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***Retrospective Cohort Study***

**Preemptive living donor kidney transplantation: Access, fate and review of the status in Egypt**

Gadelkareem RA *et al.* Preemptive access to kidney transplantation

**Abstract**

**BACKGROUND**

Preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease.

**AIM**

To assess the rate of PLDKT among patients accessing kidney transplantation (KT) in our center and review the status of PLDKT in Egypt.

**METHODS**

We performed a retrospective review of the patients who accessed KT in our center during November 2015–November 2021. In addition, the PLDKT status in Egypt was reviewed relative to the literature.

**RESULTS**

Of 304 patients accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were  $31.7 \pm 13$  years and  $12.8 \pm 3.5$  mL/min/1.73 m<sup>2</sup>, respectively. Fifty-nine patients had KT, including 3 PLDKTs only (5.1% of the total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to

receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (21.4%). In multivariate analysis, known primary kidney disease ( $P = 0.002$ ), patient age ( $P = 0.031$ ) and gender ( $P = 0.001$ ) were independent predictors of achievement of KT in our center. However, PAKT was not significantly ( $P = 0.065$ ) associated with the achievement of KT. Review of the literature revealed lower rates of PLDKT in Egypt than those in the literature.

## CONCLUSION

Patient age, gender, and primary kidney disease are independent predictors of achieving living donor KT. Despite its non-significant effect, PAKT may enhance the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

**Key Words:** Access to kidney transplantation; Donor regression; Kidney transplantation; Living donors; Preemptive kidney transplantation; Transplantation

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**Core Tip:** Patients with preemptive access to kidney transplantation (PAKT) may have significant differences from those with conventional access to kidney transplantation, warranting more evaluation and studying. In the current study, the known primary kidney disease was an independent factor of achievement of living donor kidney transplantation (LDKT). In addition, the older age and female gender were independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of living donors and patient regression on starting dialysis may prevent the achievement of preemptive LDKT (PLDKT) in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature

review may refer to that PLDKT has comparable outcomes to the conventional LDKT. Hence, PLDKT is recommended as the first choice for each candidate patient. In Egypt, the rate of PLDKT is still lower than the reported rates from other countries, warranting implementation of effective strategies to promote PLDKT.

## **INTRODUCTION**

Preemptive kidney transplantation (PKT) is defined as receiving kidney transplantation (KT) before <sup>1</sup>initiation of maintenance dialysis in patients with end-stage renal disease (ESRD). This definition may vary from a KT program to another, where patients who receive dialysis sessions sporadically or as conditioning pretransplantation sessions for no more than one week may be included in this definition<sup>[1-6]</sup>. The evolution of PKT was more than 30 years ago<sup>[7]</sup>, where it passed through an insidious course and gained variably insufficient interests among the physicians and surgeons in KT community<sup>[1,5]</sup>. Many initiatives and programs have been triggered to promote PKT, especially in the sector of living donor kidney transplantation (LDKT). These initiatives promote the living kidney donation (LKD) programs as the most effective contributor to PKT<sup>[4-7]</sup>. PKT is a time-based KT strategy controlled by setting the timing of KT surgery at a point just before the start of regular dialysis as possible as can. This philosophy represents the natural course of management of most of diseases. However, it has generated debates along the different axes of KT, such as the proposed lead-time bias effect on the outcomes of PKT<sup>[8]</sup>. Incidence of PKT has improved gradually from 2% in its early years to 6%-7% in the last years. Most cases come from LDKT programs, where it may reach up to 34% in some countries that adopt LDKT programs<sup>[6,9]</sup>. The latter percentage refers to the fundamental role of LD in the promotion of PKT strategy<sup>[10]</sup>. Preemptive access to KT (PAKT) and wait-listing are other effective contributors to PKT. Hence, they are fundamental issues in PKT literature<sup>[1,11]</sup>. However, they have mostly been ignored in researches coming from Egypt, where only LDKT is performed in adults<sup>[9,12-14]</sup> and pediatrics<sup>[15-17]</sup>. We aimed to assess the percentage of patients with PAKT and their fate, regarding the receipt of preemptive LDKT (PLDKT).

## **MATERIALS AND METHODS**

### ***Study design***

A retrospective review of the electronic and manual records of patients with ESRD who sought LDKT in our center during November 2015–November 2021. The study included both patients with PAKT which was defined as the presentation of a patient with CKD-stage 4 or 5 for KT prior to the start regular dialysis and those with a conventional access to KT (CAKT). The exclusion criterion was patients who refused KT before starting the preparation for LDKT (Figure 1). The relevant demographic characteristics of the patients and potential donors, including age, gender, and relatedness to the potential donors were reviewed. Also, the clinical data, including the primary kidney disease, estimated glomerular filtration rate (eGFR) at presentation, outcomes of preparation to KT, causes of deferring LDKT, and fate of the patients and donors were studied. We used the CKD-EPI creatinine equation to estimate eGFR for patients with PAKT<sup>[18]</sup>.

Also, a review of the literature was performed for assessment of PLDKT in KT researches coming from Egypt. The KT center volume, pre-KT characteristics, and percentages and outcomes of PLDKT were reviewed. Furthermore, the literature was reviewed for the incidence of PLDKT in studies from other countries and large-volume KT registries.

This study was conducted as a topic in a KT research project about the outcomes of LDKT at our center. The institutional review board number is 17200148/2017.

### ***Statistical analysis***

It was performed with EasyMedStat (version 3.21.4; [www.easymedstat.com](http://www.easymedstat.com)). Continuous variables were presented as mean  $\pm$  standard deviation (SD) and range. However, categorical variables were presented as the number and percentage of each category. We created 2 groups (PAKT and CAKT) according to the status of dialysis at the time of access to transplantation. Normality and heteroskedasticity of continuous

data were assessed with White test (or with Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with unpaired Student *t*-test, Welch *t*-test or Mann-Whitney *U* test according to data distribution. Categorical outcomes were compared with chi-squared or Fisher's exact test accordingly. A multivariate logistic regression was performed to assess the factors contributing to achievement of KT in our center. Data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. A *P* value < 0.05 was considered statistically significant.

## **RESULTS**

Between November 2015 and November 2021, 325 patients attended our center for KT. Twenty-one (6.5%) patients changed their mind or were not serious in accessing KT. The remaining 304 patients were differentiated into PAKT and CAKT groups (Figure 1). The former group included 32 patients (10.5%) who were not on dialysis at the time of access to KT and the latter group included 272 (89.5%) patients with a mean (range) duration of hemodialysis of  $6.3 \pm 10.5$  (0.5–108) m. Both groups were compared for the demographic and clinical characteristics (Table 1). Follow-up after regression or exclusion decision varied from 3 mo to 6 years.

In the group of PAKT, 29 patients (90.6%) failed to receive PLDKT due to donor original unavailability (25%), exclusion (28.6%), or regression (3.6%), or patient's regression from KT when started regular dialysis (39.3%) (Table 1). Hence, PLDKT was carried out in three patients only, representing 5.1% of the total KTs and 9.4% of patients with PAKT. One patient of these three patients died from complications of the corona virus disease-2019 (COVID-19), 6 mo after KT. The other two patients were still living with a functioning graft for 68 and 12 mo at the time of writing of this article (Table 2). The detailed characteristics of patients with PAKT are presented as individual patients (Table 2). The mean (range) age was  $31.7 \pm 12.9$  (13–60) years. Most of patients present at stage 5 of CKD. The mean (range) for serum creatinine level and eGFR was  $6 \pm 1.6$  (3.2–9.8) mg/dL and  $12.8 \pm 4.8$  (7–28) mL/min/1.73 m<sup>2</sup>, respectively.

In the current patients, the total number of patients who had been transplanted at our center (59 patients) or at other centers (29 patients) was 88 (28.9%) patients. In a comparison between the patients who achieved (59 patients) and those who failed to achieve (245 patients) LDKT in our center, there were significant differences in the age ( $P = 0.034$ ), gender ( $P < 0.001$ ), primary kidney disease ( $P = 0.008$ ), number of potential donors ( $P = 0.003$ ) and acceptance/exclusion rate of evaluated donors ( $P < 0.001$ ) per patient (Table 3).

In multivariate analysis, known primary kidney disease ( $P = 0.002$ ) was associated with higher rates of achievement of KT in our center. In addition, female gender ( $P = 0.001$ ) and older patients ( $P = 0.031$ ) were significantly associated with lower rates of achievement of KT in our center. However, PAKT ( $P = 0.065$ ) and multiple potential donors ( $P = 0.529$ ) were not significantly associated with the rate of achievement of KT in our center (Table 4).

Review of the literature for PLDKT in researches coming from Egypt revealed that only seven articles addressed PLDKT (Table 5). These articles came from four academic centers only, including 6 original researches and one opinion article. The percentage of PLDKT varied between 6.4% in adults and 23% in pediatrics. No articles addressed the PAKT or wait-listing. The reported patient and graft survival rates were similar to those of the conventional LDKT (CLDKT) in the literature.

In addition, review of the English literature for the incidence of PLDKT in other countries revealed higher rates than those from Egypt. However, they reported on PKT from both LDs and deceased donors. There were higher rates of PKT in patients received LDKT than in those who received deceased donor KT (Table 6). In 1987, Migliori *et al*<sup>[19]</sup> were the first to evaluate the effects and outcomes of PKT in a large study from the United States of America (USA), reporting a PKT rate of 7.6%. They were followed by two European studies with variable rates<sup>[20,21]</sup>. Then, 5 studies presented data from registries from USA and Canada and reported higher PKT rates up to 21% of the total KTs and more than 29% of LDKTs<sup>[22-26]</sup>. In addition, 3 studies from Japan, Australia, and Korea presented PLDKT rates up to 22% in patients receiving

LDKT<sup>[27-29]</sup>. In 2009, 2 studies of mixed LD and deceased donor KT showed higher rates of PLDKT about 39%<sup>[30,31]</sup>. Between 2011 and 2016, 5 studies of pediatric and adult KT showed similar rates<sup>[2,32-35]</sup>. Through the last 3 years, many studies reported high PLDKT rates more than 34% of LDKTs<sup>[36-38]</sup>.

## **DISCUSSION**

We addressed the topic of PKT in Egypt, because there is a question that whether the reported incidence of PLDKT correlates with the international values. Because this question may entail addressing the barriers and the promoting strategies of PLDKT, we performed this retrospective study to assess the outcomes of patients accessed KT at our center. In addition, review of PLDKT publications coming from Egypt was carried out in the context of the international literature, either as specific researches for PLDKT within LDKT cohorts or as combined LDKT and deceased donor KT researches. There is a significant variability in the rates of PKT all over the world. In most of studies, the proportions of PLDKT are higher than those of PKT in deceased donor KT. Most of these studies showed significantly higher incidences in adults and pediatrics. However, because the total percentages of LDKT are lower than those of KT from deceased donors, the frequency of PKT from deceased donors represented the majority of cases of PKT in some studies. However, relative to the total numbers of donor source, the percentages of PLDKT of total LDKTs are steadily higher than those of PKT from deceased donors of total KT from deceased donors.

In Egypt, there is an obvious lack of research on PKT represented by the small number of studies that was found in this topic<sup>[12-16]</sup>. These studies were mostly retrospective and presented as few centers' experiences or small cohorts of patients. Hence, the volume of research on PLDKT is relatively small, referring to that PKT does not seem to be in the focus of research. PLDKT has just been mentioned as a category within the total cohorts of KT from centers with well-established KT programs<sup>[13,17]</sup>. On the other hand, a few studies were specifically conducted to study PLDKT outcomes in comparison to CLDKT<sup>[9,12]</sup>. This may be a part of the lack in the international literature



which has a slowly propagating body of research on PKT<sup>[33,38]</sup>. Currently, the literature refers to some sort of practical negligence of PKT in many forms, including disparities in access to PKT among the waitlisted patients. In a study from the USA, relative to the rates of White (38%) and Black (31%) patients on the waiting list, there was a significant difference between the rates of White (65%) and Black (17%) patients who had PKT in 2019<sup>[1]</sup>. Also, there is a substantially lower rates of PAKT among certain demographic groups that may face challenges in engaging with complex health care systems. Patients with low levels of education and those with physician-dependent choice of KT are other groups with disparities in the access to PKT. Inequities in access to KT require substantial efforts and multiple remedies<sup>[1]</sup>. Unfortunately, there is no studies have been conducted in Egypt to measure the rates of access to PLDKT so far. The current study showed that PAKT represented only 10.5% of patients who were referred to KT in our center.

From the reviewed literature, the reported incidence of PLDKT in different Egyptian KT centers was relatively lower than the international values (Tables 5 and 6). The range was 5%-6% of the total KTs that were performed in these centers<sup>[12,13]</sup>. However, the incidence was higher, when PLDKT was studied in a certain category of population such as pediatrics with low-body weight<sup>[16,17]</sup>. Similarly, the rate of PLDKT was 5.1% in the current study. However, these values are still significantly lower than the values reported in the literature (Table 6).

Patients with PAKT may have high education levels, payment resources, married status, residence near to KT centers, and younger age than those with CAKT. Unknown primary diseases and glomerulonephritis seemed to be the most common contributor primary kidney disease in adults<sup>[9,12,21]</sup>. Among pediatrics, reflux nephropathies, nephrotic syndromes, and congenital anomalies are the commonest primary diseases<sup>[15,16]</sup>. In addition, PLDKT patients had a lower likelihood of testing positive for hepatic viruses and receiving a blood transfusion than the CLDKT patients<sup>[12]</sup>. Out of 304 patients accessed LDKT in our center, only 32 patients had PAKT. In turn, only three patients succeeded to have PLDKT and they included two children and one adult

patient. They had congenital or hereditary diseases as primary causes of ESRD and the donors were unrelated donor in one case and mothers in the other two cases.

A large retrospective study from Mansoura Urology and Nephrology Center studied the course and outcomes of PLDKT and reported an incidence of 6.4%. In addition, it showed that there was only a significant difference in the percentages of patients who died with functioning grafts due to cardiovascular disorders and respiratory infections. The former cause was higher in PLDKT, while the latter was higher in CLDKT<sup>[12]</sup>. In a smaller prospective comparative study, we found that the incidence of acute graft rejection, significantly higher among early LDKT (ELDKT) patients than the PLDKT patients. However, the incidence of lymphoceles was significantly higher in PLDKT patients than that in patients receiving ELDKT<sup>[9]</sup>. In the current study, the rates of non-candidacy and death during preparation to KT were lower in patients with PAKT (0%) than those in patients with CAKT (10.7% and 35.7%, respectively). These rates may refer to that the patients in the former group were healthier than those in the latter group.

The previous characteristic may be a surrogate of the concerns raised about the proposed effect of the lead-time bias on the advantaged outcomes of PLDKT. However, there may be a different perspective, regarding this postulation. We have hypothesized that the proposed effects are a mere component of the strategy of PKT. This could simply be explained by considering the PKT and non-PKT as consecutive rather than parallel processes along the course of ESRD. PKT is an early step in the management of ESRD. So, the time factor should be considered as a promotor rather than a confounder to PKT process. On the other hand, the idea of removal of the lead-time bias means discarding the spirit of the entire process of PKT<sup>[8]</sup>. The best support of this perspective is studying the outcomes of KT relative to the time-point at which KT is performed. Goldfarb *et al*<sup>[39]</sup> designed a study based on this idea and it revealed significant survival advantages when KT was performed before 180 days of dialysis.

Internationally, many articles have been addressed the barriers of PKT. The unavailability of a suitable, willing donor is a major confounder to PLDKT<sup>[40-42]</sup>. In

accordance, the current results revealed that the younger age, male gender and known primary kidney disease of patients accessing KT in our center were independent predictors of achievement of KT after preparation. However, the dialysis status (PAKT *vs* CAKT), number of potential donors and their acceptance/exclusion rates were not significantly associated with the achievement of KT. The non-significant effect of PAKT may be attributed to the delayed access of the patients with ESRD. Most of our patients with PAKT were in stage 5 CKD and a mean eGFR of  $12.8 \pm 4.8$  mL/min/1.73 m<sup>2</sup>, when they firstly presented to our clinic. This value of eGFR is comparable to the reported values that allow successful PLDKT<sup>[33,43]</sup>, but these patients were not prepared or waitlisted before presentation to the KT unit. Hence, they needed long duration for preparation, which might be, with donor exclusion, the causes of missing the chance of PLDKT. In addition, the delayed access might be attributed to absence of a well-configured waitlisting programs in our country to refer and prepare patients at the suitable stages of ESRD. On the other hand, there are many underlying primary renal diseases may predispose to a very late presentation of a significant proportion of patients, such as the status of pending dialysis at first discovery of their ESRD<sup>[44]</sup>.

Problems of the availability of well-integrated healthcare system that facilitates early detection of CKD patients and timely referral to KT centers. Paradoxically and despite the observable social fear of ESRD which may progress up to a disease phobia in developing countries<sup>[45]</sup>, there are many patient-related factors that influence early diagnosis and management of CKD patients such as the cultural and health illiteracies<sup>[44]</sup>. As a developing country, the healthcare authorities in Egypt have a large burden of challenges which seem hard to be overcome due to factors such as low per-capita income and slowly progressing corrections of the healthcare systems<sup>[15]</sup>. Also, the ethical problems that have been raised about the KT practice in Egypt represent another major confounder to correction<sup>[46]</sup>. However, the recent policies in the Egyptian national healthcare system seem to be promising as a mass modification to overcome these problems, including the new national health insurance coverage and national KT programs.

Limitations of the current study included the small number of patients who had PLDKT that empowered the inability to perform statistical analyses for the independent factors of failure of most patients with PAKT to achieve PLDKT. However, it is the first study from Egypt that addressed this very viable topic at a national review basis. Hence, it may unmask the vague situation of PLDKT in Egypt by configuring a step forward in building more integrated KT systems.

On the bases of relevant literature review, we may recommend implementation of different strategies to promote PLDKT in Egypt. Encouragement of LKD is the main strategy that should be extensively studied, because our national KT program is still until now devoted to LDKT only. Minimally-invasive approaches such as laparoscopic living donor nephrectomy should be introduced to all centers of KT. Also, the regulations of LKD should be organized under a well-configured national donation program, including donor exchange programs. Furthermore, promotion of healthcare facilities of early detection of CKD and education of the contributors of PLDKT process are crucial strategies for this topic. The latter includes the education of the physicians (representing the moderator of the process), ESRD patients (representing the key start of the process), and publics (representing the source of the potential donors) about the benefits of PKT.

## **CONCLUSION**

Patients with PAKT may have significant differences from those with CAKT, regarding the age, gender, primary kidney disease, number of potential donors at presentation to KT center. The primary kidney disease diagnosis is an independent factor of achievement of LDKT. In addition, the older age and female gender are independent predictors of non-achievement of LDKT. On the other hand, unavailability, regression, and exclusion of living donors and patient regression when reach dialysis may hinder the achievement of PLDKT in patients with PAKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The current literature review may refer to that PLDKT has comparable outcomes with CLDKT. Hence, PLDKT is recommended as

the first choice for each candidate patient. In Egypt, PLDKT may have similar barriers to those presented elsewhere in the literature, including the shortage of donors, delayed presentation of patients and socioeconomic factors. As a result, the rate of PLDKT is still low in Egypt, warranting implementation of many strategies to promote PLDKT. They include encouraging LKD, introduction of minimally-invasive living donor nephrectomy, configuring a specific program for LKD, and education of the physicians, patients and publics about the benefits of PKT.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Despite its low rates, preemptive living donor kidney transplantation (PLDKT) is recommended as the optimal treatment for end-stage renal disease. However, its rate is still lower than the expected rates worldwide.

### ***Research motivation***

Promotion of the rate of PLDKT seems to be a modifiable variable for improvement of the total outcomes of kidney transplantation (KT).

### ***Research objectives***

To assess the rate of achievement of PLDKT among patients accessing KT in our center and to review the status of PLDKT in Egypt in the context of the literature.

### ***Research methods***

We performed a retrospective review of the records of patients who accessed KT in our center during November 2015–November 2021. The demographic and clinical characteristics of the patients and their potential donors were reviewed. Also, the literature review was performed for PLDKT status in Egypt.

### ***Research results***

Of 304 patients accessed KT, 32 patients (10.5%) had preemptive access to KT (PAKT). The means of age and estimated glomerular filtration rate were  $31.7 \pm 13$  years and  $12.8 \pm 3.5$  mL/min/1.73 m<sup>2</sup>, respectively. Fifty-nine patients had KT, including 3 PLDKTs only (5.1% of the total KTs and 9.4% of PAKT). Twenty-nine patients (90.6%) failed to receive PLDKT due to donor unavailability (25%), exclusion (28.6%), regression from donation (3.6%), and patient regression on starting dialysis (21.4%). In multivariate analysis, known primary kidney disease ( $P = 0.002$ ), patient age ( $P = 0.031$ ) and gender ( $P = 0.001$ ) were independent predictors of achievement of KT in our center. However, PAKT was not significantly ( $P = 0.065$ ) associated with the achievement of KT. Review of the literature revealed lower rates of PLDKT in Egypt, including the current results, than the internationally reported rates.

#### ***Research conclusions***

Patient age, gender, and primary kidney disease are independent predictors of achieving LDKT. Despite its non-significant effect, PAKT may improve the low rates of PLDKT. The main causes of non-achievement of PLDKT were patient regression on starting regular dialysis and donor unavailability or exclusion.

#### ***Research perspectives***

Studying the factors that may promote the early access of ESRD patients to KT, it may improve the rates of PLDKT. This latter strategy may improve the whole outcomes of the process of KT, including avoidance of the inconveniences of dialysis and improvement of the graft and patient survival rates.

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