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EDITORIAL

Asymptomatic hyperuricemia following renal transplantation

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Abstract

Evidence is accumulating indicating a role for uric acid in the genesis and progression of kidney disease, and a few studies are beginning to show a possible beneficial effect of urate-lowering therapy. Whether this holds true for renal allograft recipients is not clear. In this short review evidence from epidemiological as well as intervention studies is summarized and discussed, with some practical considerations presented at the end.

Key words: Uric acid; Renal transplant; Urate lowering therapy; Allopurinol; Febuxostat

Core tip: Hyperuricemia is a common finding following renal transplantation; its clinical, as well as prognostic, significance, however, is not known. We have summarized available evidence from human epidemiological and intervention studies and concluded that, in the absence of gout, evidence in support of treatment for this condition in renal graft recipients is insufficient at present, although, when required, treatment with low-dose allopurinol or febuxostat appears to be safe.

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INTRODUCTION

A body of evidence, accumulated mainly in the last 15 years, based on animal and human experimental studies, as well as prospective observational and a few intervention studies, reviewed elsewhere[1-5], has lent support to the hypothesis that hyperuricemia may be linked to incident renal disease and the progression of chronic kidney disease (CKD). Fewer data are available regarding the effect of uric acid (UA) and hyperuricemia on graft function and survival following renal transplantation. Aim of this short review, which does not mean to be either exhaustive or comprehensive, is to summarize available evidence gathered from observational and intervention studies on the latter topic in adult patients; we will not cover incidence and treatment of gout after renal transplantation, referring the reader interested in a more detailed discussion to the excellent review by

Stamp *et al*[6].

Literature search was performed on the PubMed, EMBASE and Science Direct databases using the following search terms: Uric, Uric Acid, Urate, Hyperuricemia and Renal, Kidney Transplant, Transplantation, Graft, Allograft.

EPIDEMIOLOGY OF HYPERURICEMIA FOLLOWING RENAL TRANSPLANTATION

Hyperuricemia (serum UA greater or equal to 6.0 mg/dL in women and 7.0 mg/dL in men) is fairly common following renal transplantation. The prevalence of hyperuricemia in recipients of a renal allograft has been shown to range from 19% to 55% in patients whose immunosuppressive regimen did not include cyclosporin A (CsA) and from 30% to 84% in patients treated with CsA[7]. In the same series, incident gout was not observed in non-CsA treated patients, whereas it ranged from 2.0% to 28% following CsA therapy. More recently, Kalantar *et al*[8] have measured serum UA in 12767 samples from 2961 renal graft recipients; they detected hyperuricemia in 1553 patients (52.3%, 61% men, 39% women). In another study[9] of 302 patients with a well functioning kidney graft, at a median 7.6 years after transplantation, hyperuricemia was present in 42.1% of patients. Kim *et al*[10] investigated the prevalence of hyperuricemia in 356 transplanted patients with stable renal graft function (estimated GFR > 60 mL/min per 1.73 m^2). In this subgroup of patients they found raised UA levels in 55 (15.45%). Numakura *et al*[11] found hyperuricemia to be present in 38% of patients one year after transplantation; in their cohort male gender and dialytic vintage before transplantation were predictors of post-transplant hyperuricemia. According to the various studies, risk factors for hyperuricemia following renal transplantation include decreased glomerular filtration rate (GFR), diuretic use, pre-existent history of hyperuricemia, treatment with calcineurin inhibitors, in particular CsA, use of diuretics, male gender, diabetes mellitus, hypercalcemia, and higher body weight[7-11]; tacrolimus has been associated with lower odds of developing hyperuricemia, compared to CsA[9].

OBSERVATIONAL STUDIES EXPLORING THE ASSOCIATION BETWEEN HYPERURICEMIA AND GRAFT FUNCTION/SURVIVAL

Table 1 summarizes the most relevant studies exploring this relationship[10,12-32]. Although most studies tend to favour an influence of UA on graft function and survival, there are notable exceptions: for instance, Meier-Kriesche *et al*[20], reviewing their data from the SYMPHONY Study, in which a cohort of 1645 was followed-up for 3 years, found that the association of baseline UA with follow-up eGFR, disappeared when adjusting for baseline eGFR. Conversely, in the study by Haririan *et al*[21], after a mean 68 mo follow-up, hyperuricemia was associated with a 1.26 (95%CI: 1.03-1.53) hazard ratio (HR) of graft loss. Kim *et al*[24] recently reported their review of patients transplanted between 1990 and 2009, and they observed that hyperuricemia conferred an 1.45 ($P < 0.001$) HR of graft loss; however the same group, in a study enrolling transplanted patients with preserved renal function[10] found hyperuricemia to be associated with decreased renal function, but not with graft survival. Choi *et al*[27] have investigated the effect of hyperuricemia on graft survival in recipients of living-donor kidney transplants, and found a nearly double incidence of graft loss in hyperuricemic patients (22.2% *vs* 11.4%). Hart *et al*[29], in a post-hoc analysis of patients participating in the ABCAN Trial, undergoing protocol biopsies of the graft, found an association between serum UA levels and the degree of interstitial fibrosis and tubular atrophy. In patients undergoing biopsy for acute allograft dysfunction, Weng *et al*[30] found hyperuricemia to be associated with a greater cumulative incidence at one year of the combined end-point of doubling serum creatinine or graft loss (29.8% *vs* 14.9%, $P = 0.02$) compared to normouricemia. As far as cardiovascular outcomes are concerned, Dahle *et al*[28] after a 7.4 year follow-up of 2200 patients found a J-shaped association between serum UA levels and cardiovascular as well as all-cause mortality, with a significant increased HR in the 5th UA centile, and a similar tendency (though not reaching statistical significance) for the lowest UA quintile. Other studies have yielded conflicting results, although those with a longer follow-up, and those assessing graft survival (rather than eGFR) as an end-point, tend to favour an adverse effect of hyperuricemia. The reason for the discrepancies among studies are not completely clear, however differences in the definition of hyperuricemia, duration of follow-up, end-points evaluated, populations studied and in adjustment for confounders and comorbidities may have played a role. Recently Huang *et al*[33] have published a meta-analysis, including 12 studies judged to be of medium-high quality according to the Newcastle-Ottawa quality assessment scale; the results of the meta-analysis showed that hyperuricemia was a risk factor for chronic allograft nephropathy [unadjusted Odds ratio (OR) = 2.85, 95%CI: 1.84-4.38, adjusted HR = 1.65, 95%CI: 1.02-2.65] and graft loss (Unadjusted OR = 2.29, 95%CI: 1.55-3.39; adjusted HR = 2.01, 95%CI: 1.39-2.94). The authors of this meta-analysis concluded that hyperuricemia may be an independent risk factor of allograft dysfunction and may increase slightly the risk of poor outcomes.

At the moment, the evidence supporting a causative or prognostic role for serum UA in renal transplant recipients is not conclusive.

Table 1 Studies investigating the association between serum uric acid and renal function/graft survival in patients with kidney transplantation

Author	Numerosity	Average follow-up	Major findings	Ref.
Gerhardt *et al* (1999)	375	5 yr	Hyperuricemia (> 8.0 mg/dL in men and > 6.2 mg/dL in women), associated with reduced graft survival	[12]
Armstrong *et al* (2005)	90	2.2 yr	UA independent predictor of follow-up eGFR, but not of eGFR change over time	[13]
Akgul *et al* (2007)	133	3 yr	No association found between serum UA and the development of chronic allograft nephropathy	[14]
Saglam *et al* (2008)	34	Not reported	Serum UA associated to development of cyclosporine A nephropathy (biopsy proven)	[15]
Akalin *et al* (2008)	307	4.3 yr	Hyperuricemia 6 mo after transplantation significantly associated with new cardiovascular events and graft dysfunction	[16]
Bandukwala *et al* (2009)	405	2 yr	Hyperuricemia associated with cardiovascular events, and, inversely with eGFR	[17]
Meyer-Kriesche *et al* (2009)	1645	3 yr	UA levels one month after transplantation not associated with follow-up eGFR, after adjustment for baseline renal function	[20]
Karbowska *et al* (2009)	78	Not reported	Hyperuricemia associated with markers of endothelial dysfunction and inflammation	[19]
Min *et al* (2009)	368	58 ± 23 mo	Early-onset moderate-to-severe hyperuricaemia (serum 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	[18]
Haririan *et al* (2010)	212	68 ± 27 mo	Serum UA during the first 6 mo postransplant, is an independent predictor of graft survival	[21]
Kim *et al* (2010)	356	102.6 ± 27.2 mo	Patients with eGFR> 60 mL/min per 1.73 m^2. Hyperuricemia associated with decreased eGFR	[10]
Boratyńska *et al* (2010)	100	34 ± 12 mo	Serum UA not associated to graft survival during 30 mo of follow-up	[22]
Chung *et al* (2011)	351	10 yr	Hyperuricemia increased risk of cardiovascular complication; graft survival at 5 and 10 yr lower in hyperuricemic *vs* normouricemic patients (89% *vs* 96% and 81% *vs* 93% respectively, P = 0.02)	[23]
Kim *et al* (2011)	556	Not reported	Serum UA levels affect graft function, even after adjustment for baseline eGFR	[24]
Wang *et al* (2011)	524	10 yr	Retrospective study: UA significantly lower in patients with longer graft survival	[25]
Park *et al* (2013)	428	120 ± 58 mo	Serum UA associated with allograft loss, but rate of eGFR decline more potent predictor	[26]
Choi *et al* (2013)	378	10 yr	Graft survival (living donor renal transplantation) 88.6% in normouricemic *vs* 78.8% in hyperuricemic patients	[27]
Dahle *et al* (2014)	2200	7.4 yr	Highest serum UA quintile independently associated with increased HR (2.87, 95%CI: 1.55-5.32) of cardiovascular and all-cause (1.55, 95%CI: 1.09-2.25) mortality	[28]
Hart *et al* (2014)	149	5 yr	Post-hoc study of the ABCAN trial. Serum UA independently associated with increased odds of composite outcome of doubling of interstitium or ESRD from Interstitial Fibrosis/Tubular Atrophy, after adjusting for eGFR	[29]
Weng *et al* (2014)	880	43.3 ± 26.3 mo	Hyperuricemia associated with poorer graft survival (60.5% *vs* 75.8%, P = 0.007), no difference in all-cause mortality	[30]
Boratyńska *et al* (2014)	637	10 yr	Retrospective study. Hyperuricemia associated with chronic allograft dysfunction	[31]
Weng *et al* (2014)	124	14.3 mo	Patients undergoing biopsies for acute allograft dysfunction. Hyperuricemia associated with a greater cumulative incidence at one year of doubling serum creatinine or graft loss (29.8% *vs* 14.9%, P = 0.02) compared to normouricemia	[32]

UA: Uric acid; eGFR: Estimated glomerular filtration rate.

INTERVENTION STUDIES

Currently, no randomized, double-blind, controlled clinical trials of urate-lowering treatment on graft function and survival in renal allograft recipients are available. Table 2 shows the few published studies[11,34-37], all suffering from drawbacks such as low numerosity, lack of a placebo arm, single center, inconsistent reporting of adverse events and/or absence of blinding. In a study published in 2003, Perez-Ruiz *et al*[34] Studied 279 renal allograft recipient with hyperuricemia, 89 treated with allopurinol(mean dose 185 mg/d), and 190 with the uricosuric agent benziodarone(mean dose 73 mg/d); the immune-suppressive regimen included azathioprine in 49.1% of patients. Both drugs were effective in reducing serum UA, with similar withdrawal rate (11% for allopurinol and 8% for benziodarone). Major adverse events were rare, 3 in the allopurinol group (one case of pancytopenia, one hepatitis and one unexplained fever, all on high-dose treatment, 600 mg/d) and 2 in the benziodarone group (hypothyroidism). It must be remembered, however, that benziodarone was withdrawn from the market in many countries due to liver toxicity. More recently Numakura *et al*[11] studied 46 patients with post-transplant hyperuricemia treated with allopurinol (100-200 mg/d) compared

Table 2 Studies of uric-acid-lowering therapy in renal allograft recipients

Ref.	Study population	Average follow-up	Intervention/outcome(s)	Main study findings
Perez-Ruiz *et al*[34]	279 renal allograft recipients with hyperuricemia	38.6 ± 18.4 mo	Allopurinol, benziodarone/ serum UA levels	Both drugs effective in lowering serum UA; benziodarone safer in patients on azathioprine
Numakura *et al*[11]	121 renal allograft recipients with and without hyperuricemia	Up to 10 yr, mean not reported	Allopurinol/eGFR, graft survival	Hyperuricemia associated with reduced eGFR, but graft survival similar in normo and hyperuricemic patients
Osadchuck *et al*[35]	108 renal allograft recipients (54 patients treated *vs* 54 controls)	2 yr	Allopurinol/Serum UA levels, eGFR, graft survival	Reduced serum UA, preservation of eGFR in allopurinol treated patients; no differences in graft survival and blood pressure
Sofue *et al*[36]	93 renal allograft recipients (42 normouricemic, 51 hyperuricemic, 26 treated, 25 not treated)	1 yr	Febuxostat/serum UA levels, eGFR	Serum UA lower and eGFR stable in patients treated with febuxostat
Tojimbara *et al*[38]	23 renal allograft recipients with hyperuricemia	12 ± 2 mo	Febuxostat/serum UA, eGFR	Serum UA lower after treatment with febuxostat; eGFR stable

UA: Uric acid; eGFR: Estimated glomerular filtration rate.

to 75 normouricemic patients, followed up to 10 years. The former group had a lower eGFR, with a tendency for graft survival at 5 and 10 years to be reduced, with borderline statistical significancy. Rates of withdrawal from treatment or incidence of adverse events were not reported in this study. Osadchuk *et al*[35] in a retrospective case-control study, evaluated 54 hyperuricemic patients taking allopurinol because of gout, compared to 54 untreated controls matched for eGFR and time from transplant; mean baseline serum UA was 8.0 mg/dL in the allopurinol group and 6.8 mg/dL in the controls. At the end of the observation period (2 years) serum UA was reduced, and eGFR greater in the treatment group compared to controls, whereas no difference in graft survival was recorded. The dose of allopurinol used is not stated, and neither rate of withdrawal from treatment nor the incidence of adverse effects is reported. Sofue *et al*[36] studied 93 renal allograft recipients with stable renal function, 51 of them being hyperuricemic, 42 normouricemic. They treated 26 hyperuricemic patients with low-dose (10-20 mg/d) febuxostat, a novel xanthine-oxidase inhibitor associated with fewer adverse events than allopurinol[37]. After one year of treatment the majority of treated patients had achieved target serum UA levels and eGFR was stable. No serious adverse events were recorded and liver function tests were not altered by febuxostat. Finally, Tojimbara *et al*[37] assessed 22 hyperuricemic renal allograft recipients treated with low-dose febuxostat (10-20 mg/d). Despite the low dose administered, 73% of the patients achieved target serum UA levels (< 6.0 mg/dL). No serious adverse events were recorded, and only one patient withdrew from the study because of numbness in the arms. Immuno-suppressive drug levels were not affected by the co-administration of febuxostat.

CONCLUSION

Available evidence does not support widespread use of urate lowering therapies in asymptomatic hyperuricemic recipients of a renal allograft. At present, treatment should be limited to patients with gout, although patients with severe hyperuricemia (> 8.0 mg/dL) might benefit from serum UA lowering therapy; it is not known what serum UA target should be achieved, however, a recently published[39] long-term follow-up of a randomized, controlled clinical trial of allopurinol treatment in patients with CKD, has shown that nefro-protection can be attained by lowering serum UA just below its crystallization threshold (6.8 mg/dL). The therapeutic armamentarium is currently limited to xanthine-oxidase inhibitors, as uricosuric agents, with the possible exception of losartan, are mostly not indicated, or ineffective, in patients with CKD and/ or kidney transplant, uricase and its analogues are expensive, must be administered parenterally, and have important side effects; the discovery and isolation of urate transporters in the renal tubules, has led the way to the development of new hypouricemic drugs, currently under evaluation[40] but not immediately available for clinical use. The good news is that the data at hand seem to show that both allopurinol and febuxostat can be administered safely, at low doses, in renal transplant recipients, with the exception of those treated with azathioprine, the side-effects of which could be potentiated by xanthine-oxidase inhibition. In conclusion, randomized controlled trials of urate-lowering therapy are badly needed in this population of patients, to establish whether preservation of renal function and prolongation of graft survival can be achieved.

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