team.[3] In many cases, there is a poor distribution of human resources or even an actual insufficiency of staff members, which in itself is an additional barrier, and it is

important to allocate enough people to focus on transplant education, in order to improve access to KT.[46,7] The personalization of the approach is crucial because each patient needs more support in different steps of the process and, as such, increasing contact with patients who are identified as at risk by transplant staff to ensure that patients follow through on necessary testing and complete the evaluation could represent a key action. Furthermore, staff could facilitate scheduling of appointments or contact third-party clinicians to ensure patients' timely completion of these proceedings.[38]

3. System recommendations

3.1. Referral

To make the referral process easier would certainly contribute to an increase in KT interest and completion rates. Determining the suitability of a donor for KT is often a long, albeit necessary, process which leads to deteriorating conditions of those waiting for transplantation, and so it is crucial to come up with strategies to shorten this work-up.[20] Similarly to what was suggested about education, using technology to create innovative mobile applications could make a real difference when to comes to time and resources spent orienting a patient.[4] A study by Farouk et al. implemented various changes in the system, such as adding a column to the clinical process with each patient's last estimated glomerular filtration rate (eGFR), creating a list of all the patients with a low eGFR scheduled to be seen each day as a reminder to discuss KT before the start of each session, having the contact information for a KT clinic liaison to whom referral data could be directly sent and implementing annual education sessions to discuss the importance of timely KT referral. After executing all of these alterations, KT referrals increased significantly.[1] The same study defended that some of the strengths of the quality improvement intervention include simplicity, scalability, and generalizability for application to diverse nephrology ambulatory settings across electronic health record vendors.[1] These characteristics are essential in any meaningful change we want to implement at a large scale.

Another study exposed a general opinion by the nephrologists involved that the focus should be on establishing guidelines at the provincial level to streamline the referral process, since without these guidelines, the potential for early discussions about LDKT is curtailed.[18] It was observed a perceived necessity of team work between healthcare professionals, to improve understanding about the referral process itself, to perform early psychological screenings and even to

coordinate all of the obligatory evaluation testing in one place over a shorter time period so as to streamline the navigation of the patients across the required proceedings.[40,38]

Medicine and society: from theory to practice

Having recognized the lack of high quality, efficient information about KT and all it entails, as well as the difficulty it sometimes represents to discuss it as a treatment option in a clinical environment, it made sense to try to create something that could act as a concrete step in the right direction. As such, with the invaluable collaboration of Gonçalo Oliveira, a Multimedia student eager to make a difference, we developed a website (www.transplanterenal.icbas.up.pt) with the aim to create an easily accessible way to educate the population about kidney transplantation, with accurate data explained in a way anyone - from patients to their families and potential donors - could understand it. The website provides, among other things, information about what it takes to receive a KT, the requirements to become a donor, some useful contacts and current statistics, and even testimonies from previous patients. The ultimate goal when designing this modern tool was to improve access to KT, namely preemptive LDKT, thus tackling one of the main barriers discussed in this work, and increasing transplant rates, so as to move towards achieving the potential benefits of investing in this choice of treatment for patients with ESKD.

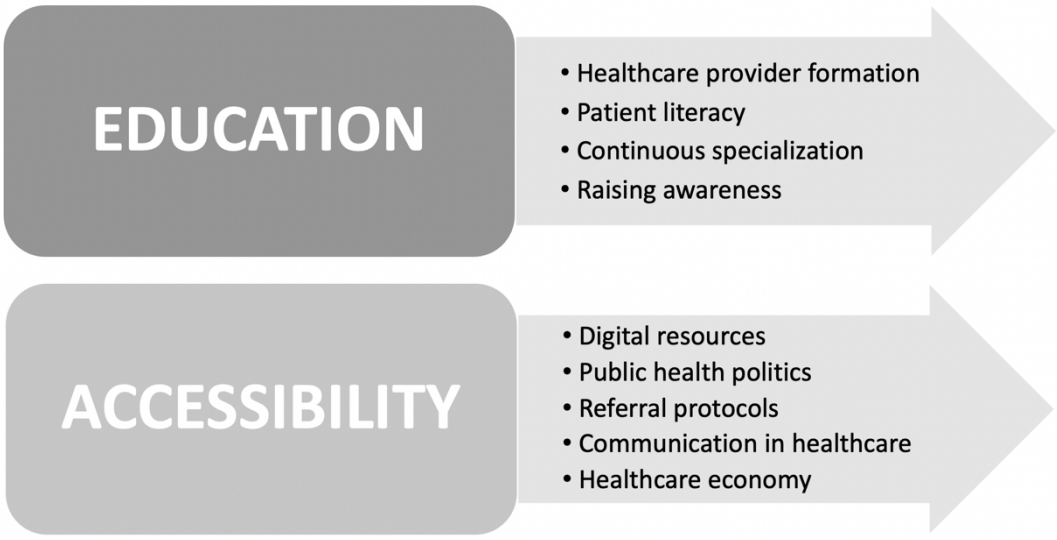

Figure 5 – Plan of action and process of intervention

Conclusion

End stage kidney disease can be overwhelming and patients frequently present with psychosocial problems, due to the intrusive nature of both the chronic pathology itself and in many cases the necessary renal replacement therapy. This often leads to encumberments in various aspects of life and can ultimately lead to worse post-KT outcomes.[53] Contrary to what might be thought true, patients prefer to start this discussion at an earlier phase of their disease, thus having more time to learn about transplantation, finding a living donor, completing the required evaluation steps and eventually getting on a KT waitlist.[5] Additionally, from the donor standpoint, the quality of life is at least equal to that of the general population, and often returns to pre-donation levels after the procedure.[32]

Recognizing the existing barriers associated with KT is the first step on a long road to their resolution. As such, it is vital that patients and their families get the opportunity to consider KT as a potential treatment in a timely manner, procuring education through reliable, culturally and demographically conscient sources, using simple and straight-forward language. In addition, it is of extreme importance that they have healthy, communicative relationships with their healthcare providers and, whenever possible, multidisciplinary teams, in which they feel the safety and confidence to inquire and explore this option realistically. Moreover, since the beginning of the current COVID-19 pandemic, transplantation rates have already started to plummet and there will undoubtedly be additional consequences, such as higher susceptibility to post-surgery complications, or a significant lack of resources, human or otherwise. Although it is still early to comprehend the full extent of that impact, it is, in a way, a potential new barrier that must be kept in mind if it is to be successfully tackled in the short-term.[54]

It is our hope that, through this work, we have made a positive and meaningful contribution to the ongoing efforts of creating a future where KT is the first line of treatment for ESKD and where patients achieve higher survival rates and quality of life, reaching the best possible outcomes.

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