# Can pre-implantation biopsies predict renal allograft function in pediatric renal transplant recipients?

*Jameela A. Kari,* MD, FRCP, *Alison L. Ma,* MRCPCH, *Stephanie Dufek,* MD, *Ismail Mohamed,* FRCS, *Nizam Mamode,* MD, FRCS, *Neil J. Sebire,* MD, FRCPath, *Stephen D. Marks,* MD, FRCP.

## ABSTRACT

**الأهداف:** تحديد مدى فائدة خزعة الكلى ما قبل الزرع للتنبؤ بنتائج الكلى المزروعة.

**الطريقة:** دراسة مرجعية من مركز واحد تشمل مراجعة لجميع المرضى الذين خضعوا لخزعة الكلى قبل الزرع، من يناير 2003م حتى ديسمبر 2011م في مستشفى جريت أورموند ستريت للأطفال في لندن، المملكة المتحدة. اثنان وثلاثون (56%) ذكور من المرضى الذين تتراوح أعمارهم بين 1.5-16 (متوسط 10.2) سنة عند تلقيهم زراعة الكلى تم إدراجهم في الدراسة ومتابعتهم لمدة 33 (6-78) شهراً. وتمت مقارنة النتائج مع 33 طفل تلقوا زراعة كلي من غير خزع قبل الزراعة.

**النتائج:** نتائج الخزع أظهرت التغيرات النسيجية الغير مرضية والعادية في 13 مريضاً (41%)، تغيرات خفيفة مزمنة للأوعية الدموية في 8 أطفال (25%)، وضمور الأنابيب الكلوية في طفل واحد، تغييرات مزمنة معتدلة إلى شديدة في الأوعية لدى 3 أطفال، تغييرات خفيفة الى معتدلة في الأنابيب الكلوية في 6 أطفال وكانت الأنسجة غير كافية في طفل واحد. وقد لوحظ تأخر في عمل الكلي المزروعة في 3 مرضى: اثنان منهم كانت الخزع أظهرت تغييرات في الأوعية الدموية وواحد كانت التغيرات النسيجية طبيعية وعادية. فقد طفلين ذو تغييرات في الخزع الكلوية كلاهم المزروعة. كان معدل الترشيح الكبيبي المقدرة أقل في الأطفال الذين يعانون من تغيرات غير طبيعية في الخزع لكلوية، مقارنة مع تلك من غير تغيرات بعد 3 و6 أشهر. نتائج المجموعتين (الخزع الكلوية ومن غير خزع) نتائج متشابهة الى حد بعيد في مجمل الدراسة. كانت هناك حالة واحدة من تأخر في عمل الكلي في المجموعة التي لم تجري لهم خزع وخسر 4 أطفال من هذه المجموعة كلاهم بما فيهم لطفل الذي تأخرت عمل كليته المزروعة.

**الخاتمة:** الخزع ماقبل زرع الكلى قد يوفر معلومات أساسية هامة تؤثر على العلاج الطبي لاحقاً لمتلقي زرع الكلى من الأطفال.

**Objectives:** To determine the utility of pre-implantation renal biopsy (PIB) to predict renal allograft outcomes.

**Methods:** This is a retrospective review of all patients that underwent PIB from January 2003 to December 2011 at the Great Ormond Street Hospital for Children in London, United Kingdom. Thirty-two male patients (56%) aged 1.5-16 years (median: 10.2) at the time of transplantation were included in the study and followed-up for 33 (6-78) months. The results were compared with 33 controls.

**Results:** The PIB showed normal histopathological findings in 13 patients (41%), mild chronic vascular changes in 8 (25%), focal tubular atrophy in one, moderate to severe chronic vascular change in 3, mild to moderate acute tubular damage in 6, and tissue was inadequate in one subject. Delayed graft function (DGF) was observed in 3 patients; 2 with vascular changes in PIB, and one with normal histopathological findings. Two subjects with PIB changes lost their grafts. The estimated glomerular filtration rate at 3-, and 6-months post-transplantation was lower in children with abnormal PIB changes compared with those with normal PIB. There was one case of DGF in the control group, and 4 children lost their grafts including the one with DGF.

**Conclusion:** Pre-implantation renal biopsy can provide important baseline information of the graft with implications on subsequent medical treatment for pediatric renal transplant recipients.

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*From the Department of Pediatrics (Kari), Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia, and the Departments of Pediatric Nephrology (Ma, Dufek, Marks), Pediatric Pathology (Sebire), Great Ormond Street Hospital for Children NHS Foundation Trust, the Department of Transplant Surgery (Mohamed, Mamode), Guy's Hospital, Great Maze Pond, London, United Kingdom.*

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*Address correspondence and reprint request to: Dr. Stephen D. Marks, Department of Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH, England, United Kingdom. E-mail: stephen.marks@gosh.nhs.uk*

Pre-implantation or implantation biopsies (PIB) have been used in adult renal transplantation for the last 2 decades.[1] The PIB of the donor kidney was initially suggested by Gaber et al[2] in 1992 as they found that pathological changes correlated with subsequent renal allograft rejection and loss. They reported that the presence of polymorphonuclear (PMN) leucocytes marginating in the peritubular capillaries is related to the subsequent occurrence of cellular rejection, and an elevated mean glomerular PMN leucocyte count in conjunction with an elevated peritubular PMN leucocyte count was always associated with hyperacute rejection.[2] Many adult renal transplant recipients have PIB performed on a routine basis, or as part of clinical studies as it is believed that major histological injuries are the leading causes of long-term chronic allograft dysfunction.[3] This includes glomerular injury, vascular injury, and tubulointerstitial injury, such as interstitial fibrosis (IF), and tubular atrophy (TA).[1] Pre-implantation or implantation biopsies is particularly useful when using marginal kidneys from deceased donors (DD), such as donation after cardiac death (DCD) as it is more likely to show donor pathology, such as glomerulosclerosis (GS), IF, hypertensive vascular changes and TA, which predict a subsequent worse renal allograft survival.[1,4-6] It was reported that baseline biopsies with severe vascular disease correlated with delayed graft function (DGF), acute rejection episodes, and renal allograft dysfunction with increased serum creatinine levels at 18 months post-transplantation.[6] Eapen et al[7] reported that the percentage of acute rejections episode with normal PIB was 48% compared with 75% of patients with abnormal PIB. Furthermore, the quality of the donor organ at implantation was strongly predictive of subsequent renal histology in allografts functioning at 3 months.[8] The GS percentage is directly correlated to renal allograft survival, DGF, and primary non-function.[9] There is evidence that early transplant damage occurs in the tubulointerstitial compartment from pre-existing donor kidney injury and subsequent chronic damage, and renal allograft failure reflect accumulated previous injury.[10] There is a lack of studies in the pediatric populations regarding the use of PIB and its correlation with renal allograft function. In this study, we investigated the utility of PIB to predict early- and long-term renal allograft outcome in pediatric renal transplant recipients (PRTR).

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**Methods.** This is a retrospective review of all patients that underwent PIB from January 2003 to December 2011 at the Great Ormond Street Hospital for Children in London, United Kingdom. Inclusion criteria were children who had PIB, and at least 6 months of follow up. Exclusion criteria were only children with less than 6 months follow up. Data were collected from medical and electronic files. Demographic data, age at transplantation, follow up duration, evidence of DGF, results of PIB, and all subsequent renal biopsies were recorded. We collected additional donor data: living (LD) or DD, age, gender, previous health, human leucocyte antigen (HLA) mismatching, and cause of death in DD. We calculated the estimated glomerular filtration rate (eGFR) using the modified Schwartz formula[11,12] at 3 months, 6 months, and one year after transplantation, and annually thereafter. We studied the incidence of post transplantation urinary tract infection, and viral status of cytomegalovirus, Epstein-Barr virus, and BK virus. Immunosuppressive regimens were also recorded. All the biopsied kidneys were implanted into PRTR; there were no discarded organs. Informed patient consent was obtained from all caregivers of the study participants. Children were divided into 2 groups; normal and abnormal, according to PIB findings. Histopathological changes were graded into minor, moderate, and severe pre-existing chronic vascular changes, with additional (ischemic, glomerular, or tubulointerstitial) features described as appropriate. The DGF was defined as the requirement of dialysis within one week of renal transplantation. Pre-implantation biopsies were performed at the time of transplantation at the discretion of the transplant surgeon. The decision of undertaking PIB was under the preference of the operating transplant surgeon, and comparing with our control group showed that the studied cohorts were representative of our patient cohort in a single center renal transplantation programme. All transplants were carried out by the same transplant surgeon. All biopsied kidneys were transplanted, and none were turned down. We searched the medical databases, PubMed and MEDLINE to identify studies that were related to PIB. We compared the results with similar number of 33 children who did not have PIB, and were matched for age and gender, type of transplant, and timing with the study group. Ethical approval was not required for this study as it was approved by clinical lead of Pediatric Nephrology unit as part of service development within the unit. This study was carried out according to the principles of Helsinki Declaration.

Statistical analysis was performed using the Statistical Package for Social Sciences version 12 (SPSS Inc., Chicago, IL, USA). Data were expressed as median (range), or as percentages. Means were compared using Student's t-test, assuming equal variance used to compare between children with normal PIB and those with abnormal changes, and between the whole study group and the control group. Estimated GFR was expressed as mean ± standard deviation (SD). Chi squared test was used to compare percentages between the 2 groups. The percentage was calculated in the presence and absence group by Pearson's Chi-square test. The limit of statistical significance was set at $p<0.05$.

**Results.** Thirty-two patients were included in the study. There were no DCDs. Controls were matched for age, gender, type of transplant, and timing. None of the children received renal transplant from extended criteria DDs, defined as age of 60 years or above, or age 50-59 years with 2 of 3 of hypertension, plasma creatinine above 130 µmol/l, and intracranial hemorrhage. The PIB showed normal histopathological features in 13 subjects (41%), mild chronic vascular changes (such as, medial hypertrophy and bland intimal thickening) in 8 (25%), focal tubular atrophy in one (3%), moderate to severe chronic vascular change in 3 (9%), mild to moderate acute tubular damage (ATD) only (focal epithelial cell sloughing, tubular irregularity and/or vacuolation) in 6 (19%), and tissue was inadequate in one subject (3%). **Table 1** gives details of children with PIB and controls in the study. **Table 2** provides summary data on the outcome and transplant details according to PIB findings.

***Delayed graft function.*** The DGF was observed in 3 patients (9%); one with severe vascular changes in PIB, one with mild chronic vascular changes, and one with normal histopathological findings. In one of the 2 DGF cases with PIB changes, the patient lost her renal allograft after 8 months. She was 14-years old with Joubert syndrome, and received a kidney from a 50-year-old hypertensive donor after brain death (DBD). The PIB revealed mild chronic hypertensive-type vascular changes. Subsequently, she had 4 renal biopsies over 8 months before she had a transplant nephrectomy. All percutaneous renal transplant biopsies showed acute T cell mediated (cellular) rejection (ACR) superimposed on the pre-existing chronic vascular changes. Another child with evidence of chronic vascular change on PIB had severe DGF, which required hemodialysis for 10 days. His donor was a 44-year-old DBD with history of obesity and hypertension. His eGFR was 53 mls/min/1.73 $m^2$ one year after transplantation. One subject out of 13 (8%) with normal PIB had DGF, and required continuous veno-venous hemofiltration for 4 weeks. She received a DBD kidney from a 49-year-old lady with 2 HLA mismatches. Her eGFR at 3 months was 42 mls/min/1.73$m^2$, and 6 months after transplantation was 28 mls/min/1.73$m^2$.

**Table 1 -** Details of children with pre-implantation renal biopsy (PIB) and controls included in a study in the United Kingdom.

| Characteristics | PIB, n=32 | Controls, n=33 | *P*-value |
|---|---|---|---|
| Age, years | 10.2 (1.5 - 16) | 10 (1.5 - 16) | 0.18 |
| Gender, male | 56% | 58% | |
| Follow up duration, months | 33 (6 - 78) | 42 (12 - 72) | |
| Deceased donors | 56% | 52% | |
| Time period | January 2003 to December 2011 | April 2005 and May 2011 | |

**Table 2 -** Summary of outcome and transplant details according to histopathological features of the pre-implantation renal biopsy (PIB) included in a study in the United Kingdom.

| PIB | Normal, n=13 | Hispathological changes present, n=18* | *P*-value |
|---|---|---|---|
| Delayed graft function | 1 | 2 | 0.79 |
| Acute rejection | 2 | 7 | 0.154 |
| Graft loss | 0 | 2 | 0.239 |

*8 mild chronic vascular changes, 1 focal tubular atrophy, 3 moderate to severe chronic vascular changes, 6 with mild to moderate acute tubular changes

***Renal allograft loss.*** One subject with changes in PIB lost her renal allograft at 14 months post-transplantation. She was a 6-year-old girl with vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (VACTERL) syndrome who received renal transplant from a living unrelated donor (stepfather). Her PIB showed mild to moderate ATD only. There was a 3 HLA mismatch, however, her graft was functioning well one year post-transplantation with eGFR of 73 mls/min/1.73$m^2$. Thirteen months post-transplantation, she developed renal allograft dysfunction with elevated serum creatinine, and her renal transplant biopsy showed acute diffuse tubular damage. She had 2 further biopsies over the following 2 weeks, which showed hemorrhagic infarction with vascular changes and ACR, and the last biopsy showed ongoing tubular damage with Grade

IIB (vascular) T-cell mediated rejection. Histological examination of her graft nephrectomy confirmed severe ACR with infarction. The DGF was observed in one child from the control group; she was a 15-year-old girl who received a kidney from a 22-year-old DD with history of diabetes mellitus. She had several episodes of acute rejection with 7 renal biopsies over one year, which showed subsequently; acute cellular rejection, mild non-specific chronic changes, severe ATD with focal tubulitis, grade 2b acute T cell mediated rejection, grade 2b acute T cell mediated rejection, and the last biopsy showed infarction secondary to severe acute T cell mediated vascular rejection. She required transplant nephrectomy by the second year post-transplantation. There was renal allograft loss in another 3 children in the control group: a 13-year-old who received a kidney from a 25-year-old DD following drug overdose and brain hypoxia with one HLA mismatch. She required 7 renal biopsies over 7 years by which time, she lost her allograft, and required hemodialysis. The second child is a 4-year-old boy who received a kidney from a 46-year-old DD following intracranial hemorrhage with 3 HLA mismatch. His renal transplant biopsy showed chronic changes prior to him requiring hemodialysis by the fourth year post-transplantation. The third child was a 3-year-old girl who received an LD kidney from her 28-year-old father (2 HLA mismatches). Her percutaneous renal transplant biopsy showed chronic changes at 28 months after transplantation, and her eGFR was 14 mls/min/1.73m$^2$ after 4 years. Therefore, there was one case of DGF in the control group, and 4 children lost their grafts including the one with DGF. None of the children had early graft loss.

There was no difference between the 2 groups in the study cohort in the rate of acute rejection episodes (**Table 1**). Estimated GFR at 3-, and 6 months post-transplantation was lower in children with changes in PIB compared with those with normal PIB (**Table 3**). There was a significant difference in the eGFR between the PIB and control groups at 3 months (56.5 [19.5] versus 73.6 [19.4], and 6 months (60.4 [14.3] versus 78.07 [25.2]), $p$=0.001. However, there was no difference in the eGFR at subsequent annual comparisons up to 4 years post transplantation. There was no difference in the donor age between the 2 groups, however, there were 3 DBD with history of hypertension and vascular changes in the PIB group. The DGF was observed in 2 of them with renal allograft loss in one child. Data on DBD donor health were available in 10 of those with abnormal PIB: 3 hypertensive, 2 obese (one of whom was hypertensive), one with Trisomy 21, one atherosclerosis, and 4 were reported to have good health. Data on DBD donor health was available in 2 patients only with subsequent normal PIB results, and they were unremarkable.

**Table 3 -** Transplantation details of children with normal and abnormal pre-implantation biopsy included in a study in the United Kingdom.

| Characteristics | Normal, n=13 | Abnormal, n=18 | *P*-value |
|---|---|---|---|
| Follow up duration, months | 36 (14 - 78) | 28 (6 - 56) | 0.39 |
| Live related donor | 6 | 7 | 0.79 |
| 0 HLA-DR mismatching | 0 | 4 | 0.10 |
| Recipient's age, years | 11 (2 - 16.5) | 12.5 (2.5 - 17) | 0.40 |
| Donor's age, years | 38 (9 - 49) | 42 (30 - 51) | 0.11 |
| Cold ischemia, hours | 11.8 (3.5 - 28) | 15 (5 - 22) | 0.52 |
| eGFR after 3 months* | 65 (41.7 - 135), (n = 13) | 48.1 (15.4 - 89), (n = 18) | 0.02 |
| eGFR after 6 months* | 65.1 (38.0 - 82.8), (n = 12) | 49.5 (7.5 - 76), (n = 17) | 0.02 |
| eGFR after one year* | 59 (43.9 - 87.5), (n = 11) | 59.0 (28.7 - 71.4), (n = 16) | 0.62 |
| eGFR after 2 years* | 60.3 (35.0 - 97.4), (n = 10) | 57.3 (34.4 - 85), (n = 6) | 0.37 |
| ***Viral status of the recipients before transplantation*** | | | |
| Cytomegalovirus positive | 4 | 5 | 0.89 |
| Epstein-Barr virus positive | 6 | 7 | 0.79 |
| Recurrent UTI | 2 | 4 | 0.69 |

*mls/min/1.73m$^2$. HLA-DR - human leucocyte antigen DR
eGFR - estimated glomerular filtration rate, UTI - urinary tract infection

**Discussion.** We observed that DGF and renal allograft loss were more frequent in children with histological changes on PIB, particularly those with pre-existing chronic vascular changes. Patients with abnormal PIB also had significantly lower eGFR at 3-, and 6-months post-transplantation. Reports in children who have had protocol biopsies at 3-, 6-, and 12-months after transplant showed that such biopsies are associated with better renal allograft function, and play an important role in the detection of subclinical rejection.[13,14] In our study, correlation of the observed presence of vascular changes and eGFR was significant at 3-, and 6-, but not at 12 months. However, this could be due to our small cohort. The results of the control group and the outcome are very similar to the study cohort. The main pre-existing changes in PIB were mild chronic vascular changes. This is similar to Lopes et al's study[15] as they reported that 83% of PIB in 30 adult subjects displayed vascular changes related to the age of the donor. Our cohort received kidneys from younger donors with all except one LD having a maximum age of 50 years.

The DGF was more frequent in children with changes in PIB, which is similar to previous reports in adults.[16,17] Gaber et al[17] reported that GS >20% in PIB is associated with DGF. However, none of our cohort had significant GS, however, 34% had chronic vascular changes. Karpinski et al[6] reported that severe vascular disease in PIB is correlated with DGF, acute rejection episodes, and renal allograft dysfunction with increased serum creatinine levels at 18 months. We did not observe a significant higher acute rejection rate in children with abnormal PIB, which has been reported previously.[7] However, it seems to be a tendency to higher rates of rejections in case of abnormal PIB. We did not repeat protocol biopsies at 3 months looking for abnormal renal histological changes, which has been reported by others.[8]

We had one child who had patchy features of ATD in the PIB and lost her renal allograft after 14 months. A similar clinical course has been reported by Nankivell et al[18] who reported that ATN in PIB was subsequently associated with increased prevalence of chronic allograft injury to 55% compared with 28% in those without ATN ($p$<0.001). Early transplant damage occurs in the tubulointerstitial compartment from pre-existing donor kidney injury and discrete events, such as vascular rejection, and DGF contributes to subsequent chronic damage and graft failure.[1] The duration of renal allograft survival is dependent and predicted by the quality of the transplanted donor kidney combined with the intensity, frequency, and irreversibility of damaging insults.[1] Another important predictor of renal allograft function at one year is the percentage of GS in PIB as it is directly correlated with renal allograft survival, DGF, and primary non-function.[9] It was reported that significant relative risk for 10% GS are hypertension, donors over the age of 50 years, and African-American recipients.[9] This could explain the DGF and the vascular changes in PIB in the 2 children who received grafts from hypertensive DD. The hemostasis of the kidney donors had a correlation with the occurrence of complications in the kidney recipients as it is connected with activation of blood coagulation.[19] We have observed lower GFR in children with abnormal PIB at 3-, and 6 months. This is similar to previous reports as both tubulointerstitial damage and GS are correlated negatively with GFR.[20] The absence of difference in GFR between the 2 groups after one year could be explained by the fact that many children had short duration of follow-up, and those children who lost their renal allografts were excluded from further follow-up analysis.

Our study has several limitations caused by the retrospective character of the analysis, small number of patients, short follow-up period, no uniform duration of follow-up, and no statistical significance concerning the outcome parameters. The PIB provides prediction of acute outcomes, chronic outcomes, and useful for interpreting subsequent biopsies. In this study, we have looked at acute outcome in the form of DGF and acute rejection, as well as long-term outcome in the form of graft loss. However, we did not look at its value in the interpretation of subsequent biopsies. Renal biopsy is essential for establishing the correct diagnosis of renal allograft dysfunction and to plan appropriate management.[21] All the samples were read by one pathologist in our study in order to avoid bias. However, the use of 2 cores of renal allograft tissue to be read by 2 pathologists were shown to provide better diagnostic information, and thereby leads to appropriate increases in antirejection therapy without increasing the complications.[22]

In conclusion, in this retrospective series of PIBs, only some preliminary ideas of the predictive value of PIBs were described. It cannot be determined whether PIBs might serve the clinician for predicting future graft loss and function. Future trials with larger patient number and longer follow-up are required to decide if PIB should be performed as a routine to all pediatric patients, or if it should be restricted to high risk donors only.

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