Can Donor Implantation Renal Biopsy Predict Long-Term Renal Allograft Outcome?

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Abstract

\textbf{Background:} Donor kidney implantation biopsy (IB) is performed on a regular basis, particularly as part of clinical studies. \textbf{Objective:} To determine the utility of donor implantation renal biopsy to predict the long-term renal allograft outcome. \textbf{Methods:} A Medline search for studies in English was performed with the following key words: implantation biopsy, renal transplantation and long-term outcome. \textbf{Results:} Sixteen trials involving 8,122 kidney transplants were identified, of which 6 were prospective studies. The histological abnormalities were scored mainly by the Banff schema and the graft outcome was defined either by delineating the delta changes in the pathology score or glomerular filtration rate. Normal histology with a well-functioning renal allograft had a favorable outcome. The extent to which the baseline tubular atrophy, interstitial fibrosis, glomerulosclerosis and vascular changes had on the long-term outcome varied from one study to another. \textbf{Conclusion:} Abnormal IB has a better chance of predicting early graft outcome. The review questions the current wisdom for routine IB on all donors. In some donor kidneys, a biopsy provides significant prognostic information, such as older donor kidney, those with history of hypertension, diabetes, cardiovascular disease, and kidneys with abnormal creatinine. Future research on IB is necessary to find a more useful method to predict the long-term transplant outcome.

Key Words
Renal allograft • Implantation biopsy • Kidney transplant

Introduction

With the improvement in early renal transplant function, more research is directed to the study of means that may prolong allograft survival. As such, several factors have been identified that influence long-term graft outcome \cite{1-3}. They can be divided into three categories: (a) donor-related factors such as age, sex and cause of death; (b) transplant-related factors such as ischemia time and the degree of HLA matching, and (c) recipient-related factors.

The impact of donor-related factors has been widely examined by measurement of early transplant function and histology. Three major histological injuries are the leading causes of long-term chronic allograft dysfunction. These are glomerular injury, vascular injury and tubulointerstitial injury, notably interstitial fibrosis (IF) and tubular atrophy (TA). Many centers perform implantation biopsy (IB) on a routine basis or as part of clinical studies. Intuitively the information obtained from these biopsies is used to predict the long-term outcome of the
Long-Term Graft Function

Impact of Implantation Renal Biopsy on
Long-Term Graft Function

A conclusion that requires validation since there are no unified practice guidelines to address how the information obtained from IB tailor our choice of immunosuppressive protocol. It is becoming clear that there is a great deal of variability in graft outcomes within groups of patients with similar types of chronic histological changes [4], which raises questions on the value and utility of IB as a proxy to predict graft outcome in clinical studies.

Therefore, in this article we shall review reports on the utility of IB to predict long-term renal allograft outcome.

Evolution of the Concept of Implantation Biopsy Concept

Histological examination of native kidney biopsy remains the gold standard to determine pathology and predict long-term native kidney function [5]. In line with this, IB of the donor kidney was initially suggested by Gaber et al. [6] for the prediction of future allograft function, and thereafter by many researchers. Most transplant centers perform IB as part of their routine clinical practice in an attempt to gain information for future patient management [7]. Outcomes after kidney transplantation using deceased donor (DD) kidneys with high terminal creatinine are potentially an underutilized source of renal allografts [8]. The utility of renal biopsy of these kidneys is more compelling since IB in this group is more likely to show donor pathology. Glomerulosclerosis (GS), IF, hypertensive vascular changes, and TA may be present in marginal donors; these are reported to predict a subsequent worse graft survival [9–16]. Based on these studies, many centers will turn down kidneys with extensive GS, fibrotic, or atrophic changes. The future of donor kidneys with less damage is less clear. There are also many differences between a transplanted kidney and a disease in a native kidney. For example, a transplanted kidney is usually a single kidney, which may succumb to several immunological and non-immunological insults after transplantation. Therefore, prediction of long-term individual allograft function heavily depends on the post-transplant events. Furthermore, transplant physicians may change the immunosuppressive protocol at different times after transplantation, which may have an impact on the post-transplant course. In fact, Kasiske et al. [17] demonstrated different patterns of failing graft functions. This may be an oversimplification of the utility of IB, however.

Complexity of the Issue

There are many donor factors that may affect the long-term graft outcome. Of these factors the impact of donor renal function is significant. Donor glomerular filtration rate (GFR) may determine thereby the pattern of graft failure. The terms ‘intercept’ and ‘slope’ have been used to describe the different influences on renal allografts as they deteriorate and fail [18]. For example, a kidney from a young living donor (LD) who suffers no early acute rejection may yield an initial GFR of 70 ml/min, which may rise to 100 ml/min in the early months because of glomerular hyperfiltration. By contrast, a kidney from an elderly DD with a history of hypertension and 20% sclerosed glomeruli on the IB, which then suffers from significant ischemic damage and early rejection, may only achieve a maximum GFR of 30 ml/min. The ‘intercept’ values are thus 100 and 30 ml/min, respectively. Even if the subsequent ‘slope’ of decline in GFR of 5 ml/min/year was identical for both kidneys, the two kidneys will have different outcomes in the following years. The GFR will reach 10 ml/min in only 4 years for the damaged kidney, but it will take around 18 years for the undamaged kidney to reach the same level. The pathophysiology of the ‘slope’ may be the same in the two instances, although the IB and the clinical outcomes are dramatically different [19].

Furthermore, the rate of decline in kidney function has different patterns including an abrupt change from one pattern to another, which makes it difficult to interpret the end points. Kasiske et al. [17] alluded to the fact that few studies have systematically examined the perfection with which different clinical measures of allograft function predict graft failure.

Interpretation of the Histological Changes

The histological manifestations of renal injury to a vast array of injuries are limited. Therefore, the pathological findings of kidney biopsy may be similar in spite of the different etiological causes. The difference in the histological prognostic findings can be explained by the likelihood that different causes of graft inflammation may have different prognostic implications despite similar pathological findings. In addition, predictions based on a single biopsy, which may not be representative of an actual ongoing intra-graft process may give less decisive findings. After all, the tools available to determine the variant histological changes, in response to vast and vari-
able insults, remain limited. To date, old methodologies are still being used and there has been insignificant development in grading the histological changes in IB. For example, subjective methods to grade glomerular, tubule, interstitial and vascular changes, based on standard pathological techniques developed many decades ago, are still being applied. Furthermore, although several schemas have been developed to grade graft pathology [20–22], no such scoring system has been discovered that is specifically tailored to interpret abnormalities in IB. All these limitations add to the further complexity in the utility of IB to predict long-term graft outcome.

**Value of Implantation Biopsy**

With the above limitations in mind, the proposed value of IB is discussed in the following section. But because early clinical events may affect the long-term outcomes, the value of IB to predict early outcomes is discussed first.

**Value of IB to Predict Early Clinical Outcome**

*(Delayed Graft Function and Acute Rejection)*

In 1992 Gaber et al. [6] reported the use of IB to predict acute rejection. Lee et al. [23] reported that peritubular neutrophil count in renal IB is a possible predictive factor for acute rejection. Conventional histology in low-risk DDs was not found to predict the onset of graft function [24]. The presence of apoptotic tubular cells was found to correlate with delayed graft function (DGF) [25]. Gaber et al. [11] reported on 65 pre-transplant biopsies with >20% GS to be associated with DGF (88%), a higher serum creatinine level at 1 year, and an increased incidence of graft loss (38%). In 34 recipients of high-risk DD kidneys (age >60 years, hypertension or vascular disease), Karpinski et al. [10] reported that baseline biopsies with severe vascular disease correlated with DGF, acute rejection episodes, and increased serum creatinine levels at 18 months.

Eapen et al. [26] retrospectively analyzed data on 73 renal allograft recipients, of whom 37 recipients had IB. For all patients, subsequent biopsies were done based on the clinical conditions of the patients. The IB showed normal histology in 56.7%. However, 29.7% showed features of acute tubular necrosis (ATN), and 8.1% showed features of rejection, of which 5.4% were hyperacute and 2.7% were grade I. Two (5.4%) showed ischemic shrinkage of the glomeruli, and I (2.7%) showed early membranoproliferative glomerulonephritis. The percentage of patients with normal IB who developed rejection was 47.6%, while the percentage of patients with abnormal IB who later developed rejection was 75%. Lee et al. [23] studied prospectively the relationship of IB and acute rejection during the immediate post-transplantation period. They reported that grade 1 interstitial cellular infiltration was present in 16.7% in the acute rejection group (ARG), and 7.1% in the non-rejection group (NRM). Grades 1 and 2 GS was seen in 33.3% of the ARG and in 21.4% of the NRM. Grades 1 and 2 tubular damage was seen in 16.7% of the ARG. Grade 1 tubular damage was confirmed in 14.3% of the NRM [23].

Kuypers et al. [27] prospectively studied the impact of implantation histology on renal transplant histology at 3 months. They studied 102 biopsies and analyzed in a multivariate analysis the impact of clinical, laboratory and pathologic variables on the chronic Banff grades at 3 months. They concluded that the quality of the donor organ at implantation was strongly predictive of subsequent renal histology in grafts functioning at 3 months.

**Value of IB to Predict Long-Term Graft Outcome**

Donor age has been a consistent correlate of allograft outcome [28, 29]. Age-related decline in renal function has been associated with the appearance of glomerular, tubulointerstitial, and vascular lesions in the kidney [30, 31]. However, when faced with a DD, age alone is not predictive enough to allow the outright exclusion of an organ. Indeed, an age-dependent fall in the GFR is not inevitable [26], suggesting that donor age may in fact be a marker of co-morbid conditions that are associated with aging. In a prospective cohort study, Remuzzi et al. [32] assessed outcomes among 62 patients who received one or two histologically evaluated kidneys from donors older than 60 years of age. These outcomes were compared with outcomes among 248 matched recipients of single kidney grafts that had not been histologically evaluated and were either from donors 60 years of age or younger (124 positive-reference recipients who were expected to have an optimal outcome) or from those older than 60 years (124 negative-reference recipients expected to have a worse outcome). Graft survival in recipients of histologically evaluated kidneys did not differ significantly from that of grafts in positive-reference recipients, but was superior to that of grafts in negative reference recipients (hazard ratio for graft failure in the negative-reference recipients relative to the recipients of histologically evaluated kidneys, 3.68; 95% CI, 1.29–10.52; p = 0.02). They concluded that the long-term survival of single or dual kidney grafts from donors older than 60 years of age
Impact of Vascular Changes on Long-Term Graft Outcome

In a prospective study on 50 consecutive DD biopsies, Bosmans et al. [33] reported that fibrous intimal thickening at implantation was the principal determinant of both the creatinine clearance and the degree of IF at 18 months after transplant. Fibrous intimal thickening represented an RR of 4.5 for IF (95% CI 1.85–11.14), and 1.9 for impaired renal function (95% CI 1.18–3.01). Although donor age was equal to fibrous intimal thickening at predicting creatinine clearance, it did not predict IF at 18 months. In contrast to previous studies, the group did not find an association between pre-implant IF or GS and the end-points examined.

Impact of GS on Long-Term Graft Outcome

Randhawa et al. [13] reported their experience on 78 recipients of cadaveric grafts with a mean donor age of 51.2 years. The incidence of creatinine clearance of <34 ml/min at 1 year was 25, 46, 60 and 100% for GS of 0, 1–10, 11–20, and over 20%, respectively. Moreover, the percentage of GS was an independent predictor of graft function at 1 year. In addition, they reported that IF is a strong predictor of poor graft function at 1 year.

In a retrospective study Lu et al. [34] reviewed the impact of severe GS in IB on graft outcome. They studied 89 patients who were transplanted between 1995 and 1998. They concluded that the kidneys from donors with ≥20% GS provide excellent outcome, being similar to the kidneys from donors with no GS. Verran et al. [35] reported that 28/40 (70%) donors with renal allograft biopsies had <20% GS. One-year renal allograft survival was not significantly different between the protocol biopsied allografts versus the other non-biopsied allografts.

The UNOS donor population from 1999 to 2002 was examined. Approximately 25% of the over 23,000 donors were biopsied. There was a significant trend of older donors (p < 0.001), cardiovascular accident, and hypertension in the biopsied group versus the non-biopsied group. The GS percentage (p < 0.001) is directly correlated to graft survival, DGF, and primary non-function. Cox regression showed significant relative risk (RR) for >10% GS, hypertension, donors over the age of 50, and African-American recipients. The RR in donors with >10% GS could be ameliorated (p < 0.001) by choosing donors with <5 HLA-A, -B, or -DR mismatches, or recipients who were non-sensitized, and/or those having first transplant [36].

Howie et al. [37] retrospectively studied 500 IB specimens of cadaveric grafts. Death-censored graft survival was calculated for up to 14 years after transplantation. The index of cadaveric grafts was applied to measure the morphometric changes in the IB. This study was unique in using the interactive image analysis system to measure the amount of chronic damage [38]. Nearly half the specimens presented no chronic damage. Most others had an index from 1 to 9%. Only 9% had an index of 10% or more. An index of 0% was associated with better survival than 1%, with little difference between 1 and 39%. An index of 40% or more GS was associated with the worst survival (p < 0.001). It was concluded that the histological markers of the chronic damage index were rare enough that the measurement is not necessary on every graft. They suggested that a kidney from virtually any donor in any age group has the same potential as a graft from nearly all others in that group.

Ugarte et al. [8] reported that among kidneys from donors with a terminal creatinine of ≥2 mg/dl and those with an abnormal biopsy demonstrated worse median estimated GFR as compared to those with no more than mild histological abnormalities at all time points analyzed. After adjusting for recipient age, a greater than mild histological abnormality was independently associated with a worse mean estimated GFR both at 12 months (–19.6 ml/min/1.73 m², p = 0.013) and on longitudinal analysis of all time points (–14.8 ml/min/1.73 m², p = 0.019).

In 2001, Nankivell et al. [39] compared the histological scores in IB and post-transplant protocol biopsies. Chronic allograft nephropathy was present in 24% of the 3-month biopsies and was predicted by microvascular disease in IB (p < 0.001). They concluded that early transplant damage occurs in the tubulointerstitial compartment from pre-existing donor kidney injury; moreover, subsequent chronic damage and graft failure reflect accumulated previous injury [39]. In 2003, Nankivell et al. [4] updated their experience. ATN was present in 22.7% of those with abnormal IB and was subsequently associated with an increased prevalence of chronic allograft nephropathy (55.3%) among those with ATN, as compared with 28.1% among those without ATN (p < 0.001).

On the other hand, Edwards et al. [40] reported that GS should not be used as the only criterion for kidney transplantation, even with a relatively high GS of >20. In another study with 200 wedge biopsied donors, there was no correlation with as high as 25% GS and graft survival up to 3 years [9]. Also the UNOS database underestimates the value of GS in donor biopsy when approximate-
Table 1. Main trials on the impact of histological changes in IB on graft outcome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Patients</th>
<th>Follow-up months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nankivell et al.</td>
<td>prospective</td>
<td>67</td>
<td>84</td>
<td>In IB, 1.7% of glomeruli were sclerosed and there was no or minimal preexisting damage. The ATN was present in 22.7% of IB and was subsequently associated with an increased prevalence of CAN and increased FIT at 1 month</td>
</tr>
<tr>
<td>Ugarte et al.</td>
<td>retrospective</td>
<td>55</td>
<td>30</td>
<td>Among kidneys from donors with creatinine ≥2 mg/dl, those with an abnormal biopsy demonstrated worse eGFR as compared to those with no more than mild histological abnormalities at all time points analyzed, although this did not achieve statistical significance at every time point. After adjusting for recipient age, a greater than mild histologic abnormality was independently associated with worse eGFR at 12 months and on longitudinal analysis of all time points</td>
</tr>
<tr>
<td>Chapman [19], 2005</td>
<td>longitudinal</td>
<td>120</td>
<td>12</td>
<td>Mild fibrosis was present in only 5% of IB. Once established, TI damage did not regress in subsequent biopsies. TI damage preceded and correlated with the degree of GS in subsequent biopsies. Renal function declined in proportion to the amount of fibrosis. GS correlated significantly but poorly with GFR, unlike the much tighter correlation with TI damage. GFR fell in parallel with the increase in GS</td>
</tr>
<tr>
<td>Lee et al. [23], 1998</td>
<td>prospective</td>
<td>20</td>
<td>1</td>
<td>Grade 1 interstitial cellular infiltration was present in 16.7% in ARG, and 7.1% in NRG. Grades 1 and 2 GS were seen in 33.3% of ARG. Grade 1 GS was confirmed in 21.4% of NRG. Grades 1 and 2 tubular damages were seen in 16.7% of ARG. Grade 1 tubular damage was confirmed in 14.3% of NRG</td>
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</tr>
<tr>
<td>Eapen et al. [26], 2000</td>
<td>retrospective</td>
<td>37</td>
<td>not mentioned</td>
<td>IB showed normal histology in 57%; 30% showed features of ATN; 8% showed features of rejection; 5% showed ischemic shrinkage of the glomeruli, and 3% showed early MPGN. The percentage of patients with normal IB who developed rejection was 48%. The percentage of patients with abnormal IB who later developed rejection was 75%</td>
</tr>
<tr>
<td>Kuypers et al. [27], 1999</td>
<td>multivariate prospective</td>
<td>112</td>
<td>3</td>
<td>DGF correlated with ATN on the IP and with the acute rejection episodes</td>
</tr>
<tr>
<td>Remuzzi et al. [32], 2006</td>
<td>prospective cohort</td>
<td>310</td>
<td>23</td>
<td>The long-term survival of grafts from donors older than 60 years of age was excellent, provided that the grafts were evaluated histologically before implantation. The performance of preimplantation histologic evaluation predicted better survival</td>
</tr>
<tr>
<td>Bosmans et al. [33], 2000</td>
<td>multivariate prospective</td>
<td>50</td>
<td>18</td>
<td>FIT was the main determinant of the functional and morphologic outcome. FIT represented a RR risk of 4.5 for IF; and 1.9 for impaired renal function. FIT adversely affected fractional interstitial volume, as well as renal function</td>
</tr>
<tr>
<td>Lu et al. [34], 2000</td>
<td>multivariate retrospective</td>
<td>89</td>
<td>24</td>
<td>Recipients of kidneys with ≥20% GS were older, had higher serum creatinine values at 1 and 2 years, but similar rates of delayed graft function and 2-year graft survival. Serum creatinine was significantly higher in recipients of kidneys with moderate vasculopathy, up to 2 years after transplantation. But this did not affect graft loss</td>
</tr>
<tr>
<td>Cicciarelli et al. [36], 2005</td>
<td>retrospective study</td>
<td>6,121</td>
<td>not mentioned</td>
<td>The percent GS was directly correlated (p &lt; 0.001) to graft survival, DGF, and primary non-function. Cox regression showed significant RR for &gt;10% GS</td>
</tr>
<tr>
<td>Howie et al. [37], 2004</td>
<td>retrospective study</td>
<td>500</td>
<td>168</td>
<td>Nearly half the specimens had no chronic damage. Most others had an index from 1 to 9%. Only 9% had index of 10% or more. An index of 0% was associated with better survival than 1%, with little difference between 1 and 39%. An index of 40% or more GS was associated with the worst survival (p &lt; 0.001)</td>
</tr>
<tr>
<td>Nankivell et al.</td>
<td>multivariate prospective</td>
<td>91</td>
<td>12</td>
<td>Mild IF (CI grades 1–2) was present in 57% of the cases. Vascular changes (intimal fibrosis or hyalinosis) were present in 24% of the cases. The mean Banff CI increased from IB to 3 months and stabilized at 12 months. Arteriolar hyalinosis score peaked at 3 months correlated with IB vascular disease</td>
</tr>
<tr>
<td>Nankivell et al. [41], 2004</td>
<td>longitudinal study</td>
<td>120</td>
<td>84</td>
<td>1.7% of glomeruli were sclerosed. Overall, the number of sclerosed glomeruli was predicted by tubulointerstitial damage. Both chronic interstitial fibrosis and TA were independently predictive of GS. Overall, isotopic GFR inversely correlated with percentage GS and periglomerular fibrosis, but not with segmental GS</td>
</tr>
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ly 25% of the over 23,000 donors were histologically examined from 1999 to 2002 [36]. Chapman et al. [19] reported that GS correlated significantly but poorly with GFR, unlike the much tighter correlation with tubulointerstitial damage. GFR declined in parallel with the increase in GS, but underestimated the degree of damage, declining from 59 ml/min with no GS to 56 ml/min with 1–20% and 52 ml/min with more than 20% of sclerosed glomeruli [19].

In 2004 Nankivell et al. [41] reported that, in time-zero biopsies, 38 of 2,281 donor glomeruli were sclerosed (1.7%), and 9 (6.7%) biopsies had a mildly increased mesangial matrix confirming that the transplanted kidneys had minimal pre-existing glomerular damage. Over a 10-year period, a nonlinear gradual increase in the global GS and intensity of glomerular injury occurred in a triphasic and time-specific pattern. Overall, the number of sclerosed glomeruli was predicted by tubulointerstitial damage, when adjusted for glomeruli number within the biopsy and for time after transplantation, using a generalized estimating equation. Both chronic IF (CIF) and TA were independently predictive of GS. Overall, isotopic GFR inversely correlated with percentage GS (r = –0.16, p < 0.001) and periglomerular fibrosis (r = –0.14, p < 0.05), but not with segmental GS (r = –0.06, p = NS). This poor correlation may be contrasted with the stronger correlations of isotopic GFR with tubulointerstitial damage including the Banff CIF and TA scores. Renal transplant function declined in parallel with increasing GS, although it often underestimated the degree of histological damage in individual patients. The mean isotopic GFR was 59.1 ± 17.6 in the absence of GS, 56.6 ± 18.5 ml/min for 1–10%, 55.9 ± 22.1 ml/min for 10–20%, and 51.8 ± 23.7 ml/min for >20% GS. Serum creatinine did not significantly correlate with the percentage of sclerosed glomeruli (r = 0.08, p < 0.08). However, it correlated weakly with the percentage of GS (r = 0.14, p < 0.01), periglomerular fibrosis (r = 0.16, p < 0.001), chronic tubular fibrosis scores (r = 0.25, p < 0.001), and isotopic GFR (r = –0.55, p < 0.001) [41].

Impact of Tubulointerstitial Disease on Long-Term Graft Outcome

In 2005, Chapman [19] reported the presence of mild fibrosis in only 5% of IB in his series of young donors selected for pancreas suitability. Tubulointerstitial damage preceded and correlated with the degree of GS observed in subsequent biopsies. Renal function, as expected, declined in proportion to the amount of fibrosis, from a measured GFR of 65 ml/min in patients with normal biopsies to 59 and 44 ml/min with mild and moderate fibrosis, respec-

Table 1 (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Patients</th>
<th>Follow-up months</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosio et al. [43], 2005</td>
<td>retrospective study</td>
<td>151</td>
<td>33</td>
<td>7% of the IB had more than 5% IF. Tubular atrophy closely parallel IF, but the incidence of TA was higher than that of IF (25%). The incidence of vascular pathology, including arteriolar hyalinosis and chronic vasculopathy, was lower. The percentage of grafts lost not due to patient death was higher in patients with IF. By Cox regression, the severity of IF correlated significantly with graft survival.</td>
</tr>
<tr>
<td>Nankivell et al. [42], 2004</td>
<td>longitudinal study</td>
<td>120</td>
<td>84</td>
<td>Mild fibrosis was present in 5% of specimens and mild patchy TA was seen in 3% of IB. ATN was present in 22.7%, which increased 1-month Banff CIF score was dependent on ATN and the 1-year CIF score was independently predicted by ATN. CIF scores correlated with serum creatinine and urea concentrations. Isotopic GFR inversely correlated with Banff CIF and TA scores. Hence, tubulointerstitial damage proportionally reduced isotopic GFR.</td>
</tr>
<tr>
<td>Cosio et al. [44], 2005</td>
<td>retrospective study</td>
<td>159</td>
<td>33 ± 16</td>
<td>In IB, 7% had &gt;5% GIF (CI score &gt;0, GIF). Thereafter, the percentage of patients with GIF increased progressively to 31, 61 and 71% on biopsies taken at 4 months, 1 year and 2 years after transplant, respectively. The percentage of biopsies with TA (ct score) closely paralleled GIF, but the incidence of TA was higher than that of GIF. The percentage of grafts lost not due to patient death was higher in patients with GIF (no GIF 2.2%, GIF 8%, p = 0.05). By Cox regression, the severity of GIF correlated significantly with death-censored graft survival (HR = 2.2; p = 0.009).</td>
</tr>
</tbody>
</table>

FIT = Fibrous intimal thickening; RR = relative risk; IF = Interstitial fibrosis; DGF = Delayed graft function; IB = Implantation biopsy; CI = Chronic interstitium; TI = Tubulointerstitial; GS = Glomerulosclerosis; ATN = Acute tubular necrosis; MPGN = Membranoproliferative glomerulonephritis; ARG = acute rejection group; NRG = non-rejection group; eGFR = Estimated glomerular filtration rate; TA = Tubular atrophy; CIF = Chronic interstitial fibrosis.
tively. Once established, tubulointerstitial damage did not regress in subsequent biopsies [19]. In 2004, Nankivell et al. [42] reported that in time-zero biopsy specimens obtained at implantation or within the first week after transplantation, mild fibrosis was present in 5% of specimens and mild patchy TA was seen in 3%. ATN was present in 22.7% of IB, which increased the 1-month CIF scores (0.53 ± 0.51 vs. 0.21 ± 0.41 for no ATN, p < 0.05). By multivariate analysis, the 1-month CIF score was dependent on ATN (coefficient = 0.26 ± 0.11, p < 0.05). By multivariate analysis, the 1-year Banff CIF score was independently predicted by ATN (coefficient = 0.35 ± 0.16, p < 0.05). The CIF scores correlated with the serum creatinine level (r = 0.25, p < 0.001) and serum urea concentrations (r = 0.24, p < 0.001). Isotopic 99mTc DTPA GFR inversely correlated with Banff CIF (r = −0.30, p < 0.001) and TA scores (r = −0.29, p < 0.001). The mean isotopic GFR was 65.1 ± 14.7 ml/min for absent CIF (n = 72 GFR measurements), 59.4 ± 18.5 ml/min for mild fibrosis (n = 322), 43.6 ± 21.6 ml/min for moderate fibrosis (n = 99), and 50.7 ± 20.3 ml/min for severe fibrosis (n = 8). Hence, tubulointerstitial damage proportionally reduced isotopic GFR, although the extent of damage for severe IF was underestimated by transplant renal function [42].

Cosio et al. [43] studied 151 IB of the 292 patients included in their study (52%). All biopsies were evaluated and scored using the Banff 97 classification. The primary end point was death-censored graft loss or a >50% reduction in GFR beyond 1 year. 7% of the IB had more than 5% IF. TA revealed closely parallel IF, but the incidence of TA was higher than that of IF, (25%). The percentage of grafts lost not due to patient death was higher in patients with IF. By Cox regression, the severity of IF correlated significantly with graft survival [43].

Cosio et al. [44] reported that at time 0, 7% of the donor biopsies had >5% graft IF (GIF) (ci score >0, GIF). Thereafter, the percentage of patients with GIF increased progressively to 31, 61 and 71% on biopsies taken at 4 months, 1 and 2 years after transplant, respectively. The percentage of biopsies with TA (ct score) showed closely parallel GIF, but the incidence of TA was higher than that of GIF. Comparing the chronic pathological scores in DD and LD kidneys at time 0, GIF was more common in DD grafts than in LD grafts (29 and 7%, p = 0.002) and it was also more severe (0.3 ± 0.4 and 0.1 ± 0.4, p = 0.002). The follow-up period after transplantation was 33 ± 16 months. The percentage of grafts lost not due to patient death was higher in patients with GIF (no GIF 2.2%, GIF 8%, p = 0.05). By Cox regression, the severity of GIF correlated significantly with death-censored graft survival (hazard ratio = 2.2; p = 0.009). In this study the authors reasoned that if pre-transplant injury was a major cause of allograft fibrosis, this process should be milder in LD kidneys than in DD kidneys [44].

Table 1 shows the main trials on the impact of histologic changes in IB on graft outcome. Sixteen clinical trials involving 8,122 kidney transplants were identified, of which 6 were prospective studies.

Conclusion

Early graft outcome which may affect long-term outcomes, such as DGF and ATN, is associated more with abnormal IB histology. The relative impact of GS, IF, and arteriolar hyalinosis present in IB on long-term graft outcome remains limited to the extent that the prognostic information obtained from IB can be modified by other donor and recipient factors. Post-transplant biopsies are usually required to enhance the use of IB to predict the long-term outcomes. As such, no accurate single consistent proxy has so far been identified in the IB to accurately predict long-term graft outcome. In addition, events that happen after transplantation can overshadow the impact of abnormal IB and follow-up biopsies are usually necessary to determine the impact of abnormal histology on graft outcome. This demands a critical look at the performance of routine IB and whether it should be restricted to high-risk donors only until future research shows otherwise.

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