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Kidney transplantation in patients with systemic lupus erythematous

LionakiS *et al*. Kidney transplantation in lupus patients

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**Abstract**

Despite improvement in overall prognosis in lupus nephritis, 10% to 30% of patients with proliferative renal involvement progress to end stage renal disease, depending basically on the severity of the disease and the associated socio-economic factors. Kidney transplantation has been recognized as the most appropriate treatment for those patients, but still several issues come up after renal function restoration in a lupus recipient. Among others, the fear of lupus nephritis recurrence in the graft, the choice of immunosuppressive therapy in cases of recurrent lupus for a patient who has already been through a toxic and prolonged immunosuppressive course and finally the management of comorbidities to reduce the related morbidity in long term. All the above topics are questioned in this review, with the hope to provide a clear picture of data as illustrated in the current literature.

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**Key words**: Kidney transplantation; Lupus; Recurrence

**Core tip:** Significant improvement has been made in the management of lupus nephritis, but still 10%-30% of patients with proliferative renal involvement progress to end stage renal disease, depending basically on the severity of the disease and the associated socio-economic factors. Kidney transplantation has been recognized as the most appropriate treatment for those patients, but still several issues come up after renal function restoration in a lupus recipient. Among others, this review provides insights in topics sucha as the frequency of lupus nephritis recurrence in the graft, the choice of immunosuppressive therapy in such cases and finally the management of comorbidities to reduce the related morbidity in long term.

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**INTRODUCTION**

Although significant progress has been noted over the last decades in the treatment of lupus nephritis, the incidence of end stage renal disease (ESRD) has raised significantly between 1982 and 2004; from 1.16 cases per million person-years in 1982 to 3.08 in 1995 and 4.9 cases per million person-years in 2004[1,2]. Kidney transplantation (KTX) is the treatment of choice for patients with incident ESRD. However, the current practice for those who end up in ESRD due to recent exacerbation of lupus nephritis or newly diagnosed lupus with rapidly progressive renal disease is to start with hemodialysis (HD). The rationale is to suppress any residual lupus activity, to permit the disease to become quiescent, mostly in these patients who experienced a rapid decline of renal function due to aggressive lupus. Remission of lupus overall is particularly important to be achieved before proceeding to transplantation, and thus, all patients with recent significant renal or extra-renal activity and ESRD begin with HD. One potential benefit from this choice is the believed “burn-out” effect of this modality on the disease[3].Secondly, 3 to 6 mo on dialysis, before proceeding to transplantation, seem to be a sufficient period of time for renal function to recover, in those individuals, who experienced rapidly progressive glomerulonephritis due to lupus. In contrast, patients who are in complete remission for a considerable time period prior to ESRD, may also precede with preemptive KTX, if there is an acceptable living donor. This practice is supported by the findings of the United Network for Organ Sharing data set from 1987 to 2009 analysis[4] which revealed that patients with lupus nephritis who received a kidney transplant preemptively, before the need for dialysis, presented better graft survival and a lower risk of recipient death. It was associated with superior patient and graft outcomes[4].

**RENAL REPLACEMENT THERAPY FOR LUPUS PATIENTS WITH ESRD**

Very few, small, retrospective studies have compared dialysis modalities to KTX in terms of cumulative survival and long term clinical outcomes of patients. Goo *et al*[5] studied 45 SLE patients who initiated HD, peritoneal dialysis (PD) or KTX, between 1990 and 2000, in Korea. Disease activity, defined by the SLEDAI score, was significantly higher after PD commencement, during the 4.5 years of follow up (HD: 5.0 ± 3.6, PD: 7.4 ± 3.7, KTX: 2.2 ± 1.7), whereas survival rates were similar in the three groups[4]. Thirteen patients died during the observation period, mainly due to infections, but the type of renal replacement therapy they were under is not known[5].Clear superiority of KTX, in terms of survival and complication rates, has been shown in a retrospective multicenter study by Kang *et al*[6]. Ten year survival in 59 individuals, who underwent KTX, PD or HD due to lupus nephritis, was 90%, 81% and 55% respectively. It should be noted however, that the transplantation group consisted of relatively younger patients. Lupus flare-up was absent among transplanted patients (0% *vs* 50% *vs* 14%) during the study period. Higher mortality rates were recorded in the HD group and they were attributed mainly to cardiovascular disease and malignancies. Only one transplanted patient died during the ten year follow-up[6]. Current practice in the US population is depicted in a large analysis by Costenbader *et al*[7], based on the US Renal Data System. Between 1995 and 2006, 12344 patients with ESRD related to lupus nephritis were identified. Hemodialysis was the most common used renal replacement therapy with a tendency to increase significantly during the study period (from 75.9% to 83.9%). Despite a raise in the number of living donors, KTX rates decreased markedly from 1995 to 2006, a fact that could be associated with the organ shortage and the low socioeconomic status of several patients. Nevertheless, survival of patients undergoing KTX has shown absolutely no improvement over the 12 years of the study[7]. Patients suffering from ESRD secondary to lupus nephritis are younger at age[7,8], severely immunocompromised due to the underlying disease and the prolonged use of immunosuppressive therapy, with several co-morbidities coming with it. Thus, when planning the future of these patients in terms of renal replacement therapy, every effort should be made towards improving survival rates and quality of life.

Finally, PD is a better choice to initiate renal replacement therapy in patients with lupus and antiphopsholipid syndrome, since access failure due to recurrent thrombosis is a major problem in this group of patients.

**LUPUS ACTIVITY IN PATIENTS WITH ESRD**

As mentioned above, from the time SLE patients enter ESRD and start dialysis, clinical and serological activity of lupus is known to decrease. Long standing clinical experience and research have shown that patients with renal failure owing to lupus frequently experience a remission of their extra-renal manifestations and improvement in lupus serologic results in dialysis so that all immunosuppression can be withdrawn[3,9,10]. First of all, Fries *et al*[3] described this quiescence of lupus in patients with ESRD and dubbed “burnt-out lupus”. Several studies afterwards, have reported significant improvement of all autoimmune phenomena following commencement of dialysis. Mojcik *et al*[10], found that the prevalence of patients with clinical lupus activity in the post-dialysis period diminished over time: 55, 6.5 and 0% after 1, 5 and 10 years, respectively[11]. They found that the serological activity in lupus was not necessarily correlated with clinical activity and that it was a more frequent condition present in 80, 60 and 22% of the patients after 1, 5 and 10 years, respectively[11]. Although the causes of this phenomenon are not completely understood, it is repeatedly reported and in many cases associated with gradual or partial resolution of the extra-renal manifestations of lupus[12-14]. Less frequently, and typically in patients of black race, some investigators have reported continuation of lupus activity and occasionally exacerbation with the onset of ESRD[15]. However, these results are better understood if we consider that they refer to varying patient populations and genetic profiles.

**INCIDENCE OF RECURRENT LUPUS NEPHRITIS IN THE ALLOGRAFT**

The standard concern in lupus patients who undergo KTX contains lupus nephritis recurrence in the graft. Variable rates of recurrent lupus nephritis (RLN) have been reported, ranging from 0 to 44%[16-33] with certain differences, *i.e.,* patients’ characteristics, the era of immunosuppresion and in the indications for renal biopsies, *i.e.,* protocol biopsies, serial biopsies, accounting for this. Moreover, it is essential to distinguish the clinically apparent RLN in the allograft from incident histopathological findings attributable to a lupus effect in the graft without any concurrent clinical, renal or extra-renal, symptoms or signs of lupus and thus with questionable clinical importance. The setting of RLN in transplant patients generally include renal dysfunction, either acute increase in serum creatinine, or slowly progression compared with the baseline value, or new onset of proteinuria, or glomerular hematuria or both.

Clinical apparent RLN is found in an incidence rate of 2% to 11%[10, 23-33]. The results from the largest cohort of patients indicate that RLN in the graft is uncommon[28]. Specifically, they found that 2.44% of 6850 recipients with SLE, transplanted between 1987 and 2006, developed RLN[28]. Similarly, Stone *et al*[33] in an earlier period, showed a rate of RLN in the graft of 2%. Burgos *et al*[32], studying 177 patients with SLE, who underwent KTX found an overall rate of RLN in 11%. In our experience, RLN in the graft was documented in 7.7% of the patients who underwent a graft biopsy by clinical indication[28]. One of these patients, in our population, experienced graft loss due to lupus. Moroni *et al*[34] reported recurrence of lupus nephritis in 8.6% of the grafts, but no graft was lost because of RLN.

**CLINIC-PATHOLOGIC CORRELATIONS**

Incidence rates of “subclinical” lupus nephritis in the allograft, *i.e.,* findings by histopathology, which were brought into light in protocol or serial biopsies, differ substantially from those which were performed solely by clinical indication. First of all, the use of light microscopy alone, in the examination of biopsy specimens likely yields a significantly lower rate of diagnosis of RLN. However, soon, it was recognized that transplant kidney biopsy specimens from patients with a history of ESRD as a result of lupus must additionally be evaluated by both immunofluorescence and electron microscopy. The diagnosis of lupus nephritis in the renal allograft should ideally be established on the complete examination of the biopsy using the World Health Organization (WHO) or the International Society of Nephrology /Renal Pathology Society Histologic Classifications[35] including a positive immunofluorescence microscopy, and/or the presence of electron dense deposits in the electron microscopic assessment. In this regard, when both immunofluoresce and electron microscopy was used for the evaluation of renal biopsies, along with a more aggressive protocol of graft biopsies, it was shown that 30% of the patients experience recurrence of lupus nephritis[26]. In the study by Goral *et al*[26], graft survival was not influenced by the recurrent disease while the authors recommended complete morphologic study of the specimen using immunofluoresce and electron microscopy[26]. Similarly, Nyberg *et al*[21], in an earlier study of 16 patients with SLE had shown that 44% of them had biopsy proven RLN. Interestingly, light microscopy findings in biopsy specimens obtained from these patients were not diagnostic for RLN, but it was diagnosed with the combined use of immunofluoresce and electron microscopy20. Ultra structural evaluation with electron microscopy can be crucial in the diagnosis of patients with SLE, especially if they do not have any strong clinical manifestations and serologic markers at the time of the kidney biopsy[26]. Norby *et al*[36], in a cross sectional study, with surveillance biopsies after KTX in lupus patients, showed that subclinical recurrence was frequent, with 54% of the patients having RLN. The type and extent of renal involvement and activity is adequately characterized by electron microscopy in such cases[37]. Additionally, combined evaluation with immunofluoresce and electron microscopy may play a role in diagnosing RLN from other accompanying renal abnormalities, such as acute rejection, which might also associated with mild glomerulitis[37].

Time to RLN may also be varying from days to decades after KTX. Goral *et al*[26], demonstrated that RLN can occur as early as 6 d after transplantation. Conversely, there are reports with very late recurrence, up to 16 years post transplantation[29]. In the same study though the median time to recurrence was 4.3 years post KTX[29]. Moreover, the histopathologic lesion may be different from the one in the native kidney, and most frequently is less severe[4,5,32]. Nevertheless, given the silent nature of many of the recurrences, it is impossible to determine the precise timing of recurrence, or the rate of recurrence in patients who did not undergo biopsies.

**RISK FACTORS FOR RECURRENT LUPUS NEPHRITIS**

The importance to practicing nephrologists of lupus recurrence in the renal graft is that, they may have poorer outcomes due to it, as compared with other kidney transplant recipients. However, a report of the American College of Surgeons/National Institute of Health Transplant Registry though in 1975 opened the door to KTX for patients with lupus, as observed that they had outcomes comparable to those in non-lupus patients[16]. Following this observation there have been numerous studies which have found that overall 5- and 10- year graft survival rates are similar[11,13,14,29,34,36,38-41] or comparable[25,29] among patients with lupus and those with other primary diseases. Recognized risk factors for allograft loss in the lupus patients include black non-Hispanic ancestry, female gender, and young age[29,32]. Patients with antiphospholipid autoantibodies[34] and those receiving the kidney from living donors[36] also have a higher risk of recurrence. African American ethnicity was shown to be independently associated with RLN in the allograft and possibly with diminished survival[32]. Dooley *et al*[42] had earlier shown that compared with Caucasians, lupus nephritis developed more frequently in African Americans (60% *vs* 25%). Furthermore, African Americans displayed a less favorable response to treatment and thus the disease progressed to ESRD at higher rates[42]. In agreement, Contreras *et al*[29] found that black non-Hispanic and female recipients were shown to have 1.88- and 1.70-fold increased odds for the development of RLN. The same study demonstrated that recipients younger than 33 years had 1.69-fold increased odds for the development of RLN. Nevertheless, onset of SLE and ESRD at a younger age in a black woman usually predicts a more aggressive disease[29]. Recurrent lupus nephritis and chronic rejection of the kidney were shown to be risk factors for allograft loss (HR = 2.48, 95%CI: 1.09-5.60 and HR 2.72, 95% CI 1.55-4.78 respectively) in the study by Burgos *et al*[32]. However, Stone *et al*[33] had found that RLN did not invariably result in allograft failure. The same study demonstrated that short length of pre-transplantation dialysis, *i.e.,* less than 6 mo, had no adverse effect on KTX outcome in 10 of 11 studies that examined the relationship[33].

**DIAGNOSIS AND TREATMENT OF RLN IN THE ALLOGRAFT**

Recurrent lupus nephritis in the allograft should be suspected in any patient who ended up in ESRD due to renal lupus, in the light of certain clinical and/or laboratory findings. In this regard, new onset of proteinuria or glomerular hematuria should directly lead to the suspicion of lupus nephritis in the allograft. However, rapid worsening of previously existing proteinuria should also raise the suspicion for recurrent lupus, especially in the coexistence of glomerular hematuria. The clinical presentation with increased serum creatinine is also typical for patients with RLN in the graft. However, among all transplant recipients who present with an elated serum creatinine there are certain other parameters that need to be excluded as possible contributors before consider RLN. These include dehydration, toxic concentrations of serum calcineurin inhibitors, and obstructive uropathy. Diagnosis of RLN is made by biopsy and histopathologic evaluation by light microscopy, immunofluoresce and electron microscopy as said earlier. Measurement of serologic parameters, such as complement levels and titers of anti-double stranded DNA antibodies is not helpful in establishing the diagnosis in the allograft[24,33].

***Immunosuppressive therapy***

Kidney transplant recipients with recurrent lupus most frequently do not require any change in the immunosuppressive regimen, as they already receive maintenance therapy for the transplant. Most of them are shown to have mild lesions in the graft due to lupus, as demonstrated by surveillance biopsy studies[36]. Specifically, most of the patients had subclinical disease with class I or II in the biopsy[36]. On the other hand, the vast majority of patients had chronic allograft nephropathy (84%)[43] while they are also susceptible to calcineurin inhibitor toxicity, as patient with SLE who have had not transplants[42]. Besides, the major impediment to the goal of improved kidney transplant survival is a cumulative and progressive immune and non-immune injury[43,44]. In kidney transplant recipients with SLE, standard immunosuppresion with a calcineurin inhibitor, mycophenolate mofetil and prednisone seems to protect against clinically overt recurrent disease but not against chronic allograft nephropathy[36]. Importantly, indexes of lupus activity were found low in the study by Norby *et al*[36], and did not differentiate between patients with RLN and those without recurrence.

However, there are selected patients that require additional immunosuppressive treatment. In terms of renal involvement, these include mostly patients with clinically evident disease and severe histopatholgic lesions, consistent with class III or IV by the WHO classification[35] in the graft. Among patients who have a histologic diagnosis of recurrent lupus in the graft, along with rapid deterioration of renal function, all other factors associated with acute renal dysfunction in a kidney transplant recipient should be excluded at first place, *i.e.,* acute rejection, chronic allograft nephropathy, calcineurin inhibitor toxicity. Following this workup any lupus patient with new onset of proteinuria or worsening proteinuria and/or hematuria in the presence of severe proliferative lesions in the graft biopsy needs modification of the existing immunosuppressive regimen. Depending on the clinical picture and morphologic lesions we use either higher doses of mycophenolate mofetil or (2-3 g/d), or initiate cyclophopshimide intravenously along with discontinuation of the current antimetabolite. Both of these options are always accompanied by glucocorticoids, usually pulses of methylprednisolone, 500-1000 mg/d for 3 consecutive days, which are followed by a tapering steroid regimen. We tend to choose cyclophopshimide in cases who present with rapid renal deterioration combined with a crescentic pattern by histology, and in all cases with severe extra renal disease, *i.e.,* pulmonary hemorrhage, central nervous system involvement, or any other life threatening phenomenon attributable to lupus. Although there is not sufficient data to support the use of the aforementioned agents in the lupus transplant recipient with recurrence, this approach is based upon studies of patients with lupus nephritis involving the native kidney[45]. Similarly, the optimal scheme of cyclophosphamide for these patients, who already carry a considerable load of immunosuppression starting from their initial diagnosis of SLE, is not known. One reasonable option is the Euro lupus regimen, which consists of 6 intravenous pulses of 0.5g cyclophosphamide[46]. Patients of black race may need more aggressive therapy with monthly courses of cyclophosphamide of 0.5-1 g/m2 body surface area. In any case, the leukocyte nadir is the main guide of therapy, *i.e.,* less than 4000/microL and absolute neutrophil count less than 1500/microL. However, the maximum dose fo cyclophosphamide should not exceed the 1g/m2 body surface area.

In cases of resistant RLN, despite the use of mycophenolate mofetil and cyclophosphamide, the only treatment option is rituximab along with the increase of glucocorticoids. Nevertheless, there are no published data to support the use of rituximab in RLN among kidney transplant recipients, but only a few observational studies and case reports of the successful use of rituximab in patients who suffer from lupus nephritis in the native kidney and are resistant to mycophenolate mofetil and cyclophosphamide[45,47-49]. As the optimal scheme is not known, one may use the same dose as has been studied for lupus nephritis in the native kidney, *i.e.,* 1g given on days 1 and 15, or 375 mg/m2 body surface area as given in ANCA glomerulonephritis[50,51]. Yet, even with data on a considerable number of patients treated with rituximab, we should always keep in mind that the long term toxicity has not been completely defined in the transplant population[51].

***Non-immunosuppressive therapy***

We treat all patients with histopathologic changes of RLN in the graft and protein excretion, typically more than 0.5 g/d with renin angiotensin system blockade. The notion for this approach is based upon studies in non-transplant patients with chronic kidney disease and proteinuria, where it has been shown that renin angiotensin system blockade decreases the progression of renal disease[52]. Anemia and hyperkalemia maybe seen with the angiotensin converting enzymes inhibitors, but this issue is usually bypassed by the fact that transplant recipients are generally closely followed and such side effects are readily detected. Moreover, the long term benefit from the renin angiotensin system blockade outweighs the risk of experience of such events.

**MANAGEMENT OF COMORBIDITIES**

Death with a functioning graft is a major cause of renal allograft loss in the general population. The same applies to recipients with ESRD due to lupus nephritis and it is mainly attributed to cardiovascular disease[53].

***Cardiovascular disease***

Although, SLE affects predominantly young, female individuals of a childbearing age, studies point out that the disease is characterized by an accelerated atherosclerotic mechanism, which increases cardiovascular morbidity and mortality[53,54]. Furthermore, the study by Costenbader *et al*[7], recorded an increased trend towards cardiovascular risk factors, namely smoking, obesity, diabetes mellitus and hypertension in incident SLE-related ESRD patients, in the years 1995-2006. Several small, mostly retrospective, single-center studies with limited numbers of patients indicate cardiovascular disease as the leading cause of morbidity and mortality in transplanted patients secondary to lupus nephritis[28,47,55]. A retrospective analysis of data from the US Renal Data System (USRDS) and the United Network for Organ Sharing (UNOS) was conducted between 1990 and 1999. Among 2886 renal transplant patients due to lupus nephritis cardiac events and cerebrovascular disease were the main causes of death. However, non-SLE recipients (*n* = 89958) exhibited a higher rate of these co-morbidities, probably because they were older with a higher prevalence of pre-existing cardiovascular disease and diabetes mellitus[55]. According to data from the National Transplant Centre in Norway, 77 patients with SLE underwent first and subsequent KTX from 1972 to 2005. They were compared to 154 well matched non-SLE transplanted patients. Norby *et al*[56], also found that the main cause of death was cardiovascular disease, with acute myocardial infarction as the major problem. Notably, death from cardiac associated events occurred much earlier in the SLE patients compared to the control group (median time: 3.9 years versus 13.0 years).

No specific data exist to date comparing morbidity between deceased and living donor KTX in this patient population, although living donation in these patients has been associated with improved patient and graft survival[41].

***Other co-morbid conditions***

An area of major concern has always been the previous history of antiphospholipid antibody syndrome (APAS), or solely the presence of these antibodies in this patient population, because of the risk for graft or other vascular thrombosis. Vaidya *et al*[57], recently showed that the ten year renal allograft survival is significantly lower among patients with APAS, compared to those who have only circulating antibodies. Careful monitoring is mandatory in order to avoid thrombotic episodes.

Infections (sepsis, pneumonia, viral infections, fungal infections, tuberculosis, urinary tract infections) have been reported as causes of morbidity and mortality after KTX due to lupus nephritis[6,28,47,53-55]. One could hypothesize, that prolonged exposure to immunosuppressive agents prior to ESRD, as well after ESRD and KTX predisposes to infections. However, published data are contradictory as the prevalence of serious infections is not always higher in the SLE recipients compared to the non-SLE ones[6,57].

Malignancies, orthopedic complications, such as avascular necrosis of the femur head and osteoporosis have been scarcely reported in various studies as late complications in kidney transplant SLE recipients[6,47].

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