Moderate-to-severe early-onset hyperuricaemia: a prognostic marker of long-term kidney transplant outcome

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Abstract

Background. Hyperuricaemia commonly occurs in renal transplant recipients (RTRs), but the effects of post-transplant hyperuricaemia on kidney transplant outcome have not been clearly established. This work was designed to explore the impact of hyperuricaemia on renal transplant outcome.

Methods. The authors examined this issue by analysing the clinical outcome of 281 RTRs. Hyperuricaemia (defined as UA ≥ 7.0 mg/dl in men and ≥ 8.0 mg/dl in women for at least two consecutive tests, n = 121) was classified as early onset (within 1 year of transplant, n = 90) or late onset (n = 31). Graft function was estimated using the MDRD Study Equation 7 (eGFRMDRD).

Results. As late-onset hyperuricaemia was found to be induced by a progressive decline in the graft function (P < 0.01), data from early-onset hyperuricaemic recipients were used. Early-onset moderate-to-severe hyperuricaemia (defined as UA ≥ 8.0 mg/dl) was found to be a significant risk factor for chronic allograft nephropathy (P = 0.035) and a poorer graft survival (P = 0.026) by multivariate analysis, whereas mild hyperuricaemia was not. The impact of moderate-to-severe hyperuricaemia on renal transplant survival was dependent on the duration of exposure. Likewise, the detrimental effect of early-onset hyperuricaemia on the graft function was dependent on UA levels and exposure time. After control of the baseline graft function by analysis of only recipients with a good graft function at 1 year post-transplantation (eGFRMDRD > 60 ml/min), moderate-to-severe early-onset hyperuricaemia was also found to be a marker of long-term graft dysfunction and failure.

Conclusion. Moderate-to-severe early-onset hyperuricaemia may be a prognostic marker of the long-term graft outcome in RTRs, which needs further investigation.

Keywords: chronic allograft nephropathy; graft function; graft survival; hyperuricaemia; renal transplantation

Introduction

Hyperuricaemia is frequently observed in organ transplant recipients, and incidences of post-transplant hyperuricaemia depend on the organ transplanted and immunosuppressive regimen used. Renal transplant recipients (RTRs) on cyclosporine-based immunosuppression are prone to develop post-transplant hyperuricaemia, with a highest prevalence rate of up to 80% [1]. Hyperuricaemia following transplantation is primarily attributed to cyclosporine therapy, but is also associated with a decreased glomerular filtration rate (GFR), diuretic use and obesity [2–4]. It has been suggested that an elevated uric acid (UA) level is a prognostic marker for the development of renal insufficiency in individuals with a normal kidney function and of the progression of disease among patients with established renal disease [5–7]. Furthermore, experimental hyperuricaemia models have provided evidence that renal injuries, such as glomerulosclerosis and albuminuria, occur in hyperuricaemic rats [8] and that renal changes are prevented if serum UA is maintained in the normal range with allopurinol [9,10]. However, the impact of post-transplant hyperuricaemia on renal transplant outcome has not been fully established. A small number of studies have evaluated the effect of hyperuricaemia on graft survival and dysfunction in RTRs, but results obtained have been inconsistent [11–14]. In addition, it is hard to disentangle the relationship of UA with renal function. Simply, hyperuricaemia may be a consequence of the reduced GFR in renal allograft or, on the other hand, hyperuricaemia in itself contributes to glomerulohypertrophy and tubulointerstitial fibrosis [8,9].

Thus, the aims of the present study were (1) to assess the prevalence of hyperuricaemia in RTRs and the predisposing factors for post-transplant hyperuricaemia, (2) to evaluate which came first, the hyperuricaemia or the decline of renal graft function and (3) to identify the impact of hyperuricaemia on the kidney transplant outcome.
Patients and methods

Study population
Between August 1999 and July 2006, 368 single-kidney-only transplants were performed at Seoul National University Hospital. Recipients older than 18 years of age at the time of transplantation and those whose graft survived at least 1 year were included. This study was approved by the Institutional Review Board of Seoul National University Hospital.

Immunosuppression
All recipients received triple immunosuppressive therapy: (1) cyclosporine (targeting a trough level of 100–250 ng/ml for the first 6 months and 40–80 ng/ml thereafter) or tacrolimus (targeting a trough level of 6–10 ng/ml for the first 6 months and 4–6 ng/ml thereafter); (2) azathioprine (1–2 mg/kg per day) or mycophenolate mofetil (1000–1500 mg per day) and (3) prednisolone (initially 1 mg/kg daily with rapid tapering to <5 mg per day). Protocol biopsies were not performed. Recipients with ≥25% elevation in the serum creatinine level underwent ultrasound-guided percutaneous allograft biopsy. The histopathological lesions such as acute rejection (AR) or chronic allograft nephropathy (CAN) were classified and scored according to the Banff 97 classification [15]. Episodes of biopsy-proven AR were treated with 1–1.5 g of intravenous methylprednisolone.

Clinical and biochemical data collection
The following clinical data were recorded for this study: age at transplantation, body mass index (BMI, kg/m²) at transplantation, smoking status, donor source, immunosuppressive regimen, diuretic use, underlying nephrologic disease, number of human leukocyte antigen (HLA) mismatches, waiting time, presence of AR, transplant kidney biopsy results and post-transplant medications including immunosuppressives, diuretics and antihypertensives. The following biochemical data were measured at pretransplant evaluations and also measured, at least, at 1 and 3 months after transplantation and at intervals of 6 months throughout the follow-up period: serum concentrations of uric acid, glucose, blood urea nitrogen (BUN), creatinine, albumin, lipids (total cholesterol, high-density lipoprotein-cholesterol and triglyceride). The above-mentioned factors predisposing post-transplant hyperuricaemia were included in the multiple logistic regression analysis: age at transplantation, gender, smoking status, BMI at transplantation, history of hypertension, history of diabetes, deceased donor, presence of AR, waiting time, pre-existing hyperuricaemia, transplant duration, immunosuppressive agents and antihypertensives such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, beta blocker or alpha blocker. However, significant differences were found in terms of gender (P = 0.000), donor source (P = 0.026) and waiting time (P = 0.010). The prevalence of hyperuricaemia among all patients was 20.9% at 6 months after transplantation, but this increased to 41.1% by the end of the fourth post-transplant year (P < 0.05).

Factors predisposing post-transplant hyperuricaemia
The following potential risk factors of hyperuricaemia were included in the multiple logistic regression analysis: age at transplantation, gender, smoking status, BMI at transplantation, history of hypertension, history of diabetes, deceased donor, presence of AR, waiting time, pre-existing hyperuricaemia, transplant duration, immunosuppressive agents, a blood trough level of calcineurin inhibitor and diuretic use. Male gender was found to significantly influence serum UA (P = 0.000; OR 8.66; 95% CI 3.11–24.11), and the UA level was found to be independently associated with a waiting time of <12 months (P = 0.043; OR 0.47; 95% CI 0.23–0.98). However, the usage of cyclosporine and diuretics was not found to have significant effects on the development of post-transplant hyperuricaemia.

Early- versus late-onset post-transplant hyperuricaemia
Because recipients showing progressive renal deterioration were believed to be more likely to become hyperuricemic, the authors sought to determine which occurred first, that is, hyperuricaemia or a decline in the graft function. Therefore, the authors classified hyperuricaemic recipients as early-onset (n = 90, within the first post-transplant year)
Impact of early-onset hyperuricaemia on the graft outcome and its dependence on UA levels

Over a follow-up of ~5 years, 13 patients had graft loss, and 20 developed biopsy-proven CAN in the recipients with early-onset hyperuricaemia or normouricaemia. To determine whether early-onset hyperuricaemia has an adverse effect on the renal transplant outcome and whether the effects of early-onset hyperuricaemia on the renal transplant outcome are dependent on the severity of hyperuricaemia, the authors classified patients with early-onset hyperuricaemia into mild (MI, UA ≥ 8.0 mg/dl, n = 51) and moderate-to-severe (MS, UA ≥ 8.0 mg/dl, n = 39) hyperuricaemia groups. As Figure 2A illustrates, MS hyperuricaemic recipients showed significantly poorer graft survivals than normouricaemic recipients (P = 0.001). On the other hand, MI hyperuricaemic recipients and normouricaemic recipients showed no significant differences in terms of graft survival rates (P = ns). Likewise, MS hyperuricaemic recipients showed significantly poorer CAN-free graft survivals than normouricaemic recipients (P = 0.019) (Figure 2B).

Tables 2 and 3 depict univariate and multivariate analysis results of risk factors for the development of CAN and graft failure. By univariate analysis, deceased donor (P = 0.001), MS early-onset hyperuricaemia (P = 0.022), a long wait > 365 days (0.097) and AR episode (0.036) showed

Fig. 1. Mean eGFRMDRD changes over 1 year after hyperuricaemia detection in patients with early-onset (within the first post-transplant year) hyperuricaemia (A) and patients with late-onset (after the first post-transplant year) hyperuricaemia (B) are shown. Note that the patients with late-onset hyperuricaemia experienced a significant decline in the graft function immediately after hyperuricaemia was detected. GFR, glomerular filtration rate; Dx, detection; mo, month.

or late-onset (n = 31, after the first post-transplant year) and evaluated eGFRMDRD changes in both of these groups, based on eGFRMDRD values at the time of hyperuricaemic group assignment. No differences in baseline demographic data were found between these early- and late-onset groups. In particular, no differences were found in terms of factors that predisposed post-transplant hyperuricaemia, such as gender and waiting time. However, as illustrated in Figure 1, a striking difference was observed in terms of eGFRMDRD changes over the year following the detection of hyperuricaemia. Specifically, recipients in the early-onset group had a stable graft function (58.7 ± 10.8, 58.9 ± 11.5 and 58.8 ± 10.7 ml/min per 1.73 m², respectively, for eGFRMDRD at detection of hyperuricaemia, at 6 months post-detection, and at 12 months post-detection, P = ns, ANOVA), whereas recipients in the late-onset group showed significant declines in eGFRMDRD post-detection (i.e. mean eGFRMDRD values of 60.3 ± 13.6, 53.9 ± 11.7 and 49.4 ± 12.4, respectively, at detection of hyperuricaemia at 6 months post-detection and at 12 months post-detection, P < 0.01, ANOVA). These results indicate that renal deterioration is an on-going process in recipients with late-onset hyperuricaemia, and the data from those recipients are not appropriate for this study. Hence, the authors used the data for further analyses from only those patients who developed hyperuricaemia within the first post-transplant year.

Impact of early-onset hyperuricaemia on the graft outcome and its dependence on UA levels

Over a follow-up of ~5 years, 13 patients had graft loss, and 20 developed biopsy-proven CAN in the recipients with early-onset hyperuricaemia or normouricaemia. To determine whether early-onset hyperuricaemia has an adverse effect on the renal transplant outcome and whether the effects of early-onset hyperuricaemia on the renal transplant outcome are dependent on the severity of hyperuricaemia, the authors classified patients with early-onset hyperuricaemia into mild (MI, UA < 8.0 mg/dl, n = 51) and moderate-to-severe (MS, UA ≥ 8.0 mg/dl, n = 39) hyperuricaemia groups. As Figure 2A illustrates, MS hyperuricaemic recipients showed significantly poorer graft survivals than normouricaemic recipients (P = 0.001). On the other hand, MI hyperuricaemic recipients and normouricaemic recipients showed no significant differences in terms of graft survival rates (P = ns). Likewise, MS hyperuricaemic recipients showed significantly poorer CAN-free graft survivals than normouricaemic recipients (P = 0.019) (Figure 2B).

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![Graph](image_url)
a tendency to be associated with CAN, but only deceased donor \((P = 0.032; \text{HR} = 1.24; 95\% \text{CI} 1.02–1.50)\) and MS early-onset hyperuricaemia \((P = 0.035; \text{HR} = 1.89; 95\% \text{CI} 1.05–3.43)\) were found to be significant risk factors for CAN by multivariate analysis. Furthermore, significant independent risk factors for graft loss were the occurrence of \(\geq 1\) AR episode \((P = 0.006; \text{HR} = 2.92; 95\% \text{CI} 1.37–6.23)\), a long wait >365 days \((P = 0.004; \text{HR} = 2.37; 95\% \text{CI} 1.32–4.24)\) and MS early-onset hyperuricaemia \((P = 0.026; \text{HR} = 2.01; 95\% \text{CI} 1.09–3.72)\). MI early-onset hyperuricaemia was not found to be an independent risk factor for CAN \((P = 0.54)\) and graft failure \((P = 0.35)\) by multivariate analysis. The number of HLA mismatches \((P = 0.05)\), ESRD due to diabetic nephropathy \((P = 0.08)\), deceased donor \((P = 0.10)\) and delayed graft function \((P = 0.08)\) showed a tendency to be associated with graft failure by univariate analysis but no such trend was found by multivariate analysis.

Changes in eGFR\textsubscript{MDRD} in this cohort also revealed the impact of early-onset hyperuricaemia, which is dependent on the UA level. The mean eGFR\textsubscript{MDRD} at 1 year post-transplantation was similar for normouricaemic, MI hyperuricaemic and MS hyperuricaemic recipients \((65.4 \pm 14.2, 62.1 \pm 15.9\) and \(61.9 \pm 12.5\), respectively; \(P = \text{ns}\)). The graft functions of MI hyperuricaemic recipients remained stable like those of normouricaemic recipients, but MS hyperuricaemic patients showed a persistent sustained decrease in the mean eGFR\textsubscript{MDRD} during the follow-up. In MS hyperuricaemic recipients, the mean eGFR\textsubscript{MDRD} was \(53.7 \pm 15.2\) at the fourth post-transplant year and subsequently, graft functions were significantly lower than those at 1 year post-transplantation (Figure 2C).

Because GFR is well known as a predictor of late graft function and therefore it needs great caution to interpret the data without baseline GFR control, the authors adjusted baseline GFR through selection of only those recipients who had a good graft function at 1 year post-transplantation \((\text{eGFR}\textsubscript{MDRD} > 60 \text{ ml/min})\) and evaluated the impact of early-onset hyperuricaemia again. After control of the baseline graft function, the mean eGFR\textsubscript{MDRD} at 1 year post-transplantation was really similar for normouricaemic \((n = 97)\), MI hyperuricaemic \((n = 32)\) and MS hyperuricaemic recipients \((n = 24)\) \((71.6 \pm 9.5, 72.5 \pm 8.1\) and \(73.3 \pm 13.1\), respectively; \(P = \text{ns}\)). As Figure 3 illustrates, the impact of early-onset hyperuricaemia on the graft outcome, which is dependent on the UA level and exposure time, was also demonstrated by recipients with a good graft function at 1 year post-transplantation.

### Discussion

Hyperuricaemia is a frequent finding among RTRs and can occur in up to 80% [1]. Furthermore, diuretics and

| Table 2. Univariate and multivariate analysis findings for risk factors of chronic allograft nephropathy in early-onset hyperuricaemic recipients |
|-----------------|--------------------|------------------|-----------------|--------------------|------------------|
| Covariate       | Univariate\(^a\)   |                  |                | Multivariate       |                  |
|                 | HR                 | 95\% CI          | \(P\)-value    | HR                 | 95\% CI          | \(P\)-value    |
| Long wait: >1 year | 2.11               | 0.88–5.10        | 0.097           | 1.18               | 0.44–3.26        | 0.850          |
| Deceased donor  | 1.29               | 1.11–1.50        | 0.001           | 1.24               | 1.02–1.50        | 0.032          |
| Acute rejection episode (at least 1) | 2.19                | 1.05–4.53        | 0.036           | 1.71               | 0.49–5.92        | 0.401          |
| Early-onset hyperuricaemia |         |                  |                |                    |                  |
| Mild            | 2.05               | 0.67–6.26        | 0.209           | 1.75               | 0.21–4.52        | 0.540          |
| Moderate-to-severe | 2.24              | 1.09–3.00        | 0.022           | 1.89               | 1.05–3.43        | 0.035          |

\(^a\)The other variables that did not meet criteria \((P < 0.10)\) for inclusion into the multivariate analysis were recipient sex \((P = 0.59)\), donor sex \((P = 0.99)\), recipient age \((P = 0.63)\), donor age \((P = 0.83)\), retransplantation \((P = 0.95)\), human leukocyte antigen mismatch \((P = 0.78)\), cause of end-stage renal disease \((P = 0.52)\), delayed graft function \((P = 0.37)\), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use \((P = 0.24)\), hypertension \((P = 0.40)\) and hypercholesterolaemia \((P = 0.42)\).
Table 3. Univariate and multivariate analysis findings for risk factors of graft failure in early-onset hyperuricaemic recipients

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<tr>
<th>Covariate</th>
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<td>HR</td>
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<td>ESRD due to DM nephropathy</td>
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<td>0.09–11.35</td>
<td>0.078</td>
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<td>0.25–4.03</td>
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<td>Long wait: &gt; 1 year</td>
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<td>1.59–3.95</td>
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<td>2.37</td>
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<td>Deceased donor</td>
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<td>0.96–1.56</td>
<td>0.103</td>
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<td>HLA antigen mismatch</td>
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<td>1.07–2.10</td>
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<td>1.39</td>
<td>0.90–2.14</td>
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<td>Delayed graft function</td>
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<td>0.87–5.70</td>
<td>0.075</td>
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<td>Mild</td>
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<td>Moderate-to-severe</td>
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<td>Acute rejection episode (at least 1)</td>
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<td>1.98–6.68</td>
<td>0.000</td>
<td>2.92</td>
<td>1.37–6.23</td>
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*The other variables that did not meet criteria (P < 0.10) for inclusion into the multivariate analysis were recipient sex (P = 0.56), donor sex (P = 0.21), body mass index (P = 0.66), recipient age (P = 0.26), donor age (P = 0.50), ESRD due to hypertension (P = 0.74), retransplantation (P = 0.55), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use (P = 0.32) and hypercholesterolaemia (P = 0.94). ESRD, end-stage renal disease; DM, diabetes mellitus; HLA, human leukocyte antigen; HR, hazard ratio; CI, confidence interval.

Fig. 3. Moderate-to-severe early-onset hyperuricaemia was also found to be predictive of long-term graft failure and dysfunction, when only recipients with eGFRMDRD > 60 ml/min at 1 year post-transplantation were considered. Differences in graft survivals (A), CAN-free graft survivals (B) and eGFRMDRD changes (C) according to UA levels are illustrated. MI; mild, MS; moderate-to-severe; CAN, chronic allograft nephropathy. *P < 0.05; eGFRMDRD at follow-up versus eGFRMDRD at 1 year post-transplantation.

Obesity are well-known contributors to the development of hyperuricaemia in recipients receiving cyclosporine [2–4]. The present study shows that hyperuricaemia is common in RTRs and increases with time. However, the prevalence of post-transplant hyperuricaemia at 4 years after transplantation in the present study was 42.2%, which is clearly lower than those of previous series [1,12,13]. In fact, this prevalence varies according to the definition of hyperuricaemia. In the present study, the authors took acute changes in the serum UA level, which might be induced by alcohol, diet or exercise [17], into consideration and defined post-transplant hyperuricaemia as a UA level of >7.0 mg/dl in males and 6.0 ml/dl in females that persisted for at least two consecutive tests performed of a period of 6 months. In addition, it should be added that no morbidly obese patients were included in our study population. The rate of adult obesity is remarkably low in South Korea, which is attributed to a low-fat, high-vegetable diet [18]. Furthermore, the authors have a policy that diuretics are only administered to patients with a small urine output (<50 ml per hour) during the early postoperative period—only two of our study subjects routinely received diuretics. Although previous studies have shown the beneficial effect of tacrolimus in hyperuricaemic and gout patients compared to cyclosporine [19,20], the authors found no such association. There was no difference in the development of hyperuricaemia in those receiving cyclosporine and tacrolimus. Armstrong et al. [12] found that the UA level after renal transplantation is independently associated with male gender (P = 0.005), and likewise, the authors found that male gender significantly predisposed (P = 0.00) post-transplant hyperuricaemia. In addition, the authors found that a short waiting time (<12 months) had a protective effect (P = 0.043) against the development of post-transplant hyperuricaemia.

Experimental studies have shown that renal injury, comprising tubulointerstitial fibrosis, glomerulohypertrophy and glomerulosclerosis, occurs in hyperuricaemic rats, and that renal changes are prevented if serum UA is maintained in the normal range with allopurinol [8–10]. UA is found to be an important mediator of renal progression in the remnant kidney model of progressive renal disease and leads to injuries histologically identical to CAN [21]. In humans, hyperuricaemia is a known prognostic marker for the development of end-stage renal disease in individuals with or without kidney disease [5,6,22]. However, reports are conflicting in terms of the role of UA in the pathogenesis of renal transplant dysfunction and graft failure [11–14].
Controversy also exists about the need for treatment of hyperuricemia in RTRs [14,23]. Gores et al. [11] reported that no differences were observed between hyperuricaemic patients and normouricaemic patients with respect to serum creatinine levels, and recommended that no specific therapy is required for asymptomatic hyperuricemia in RTRs. Akgul et al. [13] also concluded that hyperuricemia had no effect on CAN during the first three post-transplant years. On the other hand, Gerhardt et al. [14] found that UA influenced graft survival and reported that the mean transplant survival rate at 5 years post-transplantation in hyperuricaemic patients (68.8%) was significantly lower than that in normouricaemic patients (83.3%). However, in the same study, treatment of hyperuricemia with allopurinol had no impact on graft survival. Armstrong et al. [12] demonstrated that UA is independently associated with eGFR$_{MDRD}$ at follow-up and that it is predictive of graft dysfunction, but they did not identify any relationship between the UA level and the change in the graft function over time.

It should be noted that a key problem in the epidemiological studies regarding hyperuricemia in RTRs is the disentangling of the chicken and egg relation between UA and graft function. Hyperuricemia may be a consequence of reduced GFR in renal allograft patients, or hyperuricemia may itself contribute to glomerulohypertrophy and tubulointerstitial fibrosis [8,9]. However, no previous study has determined which takes precedence over which [11–14]. To unravel this relationship, the authors classified hyperuricaemic recipients as early- and late-onset and evaluated eGFR$_{MDRD}$ changes in these groups, based on eGFR$_{MDRD}$ at the time of hyperuricaemic group assignments. In contrast with early-onset hyperuricaemic recipients, late-onset hyperuricaemic recipients showed an abruptly decreasing eGFR$_{MDRD}$ after the development of hyperuricemia (Figure 1), which indicates that progressive renal deterioration is already present in late-onset hyperuricaemia recipients, even though graft function at the time of hyperuricaemic group assignment appears satisfactory, and also suggests that only recipients with early-onset hyperuricemia should be included in analyses of the relationship between UA and renal transplant outcome.

The most important observation in this study was that moderate-to-severe (UA level $\geq$8.0 mg/dl) early-onset (within the first post-transplant year) hyperuricemia is not just a consequence of renal graft dysfunction and may be a risk factor of CAN, graft loss and changes in eGFR$_{MDRD}$ over time. In this study, it took $\geq$3 years before the adverse effects of hyperuricemia on graft function became evident, and $\geq$5 years before the impact of hyperuricemia on graft survival became obvious, which implies that the impact of hyperuricemia on the renal transplant outcome is dependent on the duration of exposure. In fact, short-term follow-up studies have not reported that hyperuricemia has any adverse effect on the kidney graft outcome [11,13]. In the present study, it was also found that allograft decline is dependent on UA levels. Contrary to the effect of mild hyperuricaemia, moderate-to-severe hyperuricemia was found to have a serious effect on GFR changes over time, and was identified as a significant risk factor of CAN and graft loss by univariate and multivariate analyses. The impacts of early-onset hyperuricemia on renal transplant outcome, which were dependent on exposure time and UA levels, were also evident when recipients with a good baseline GFR (eGFR$_{MDRD}$ at 1 year post-transplantation $>60$ ml/min, Figure 3), which strengthens the hypothesis that moderate-to-severe early-onset hyperuricemia may be a cause of long-term kidney transplant dysfunction and loss.

The results of this study should be interpreted in the context of its limitations. As early renal dysfunction is characterized by an increase in filtration fraction, and impaired tubular handling of UA with augmentation of UA reabsorption is the cause of cyclosporine-related hyperuricaemia [24,25], in order to affirm that the early elevation of UA levels before renal dysfunction indicates that hyperuricemia precedes renal function decline, functional studies such as determination of UA clearance, fractional UA excretion, renal plasma flow, and filtration fraction are required. This study has other limitations, which include a small study population, lack of protocol biopsies and the calculated GFR (eGFR$_{MDRD}$). Although acute changes in serum UA levels were taken into account and hyperuricemia was defined as a UA level of $>7.0$ mg/dl in males and 6.0 mg/dl in females that persisted for at least two consecutive follow-up tests with an interval of 6 months, this definition is not still flawless and a more clinically relevant definition is needed. There is also a possibility that bias was introduced by excluding recipients with grafts that had survived for $<$1 year. Additional studies with a larger cohort size are needed to confirm the impact of early-onset hyperuricemia, which was found to be dependent on the UA level and duration of exposure in the present study. Furthermore, to draw a firm conclusion about the cause and effect relationship of UA and graft dysfunction, the beneficial effect of urate-lowering therapy should be confirmed with prospective randomized trials involving a larger cohort of patients. Nevertheless, the data of this study are still reliable because of the prospective data collection and the long-term follow-up.

In summary, this study shows that early-onset ($<$1 year post-transplantation) hyperuricemia affects the renal transplant outcome in the long term, and that the impacts of early-onset hyperuricemia are dependent on UA levels, even after adjusting for other confounding variables and control of baseline graft function. Moderate-to-severe early-onset hyperuricemia following renal transplantation may be a prognostic marker of long-term kidney transplant dysfunction and failure. The findings of this single-centre study should be replicated with additional prospective trials involving a larger cohort of patients. In addition, the benefit of treating hyperuricemia should be determined in RTRs before it can be recommended.

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References


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