

Proteinuria as a Prognostic Factor for Graft and Patient Survival after Kidney Transplantation

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Abstract

This review intends to make an update concerning the role of proteinuria and albuminuria as risk and prognostic factors for graft and patient survival. Current therapeutics to modify proteinuria and its significant consequences will be also discussed. The following subjects will be considered: (i) screening methods for proteinuria, (ii) proteinuria as an individual prognostic factor, (iii) proteinuria in prognostic scores, (iv) proteinuria and graft histopathology, (v) albuminuria, and (vi) therapeutic interventions. A search in the literature has been made and only clinical reports in adults with at least 50 patients were included in the analysis. Studies concerning the association between immunosuppression and posttransplant proteinuria were excluded. Finally, 92 studies have been analyzed in this review.

Proteinuria and albuminuria, frequently observed following renal transplantation (9-42%), has been mentioned, not only as a significant marker of long-term graft dysfunction, but also as a major prognostic factor of patient survival. With reference to this relationship between proteinuria and renal dysfunction, it has been shown that increasing proteinuria (> 1.5 g/day) correlates with allograft that may have de novo glomerular pathology. Conversely, lower levels of proteinuria are generally associated with non-glomerular, nonspecific histological changes. Graft survival rate with persistent proteinuria was significantly lower than without persistent proteinuria, and the result was not related to the causes of proteinuria (chronic rejection versus other causes).

Concerning the main subject of this review, 22 studies comprising 18,179 individuals have been analyzed in three groups: proteinuria as an independent risk factor unrelated to post-transplant events (14,839 patients), and related with posttransplant events (2,724 patients); in addition, in 616 patients, albuminuria was also analyzed as risk factor in kidney graft outcome. In an attempt to simplify the evaluation of results, the degree of urinary protein excretion was categorized in three levels of proteinuria: low, middle, and high.

The importance of proteinuria/albuminuria as an independent risk factor is extensively discussed in this review. From 22 studies evaluated (21 concerning proteinuria and 1 albuminuria), 19 with 16,821 patients categorized proteinuria/albuminuria as a significant risk factor for outcome of kidney transplantation.

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As regards its relevance in the prognosis of graft survival, this subject was mentioned in 20 studies and it was significant for proteinuric/albuminuric graft recipients, from a cohort of 12,647 patients.

As regards mortality, this issue was analyzed in 10 of the 22 studies. Eight confirmed proteinuria as a significant predictor of mortality evaluating a cohort of 12,091 patients. Furthermore, two analyses with 463 patients did not find proteinuria as a prognostic risk factor for patient mortality.

In conclusion, the analysis performed in this review concerning the prognostic value of proteinuria/albuminuria in kidney transplantation suggests that abnormal urine protein excretion at any time and grade is a significant prognostic factor of graft and patient survival. Systematic proteinuria screening during the follow-up of renal transplantation should be considered a mandatory rule that will make possible the early diagnosis of possible clinical and/or histopathological etiologies and opportune therapeutic prescription. (Trends in Transplant. 2011;5:23-48)

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Key words

Proteinuria. Renal transplantation. Risk factor. Prognosis. Graft outcome. Patient outcome.

Introduction

As a consequence of unmodified inactive organ shortage, the course of action of renal transplantation has experienced a major change. Increasing acceptance of expanded criteria donors (ECD), mainly old and very old recipients, undoubtedly generates new alternatives in the follow-up, prognosis, and treatment, in the search for long-term survival of patients and transplants organs¹.

Despite the improved management of acute rejection episodes and the ensuing impact on short-term kidney graft survival, long-term graft failure related to interstitial fibrosis and tubular atrophy, previously identified as "chronic allograft nephropathy" remained almost constant²⁻⁴.

Proteinuria and albuminuria, frequently observed following renal transplantation (9-42%), has been mentioned, not only as a significant marker of long-term graft dysfunction,

but also as a major prognostic factor of patient survival and even recently as a strong predictor of successful switch from cyclosporin A to sirolimus⁵⁻¹⁰.

The mechanisms through which particular proteins may cause renal pathology are of interest as regards the potential feasibility for therapeutic interventions. Burton, et al. reviewed the subject and suggested that the abnormal filtration of proteins across the glomerular basement membrane will bring them into contact with the mesangium and with the tubular cells. The authors considered that current evidence supports the role of lipoproteins on mesangial cell function, which could contribute to glomerular sclerosis. The proximal tubular cells reabsorb proteins from the tubular fluid, which leaves them particularly vulnerable to any adverse effects proteins may have. The increased metabolism of proteins may result in the production of ammonia, which can mediate an inflammatory state through the activation of complement.

The resultant stimulation of cytokines, chemo-attractants, and matrix proteins by the tubular cells may generate interstitial inflammation and scarring of the renal tissue¹¹.

Massy, et al. reported that the prevalence of proteinuria > 0.5 g/day is four-times higher in patients with chronic allograft rejection than in patients with stable transplant function¹², and it was also suggested that proteinuria > 0.5 g/day is widely considered a reasonable risk factor threshold level¹³⁻¹⁷.

Moreover, retrospective analysis showed that the degree of proteinuria was the most powerful predictor of the decline of creatinine clearance^{18,19}. Concerning the relationship between proteinuria and renal dysfunction, it has been shown that increasing proteinuria > 1.5 g/day correlates with allograft that may have *de novo* glomerular pathology. Conversely, lower levels of proteinuria are generally associated with non-glomerular, nonspecific histological changes. As a result, the authors suggested that the relationship between proteinuria and graft survival is independent of other variables, including graft function and graft histology²⁰.

Graft survival rates in renal transplant recipients with persistent proteinuria are significantly lower than in those recipients without persistent proteinuria⁵, and this was unrelated to the causes of proteinuria (chronic rejection vs. other causes). This finding suggests that proteinuria itself is an important risk factor for allograft failure¹⁹.

The relevant importance of proteinuria as a risk factor as well as an indicator of outcome of patient and graft survival in kidney transplantation has concomitantly intensified clinical approaches to evaluate positive therapeutic interventions, mainly with angiotensin-converting enzyme (ACE) inhibitors/blockers, aimed at controlling this nonimmunologic risk factor of graft failure²⁰⁻²⁷.

This review proposes to formulate up to date information about the role of proteinuria and albuminuria as risk factors for posttransplant kidney damage, as well as its usefulness as a prognostic factor for graft and patient survival. Current therapeutic possibilities to modify the association of proteinuria with progressive disease and its critical consequences will also be discussed.

Therefore, we intend to review and discuss below the following subjects related with proteinuria/albuminuria as a prognostic predictor:

- Screening methods for proteinuria.
- Proteinuria as a predictor.
 - In unrelated transplant events.
 - In related transplant events.
 - Of posttransplant cardiovascular events.
- Proteinuria in prognostic scores of kidney graft outcomes.
- Proteinuria and graft histopathology.
- Albuminuria.
- Therapeutic interventions.
- Discussion and conclusion.

A literature search has been made (Scopus and PubMed) involving the subject posttransplant proteinuria and particularly proteinuria as a prognostic factor for graft and patient survival. Only clinical reports in adults with a cohort of at least 50 patients were included in the analysis. Studies concerning the association between immunosuppression and posttransplant proteinuria were excluded. Finally, 92 studies have been evaluated in this review.

Screening methods for proteinuria

The reference test (24-hour urine protein estimation) is a result of the high degree of variation in the urinary protein concentration during the course of the day. This precludes the use of a shorter collection period or the use of a random urine sample for protein concentration measurements.

An alternative approach that has been proposed and utilized is that of expressing the protein excretion in a random urine collection as a ratio to the creatinine concentration. Ginsberg, et al. studied the relationship between the protein-to-creatinine ratio (PCR) and 24-hour protein excretion and found an excellent link between the protein content of a 24-hour urine collection and the PCR in a single urine sample. The authors considered that the determination of the PCR in single urine samples obtained during normal daylight activity, when properly interpreted by taking into consideration the effect of different rates of creatinine excretion, can replace the 24-hour urine collection in the clinical quantitation of proteinuria²⁸.

Proteinuria and albuminuria are recognized to have diagnostic and predictor value in the early detection of renal disease and can be of considerable importance in assessing the effectiveness of therapy and the progression of the disease²⁹⁻³². Krishna, et al. found an excellent correlation between the protein content of 24-hour urines and urine PCR in overnight urine samples. Also, 89% of all clinically observed acute rejection episodes were accompanied by an increase over baseline of urine PCR; in 56.5% of these episodes elevation of urine PCR preceded that of serum creatinine (SC). Persistent proteinuria with urine PCR > 100 mg/mmol preceded significant deterioration of graft function. Therefore, a urine PCR of 100 mg/mmol can be considered as an apparent cutoff to differentiate stable from deteriorating graft function in long-term evaluation

of transplant recipients³³. In a prospective study in 133 kidney transplant patients, Steinhäuslin, et al. evaluated the accuracy of the urine PCR determined in morning urine specimens in assessing 24-hour proteinuria. The results confirm that the urine PCR in morning samples is a reliable estimate of the 24-hour proteinuria in kidney transplant patients. Additionally, its variation appears to accurately reflect changes in the rate of protein excretion³⁴.

Torng, et al., studying 289 patients, also conclude that the urine PCR is a useful and convenient screening and longitudinal test for proteinuria³⁵. To confirm the value of this method, a systematic review of the literature on measurement of the urine PCR on random urine compared with the respective 24-hour protein excretion was performed by Price, et al. Likelihood ratios were used to determine the ability of a random urine PCR to predict the presence or absence of proteinuria. This systematic review showed that there are sufficient data in the literature to demonstrate a strong correlation between the urine PCR in a random urine sample and 24-hour protein excretion³⁶.

Proteinuria as predictor

In unrelated transplant events

To assess its importance as a predictor of graft and patient survival posttransplantation, the nature and severity of proteinuria was evaluated. Individuals with sustained proteinuria > 0.5-1 g/day for more than three months displayed one- and five-year graft survival significantly different from those non-proteinuric patients^{37,38}.

Yildiz, et al. reviewed 514 renal graft patients: 56 of them (11%) had good allograft function and proteinuria. Patients were classified in two groups according to the type of proteinuria: permanent proteinuria (P) or temporary proteinuria (T), and considering the

amount of proteinuria as massive vs. non-massive proteinurics. Regarding to the type of proteinuria, two- and five-year allograft survival rates were 70 and 58% in group P and 92 and 87% in group T, respectively ($p = 0.02$). Eighty-five per cent of the patients with permanent proteinuria also had massive proteinuria. This study suggests that the type of posttransplant proteinuria had a stronger effect on allograft outcome than the severity of proteinuria³⁹.

In their analysis, Bear, et al. recognized that the difference in graft survival observed in non-proteinuric and proteinuric patients is 88.7 and 61.8%, respectively. In addition, in this study no significant difference was observed if proteinuria is only sustained for less than six months (93.3 and 81.7%)⁴⁰.

In 357 patients followed retrospectively over a period of five years, Hohage, et al. found that 25.5% of these patients developed proteinuria ranging from 0.25 to 1.0 g/day over six or more months. These patients were well matched with a group without proteinuria ($n = 266$). Five-year transplant survival in the group with proteinuria was 58.9% compared to 85.6% in non-proteinuric recipients. Permanent proteinuria over 12 months further reduced five-year transplant survival to 42.6%. Intermittent proteinuria did not worsen the long-term prognosis throughout the whole observation period. Serum creatinine in proteinuric recipients was almost 0.5 mg/dl higher compared with patients without proteinuria. No correlation between proteinuria and gender, age of recipient, duration of hemodialysis, and age of donor, cold ischemia time, and mismatches could be detected, suggesting that proteinuria within the first six months apparently is not due to donor or recipient factors. The authors found a significant relationship between proteinuria and graft failure⁴¹.

Considering the degree of proteinuria, it has been stated that early low-grade posttransplant proteinuria at three months represents a

risk factor for graft survival. In a recent study involving 477 patients, with a mean follow-up of 122 months, the participants were classified into four groups based on the urine PCR (< 0.15 : group 1, $n = 85$; $0.15-0.5$: group 2, $n = 245$; $0.5-1.00$: group 3, $n = 96$; and > 1.00 : group 4, $n = 51$). Multivariate analysis revealed that even low-level proteinuria at three months predicted death-censored graft failure (group 1 [reference] hazard ratio [HR]: 1; group 2 HR: 7.1; group 3 HR: 10.5; group 4 HR: 16.0; $p = 0.001$). In this study, the impact of the degree of proteinuria on patient survival and the occurrence of vascular events was only significantly higher for group 4⁴².

Ibis, et al. analyzed the significance of proteinuria > 0.3 g/day as marker of graft survival in a cohort of 130 individuals. The occurrence of graft dysfunction was significantly different in patients with and without proteinuria (54.17 vs. 82.62%, respectively). The authors concluded that proteinuria and panel reactive antibodies were significant predictors of graft failure and that early proteinuria is a significant risk factor in kidney transplantation⁴³.

Pérez Fontán, et al. performed a study on the prognostic significance of proteinuria with a survival analysis and its correlation with late markers of graft dysfunction. In 560 cadaveric renal transplants, the intensity and persistence of early proteinuria was evaluated. The results, at any considered background, showed that early proteinuria is a strong predictor of poor patient and graft survival. This effect is directly related to the intensity and persistence of the disorder⁴⁴.

Amer, et al. also mentioned that lower levels of proteinuria are in general associated with non-glomerular, nonspecific histological changes. These authors suggested that the relationship between proteinuria and graft survival is independent of other variables, including graft function and histology⁴⁵.

Concerning its effects on graft and patient outcome, minimal proteinuria (< 0.5 g/day) has been analyzed by Kang, et al. in 272 renal recipients surviving for one year with a functioning graft. Patients were classified according to the one-year posttransplant proteinuria as: non-proteinuric group (< 0.2 g/day), minimal proteinuria group (0.2-0.5 g/day), and overt proteinuria group (\geq 0.5 g/day). Fifteen percent of patients had minimal proteinuria and 7.8% had overt proteinuria. Five-year graft survival in the minimal proteinuria group was 83%, and 73% in the overt protein group, in contrast to 97.1% in the non-proteinuric cohort ($p = 0.01$ for trend). In a multivariate analysis, the minimal and overt proteinuria groups had higher risks of graft failure. This study also showed that even minimal proteinuria one year posttransplantation was associated with poor graft outcome⁴⁶.

The association with endothelial dysfunction is considered the mechanism that may increase the mortality risk of proteinuria. Van Ree, et al., in 604 renal transplant patients, investigated whether urinary protein excretion is correlated with markers of endothelial dysfunction and whether these markers affect the association of proteinuria with mortality in renal transplant recipients. Patients were grouped according to proteinuria: < 0.3, 0.3-1.0, and > 1.0 g/day. Soluble intercellular adhesion molecule type 1 (sICAM-1) and soluble vascular cellular adhesion molecule type 1 (sVCAM-1) were measured using ELISA. All participants were followed up at least once a year; median value for proteinuria: 0.2 (0.0-0.5 g/day). Patients with urine protein excretion > 1.0 g/day and high concentrations of sICAM-1 or sVCAM-1 are at high risk of death ($p < 0.0001$). This study showed that patients with proteinuria and high concentrations of sICAM-1 or sVCAM-1 have an increased risk for death, compared with patients without proteinuria, whereas this is not the case in patients with proteinuria but low concentrations of sICAM-1 and sVCAM-1.

The results of this trial suggested that the association of proteinuria and increased mortality after renal transplantation is related to a possible important role of endothelial dysfunction⁴⁷.

In 722 patients surviving at least one year with a functioning graft, the incidence of proteinuria as a mortality risk factor was reviewed by Roodnat, et al. Proteinuria was analyzed both as a categorical variable (presence vs. absence) and as a continuous variable to consider its influence as a risk factor for graft failure or death. Statistical analysis showed that proteinuria at one year posttransplantation, both as a categorical and continuous variable, was an independent variable for graft failure. A correlation was also found with the type of underlying disease (higher risk of graft failure in patients with glomerulonephritis), history of hypertension, and presence of systemic disease. Patient death was also higher in graft recipients with proteinuria as compared to non-proteinuric patients. Death risk was almost twice as high for patients with proteinuria at one year compared with patients without proteinuria. Globally, mortality risk is higher with increasing amounts of proteinuria at one year, both for cardiovascular and non-cardiovascular death in these patients⁴⁸.

Concerning the importance of heavy proteinuria > 1 g/l in graft dysfunction and its significance as a risk factor for prognosis of graft and patient outcome, Kim, et al. highlighted the responsibility of chronic rejection and recurrent or *de novo* glomerulonephritis as a determinant of heavy proteinuria developed post renal transplantation. Heavy proteinuria was present in 54 (6.7%) of 797 patients and persisted for at least six months (the mean follow-up period was 3.7 years). Improvement of proteinuria was defined by reduction in proteinuria to below 0.5 g/day for more than six months in patients treated with angiotensin-converting enzyme inhibitors (ACEI) or other medications. The five-year allograft survival rate in patients with heavy proteinuria > 1 g/day was

56.3%, and 88.1% in patients with proteinuria < 1 g/day ($p = 0.01$). The five-year graft survival rate in patients with chronic vascular rejection was 35.7%, and 67.5% for those with recurrent or *de novo* glomerulonephritis ($p = 0.002$). There was no difference in the survival according to the amount of proteinuria. The incidence of persistent proteinuria in renal transplant recipients had been reported to be from 3-30% in the pre-CsA period. In the CsA era, it was reported to be 12.8% of patients with proteinuria > 1 g/day and 27.9% in patients with proteinuria > 2 g/day⁴⁹.

Recently, in 454 first transplants (follow-up: 100 ± 3.2 months), the significance for graft and patient survival of high serum creatinine > 120 $\mu\text{mol/l}$ (HSC) and high proteinuria > 0.5 g/day (HP) at three months, and two and five years was also compared and evaluated. Donor/recipient age, sex, panel reactive antibody, HLA mismatches, cold ischemia time, delayed graft function, acute rejection, blood pressure and its treatment, diabetes and anticalcineurin use were also evaluated. This study showed that HSC is a prognostic factor of graft survival ($p < 0.01$) only at five years, but not at any other study period. In addition, HSC does not predict mortality at any period. High proteinuria at three months ($p < 0.001$) and at two years ($p < 0.001$) significantly predicts graft failure. High proteinuria at two years is the prevailing prognostic factor of patient survival in kidney transplantation. Conversely, HSC is a significant prognostic factor of graft survival ($p < 0.01$) only at five years, but not at any other study period. On the other hand, proteinuria > 0.5 g/day at three months ($p < 0.0001$) and at two years ($p < 0.001$), but not at five years, is a significant risk factor for graft failure⁹ (Figs. 1-3).

The relationship between renal function within one year after transplantation expressed as SC level at six months and at one year, and the change in SCr (ΔCr), between six months and one year and proteinuria as

parameters influencing long-term survival, have been studied by Fernández-Fresnedo, et al. in 365 renal transplants. The authors concluded that graft survival was worse among patients with higher ΔCr , especially among those who developed proteinuria. In addition it is suggested that using a combination of SCr and ΔCr with proteinuria, it is possible to identify transplant recipients with a predictably shortened half-life⁵⁰.

The significance of proteinuria > 0.5 g/day as a prognostic factor, not only for graft failure but also for patient survival, is not confirmed regarding mortality by Sancho, et al. Among 337 kidney allograft recipients, patients with proteinuria > 0.5 g/day were treated with ACEI and/or angiotensin-receptor blockers (ARB). Graft survival at five years was 69% among patients who developed proteinuria and 93% in those without proteinuria ($p = 0.000$), but no impact in patient survival was observed in this study ($p = 0.062$)¹⁷.

The significance of persistent proteinuria following renal transplantation on graft and patient survival was tested in 3,365 kidney graft patients included in the Spanish Chronic Allograft Nephropathy Study by Fernández-Fresnedo, et al. Proteinuria at one year post-transplantation, considered as a categorical variable (< 0.5, 0.5-1, > 1 g/day), was identified in 15.3% of patients. Proteinuric patients presented a reduced graft survival versus non-proteinuric patients. Furthermore, a high degree of proteinuria increased graft failure. The main cause of death in all groups, but especially in proteinuric patients, was vascular disease. The relative risk of graft failure and patient death was higher in proteinuric patients⁵¹ (Figs. 4, 5).

In related transplant events

The current expanded criteria donor policy, related with organ shortage, increases

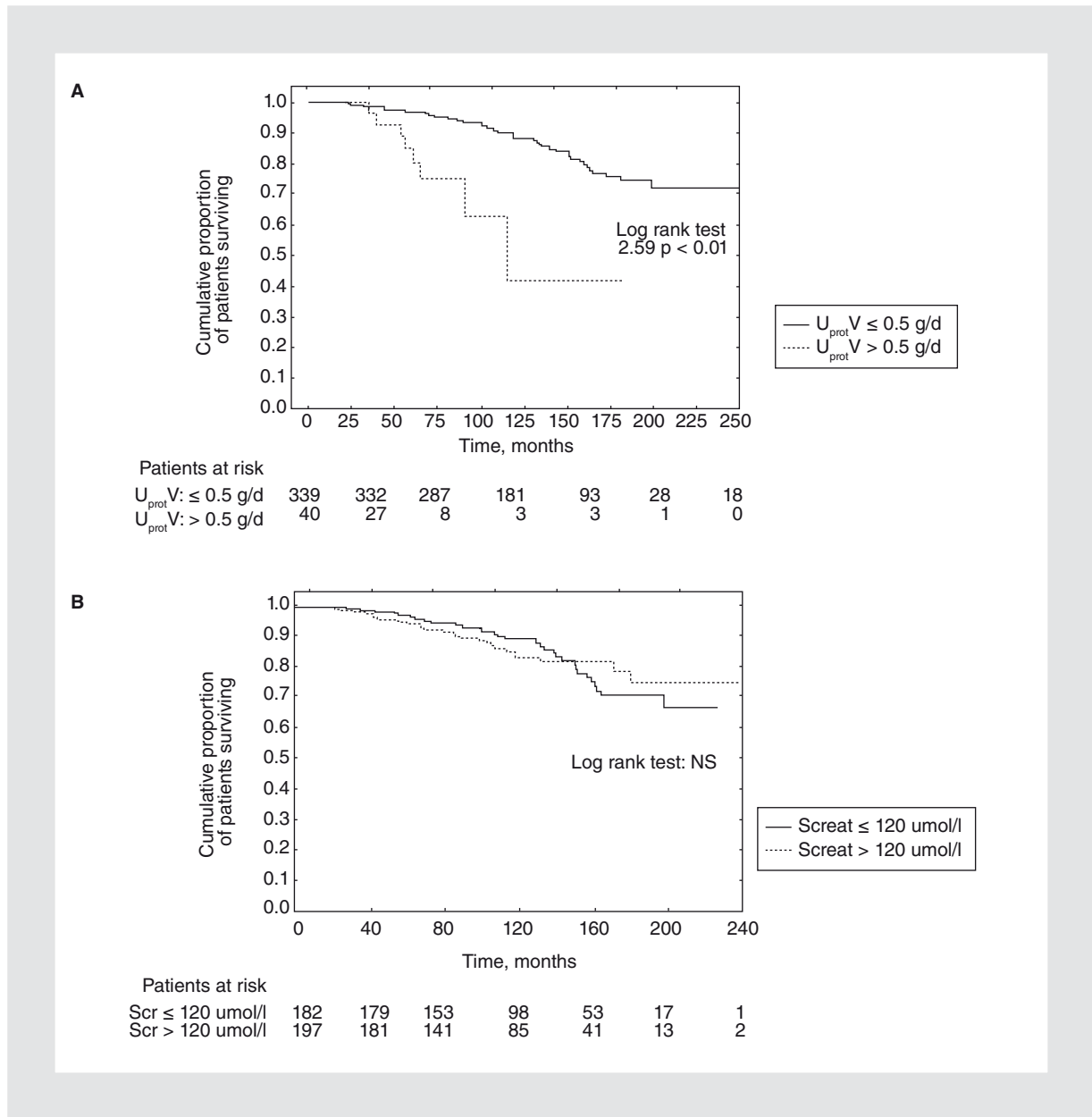


Figure 1. A: Kaplan-Meier product-limit estimates of patient survival according to the level of proteinuria (\leq or $>$ 0.5 g/d – upper panel) or **B:** serum creatinine (\leq or $>$ 120 $\mu\text{mol/l}$ –lower panel) at two years. The log-rank test was used for all comparisons (adapted from Cantarovich F.)⁹.

the likelihood of posttransplant proteinuria. Pretransplant renal lesions as well as ischemia-reperfusion and immunologic injury have been incriminated as responsible for early low-grade proteinuria that may influence long-term graft and patient survival.

Early proteinuria ($<$ 1 g/day) observed one and three months posttransplantation was

retrospectively evaluated by Halimi, et al. in 484 patients. Proteinuria was correlated with other risk factors such as donor characteristics (age and cause of death), prolonged ischemia times, and acute rejection. The results of the study suggest that early proteinuria related with pre-and/or posttransplant injuries to the graft, represent a potent independent predictor of graft loss and may have an effect

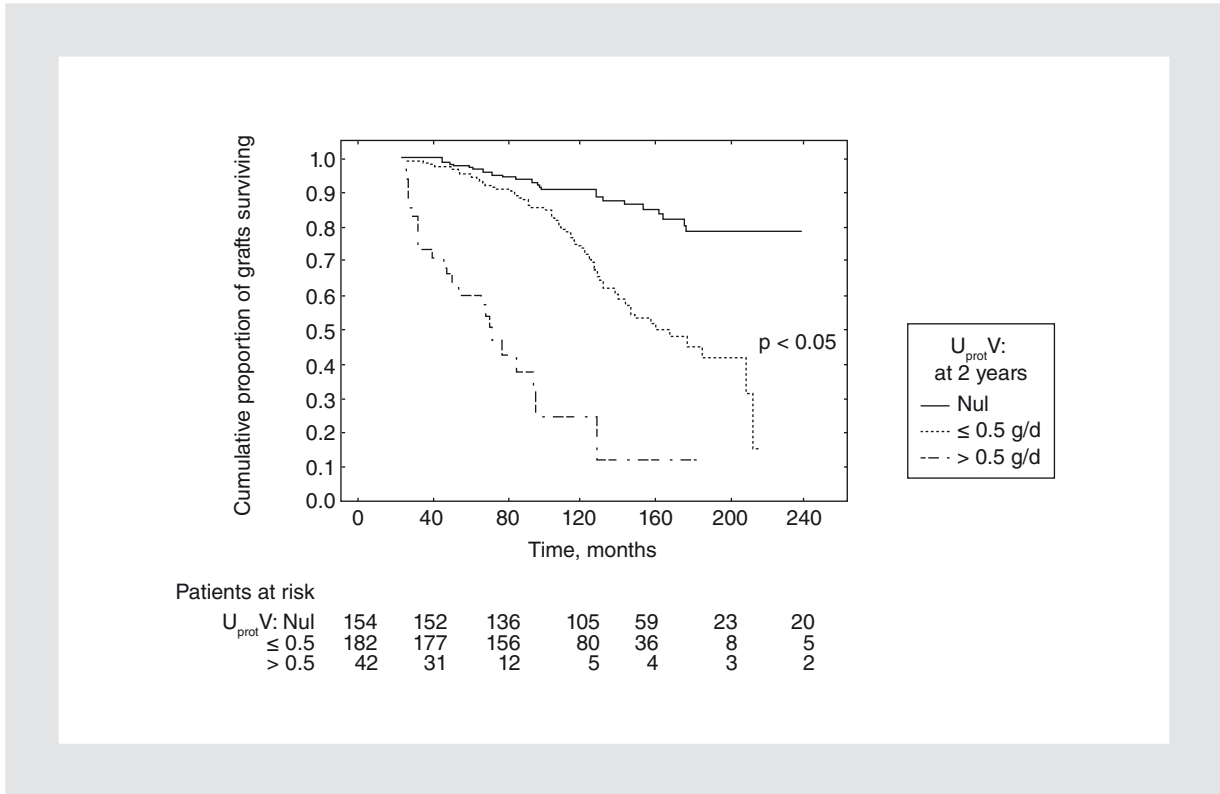


Figure 2. Kaplan-Meier product-limit estimates of graft survival according to the level of proteinuria (nil, ≤ 0.5 g/day or > 0.5 g/day) at two years. The log-rank test was used for all comparisons (adapted from Cantarovich F)⁹.

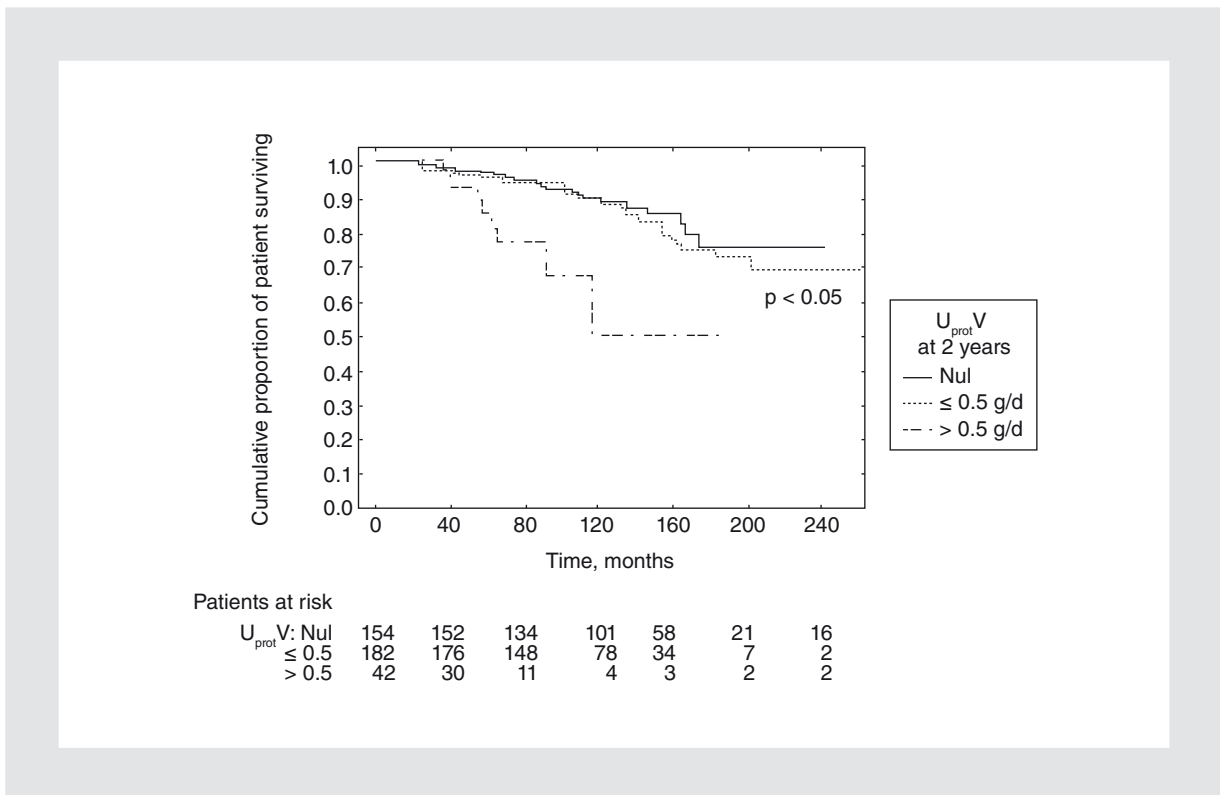


Figure 3. Kaplan-Meier product-limit estimates of patient survival according to the level of proteinuria (nil, ≤ 0.5 g/day or > 0.5 g/day) at two years. The log-rank test was used for all comparisons (adapted from Cantarovich F)⁹.

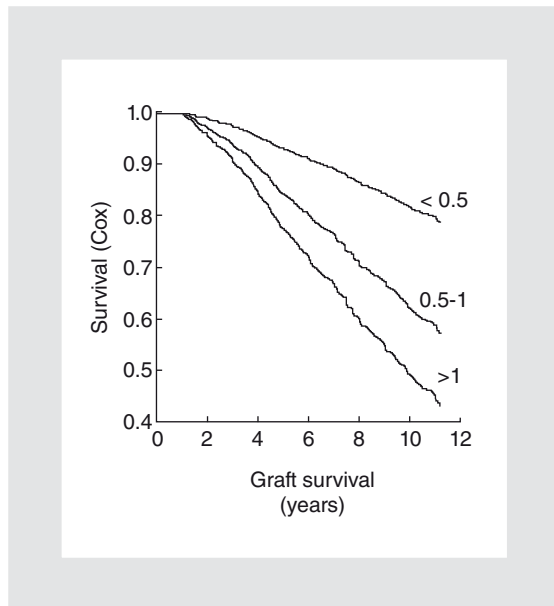


Figure 4. Graft survival depending on 1 year proteinuria (reproduced with permission from Fernández-Fresnedo G)⁵¹.

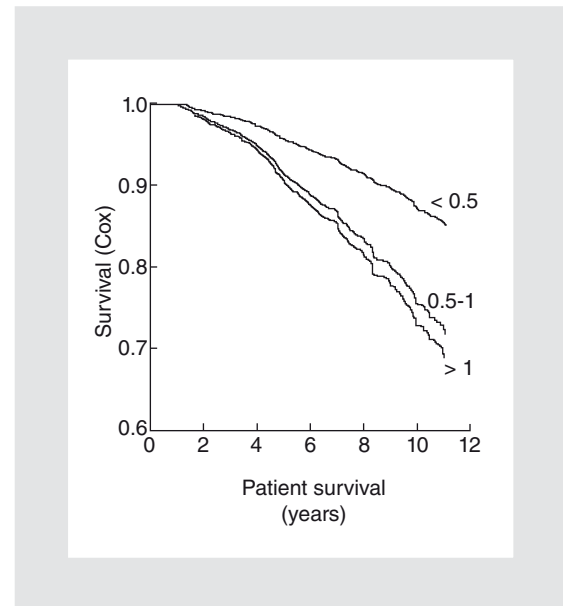


Figure 5. Patient survival depending on 1 year proteinuria (reproduced with permission from Fernández-Fresnedo G)⁵¹.

on long-term graft survival. It was also suggested that short-term proteinuria reduction is associated with improved long-term graft survival⁷.

Aiming at identifying early predictors of graft survival in recipients of ECD, Martínez Esteban, et al, in a recent study, evaluated 180 recipients of ECD kidneys that had undergone a preoperative biopsy. After adjusting for donor age and acute rejection episodes, the results of this study showed that a glomerular filtration rate (GFR) < 40 ml/min in the first year ($p = 0.007$) and one-year proteinuria > 0.1 g/day ($p = 0.002$) were independent risk factors for death-censored graft loss⁵².

Concerning the association between proteinuria and immunological events, the incidence of rejection on graft and patient survival has been the focus of several studies. Djamali, et al. retrospectively investigated, in a cohort of 925 patients, the effects of proteinuria on graft and patients outcomes following rejection. The effects of changes in UP/C ($\Delta\text{UPC} = \text{UPC one month after biopsy} - \text{baseline UPC}$) were

examined in 82 patients with both acute rejection and available data on proteinuria with a follow up of 38.7 ± 2.6 months after transplantation. Mean time to acute rejection was 19 ± 2.3 months, whereas the median ΔUPC was 200 mg/g. Forty-two patients had a $\Delta\text{UPC} \geq 200$ (high proteinuria group). Baseline characteristics were similar for high and low proteinuria groups except for more induction therapy with interleukin-2 receptor blockade in the former (71 vs. 47%; $p = 0.04$). This study showed that patients with $\Delta\text{UPC} \geq 200$ had higher rates of graft loss (26 vs. 15%; $p = 0.01$) or combined graft loss or death (38 vs. 20%; $p = 0.002$ by log-rank). Univariate and multivariate Cox regression analyses, showed that $\Delta\text{UPC} \geq 200$ mg/g, sirolimus therapy one month after rejection, and re-transplant status were significant factors associated with death-censored graft loss ($p = 0.008$) or combined graft loss or patient death ($p = 0.03$)⁵³.

With regard to the relationship between rejection, proteinuria, and chronic allograft failure (CAF), McLaren, et al. studied a cohort of

862 renal transplant recipients. Throughout the first six months of follow-up, 117 graft failures were excluded from the study. Seventy-seven patients with progressive loss of renal function and biopsy proven CAF presented after this period were analyzed. Multivariate analysis showed that early, and mainly late acute rejection episodes (after three months post-transplantation), proteinuria at one year and serum triglycerides were significant individual risk factors for CAF. This analysis also showed that SC at six months had a minimal impact as a risk factor for graft survival⁵⁴.

Chronic hepatitis C virus (HCV) has been associated with glomerular disease in native and transplanted kidneys. The incidence of hepatitis C-associated *de novo* glomerulonephritis has been evocated^{55,56}.

Sabry, et al. retrospectively evaluated the presence of HCV and the occurrence of proteinuria and its possible link with graft survival in renal transplant patients (169 ELISA-positive and 104 ELISA-negative HCV antibodies). Both groups were comparable regarding the incidence and quantity of HCV-positive. Individuals either HCV-positive or HCV-negative with nephrotic range proteinuria showed worse graft survival ($p = 0.001$) and higher frequency of chronic allograft nephropathy ($p = 0.05$) compared with non-proteinuric patients. This study also showed that the incidence and quantity of proteinuria is similar in both groups of HCV-positive and HCV-negative transplant recipients. Nephrotic range proteinuria, independently from serology, is associated with poorer graft outcome⁵⁷.

Proteinuria as predictor of posttransplant cardiovascular events

Cardiovascular complications affected at least 33% of patients three to seven years after transplantation and are a significant cause of patient death with functioning graft.

Among several risk factors for left ventricular hypertrophy (LVH), such as age, duration of chronic renal failure and time on dialysis, along with reduced nephron mass, high blood pressure, anemia, functioning arteriovenous fistula and chronic inflammatory syndrome, posttransplant proteinuria (a marker of generalized endothelial dysfunction) was also significantly associated with LVH. The significant role of persistent proteinuria as a prognostic factor of cardiovascular disease and the risk of death with functioning grafts, as well as the benefits of an anti-proteinuric strategy that may improve patient and graft survival, has been confirmed by several studies⁵⁸⁻⁶⁰.

Proteinuria in prognostic scores of kidney graft outcomes

Concerning the role of proteinuria in the outcome of renal transplanted patients, a brief assessment of the incidence of proteinuria in the outcome of a general non-transplanted population could be of interest.

A cohort of 920,985 adults who had at least one outpatient SC measurement and who did not require renal replacement treatment at baseline has been observed. Proteinuria was assessed by urine dipstick or urine PCR. During the median follow-up of 35 months (range 0-59 months), 27,959 participants (3.0%) died. The fully adjusted rate of all-cause mortality was higher in study participants with lower estimated glomerular filtration rate (eGFR) or heavier proteinuria. Adjusted mortality rates were more than two-fold higher among individuals with heavy proteinuria measured by urine dipstick and eGFR of 60 ml/min/1.73 m² or greater, as compared with those with eGFR of 45-59.9 ml/min/1.73 m² and normal protein excretion. This study showed that the risks of mortality, myocardial infarction, and progression to kidney failure associated with a given level of eGFR are

independently increased in patients with higher levels of proteinuria⁶¹.

Extrapolating these results to renal transplantation in order to improve long-term outcomes is crucial to define risk factors that differentiate patients in excellent and stable allograft function from recipients at risk of losing their transplants^{62,63}.

To evaluate the prognostic role of proteinuria in the outcome of patients and grafts in kidney transplantation, it is worthwhile to review the basis of short-term and long-term graft survival. Many of these factors influence each other, such as HLA mismatching that may increase the risk of acute renal rejection and subsequent premature allograft failure⁶⁴.

Increasing donor age ($p < 0.001$), recipient age ($p = 0.001$), recipient weight ($p = 0.029$), waiting time on dialysis ($p = 0.006$), pretransplant hypertension ($p < 0.001$), pretransplant diabetes ($p < 0.001$), delayed graft function ($p < 0.001$), proteinuria ($p = 0.001$), posttransplant diabetes ($p = 0.015$), posttransplant hypertension ($p = 0.017$), and acute rejection ($p < 0.001$) are the generally accepted risk factors for graft dysfunction and patient survival. Nevertheless, it was considered that proteinuria and stage of allograft dysfunction at the start of chronic allograft failure are the major risk factors for late renal allograft dysfunction⁶⁵.

Hernández, et al. studied a cohort of 4,928 kidney transplant patients to develop and validate a prognostic index to estimate patient survival beyond the first posttransplant year. Proteinuria was included within several analyzed covariates. The largest positive weights (β coefficient) were obtained for the age range 50-60 years and proteinuria > 1 g/day at the first posttransplant year, new onset diabetes, and SC at the first year. The authors remarked that proteinuria is a significant predictor of cardiovascular disease and death post-kidney transplantation⁶⁶.

In another review, Reichel, et al. estimated that proteinuria (0.25-1.0 g/day) six months after transplantation was noted in 25.5% of the patients. Non-proteinuric patients had a five-year graft survival of 85.6% as compared to a much lower graft survival in proteinuric patients (58.9%). In this analysis, no correlation was found between gender or age of recipient, duration of hemodialysis, donor age, cold ischemia time, or mismatches. It appears that mild proteinuria six months after transplantation is a predictor of decreased long-term graft function⁶⁷.

Proteinuria and graft histopathology

Proteinuria, predominantly persistent heavy proteinuria (> 2 g/day), underlying pathology, and patient and graft outcome have been subjects of interest and research from the beginning of the transplant era. Harlan, et al., in the 1960s, associated proteinuria with chronic rejection and glomerular and tubular pathological changes⁶⁸.

Among 125 recipients surviving for more than eight years after transplantation, Petersen, et al. analyzed heavy proteinuria and declining graft function in 22 patients. Complete graft failure had occurred in 12 of the 22 patients. Based on clinical findings and pathophysiological features, patients were classified into two groups. Sixteen of them with glomerular pathology presented non-selective heavy proteinuria and glomerular histology with polymorphous lesions. Interstitial fibrosis, tubular atrophy, and vascular lesions were described as non-glomerular transplant disease. This study suggested the relationship among proteinuria, chronic or late rejection, and different pathogenic mechanisms⁶⁹.

First, et al.⁷⁰ and Peddi, et al.⁷¹ analyzed the correlation of clinical outcome and

histopathology findings in two studies including 1,148 patients; 11 and 22% of them, respectively, displayed persistent heavy proteinuria (> 2 g/day). Transplant glomerulopathy, allograft glomerulonephritis, and chronic rejection were the main histopathology findings in both studies. In the study of First, et al., only 23.4% (18 of 77) of the patients maintained prolonged graft function, the majority of grafts being lost within one year of the development of persistent heavy proteinuria.

The analysis of Peddi, et al. showed that persistent proteinuria indicated a poor outcome, with graft loss occurring in 69% of the allografts with a half-life of 5.6 years, which was significantly lower than in controls (16.5 years). This trial also mentioned that among patients with persistent proteinuria, there was no difference in graft survival if proteinuria was due to chronic rejection or to other causes (half-life 5.2 vs. 5.7 years). Regarding the association between posttransplant nephrotic-range proteinuria, graft histopathology, and poor allograft survival, it has been suggested that it is independent of the time of onset of presentation of proteinuria, especially when renal function was reduced at the time of biopsy⁷².

Besides, concerning the physiopathology of proteinuria and graft histopathology, it has been shown that the development of nephrotic-range proteinuria is also associated with a defect of glomerular size selectivity, which correlates with prominent glomerular pathology⁷³.

It therefore can be speculated that therapeutic interventions, which have been shown to reduce proteinuria in patients with chronic native kidney disease, will also beneficially affect permselectivity in chronic kidney graft failure⁷⁴.

Concerning the link between proteinuria and graft histopathology, Amer, et al. analyzed this association in 613 kidney allograft recipients with proteinuria and surveillance

biopsies at one-year posttransplantation. Of these, 84% patients with proteinuria between 0.150-0.5 g/day had albuminuria and 100% of patients with proteinuria > 0.5 g/day had abnormal albuminuria. Proteinuria was mainly associated with the presence of graft glomerular pathology and the use of sirolimus. Glomerular pathology on biopsy was present in 80% of patients with proteinuria > 1.5 g/day. Conversely, lower levels of proteinuria were not associated with specific graft histology at one year. This analysis shows that proteinuria was associated with reduced graft survival ($p < 0.001$) independent of other risk factors including, glomerular pathology, graft function, recipient age, and acute rejection. Glomerular pathology was the predominant finding in lost allograft, mainly in patients with > 0.5 g/day proteinuria at one year. The authors mentioned that 45% of patients presented low-level proteinuria < 0.5 g/day at one year, remarking that even this low level related to poor graft survival⁷⁵.

Concerning the prognostic value of proteinuria and histopathology findings, Knoll stated that in addition to glomerulonephritis, proteinuria in kidney transplant recipients is commonly associated with such transplant-specific diagnoses on biopsy as allograft nephropathy, transplant glomerulopathy, and acute rejection⁷⁶.

Albuminuria

Urinary albumin and non-albumin proteins constitute proteinuria. Urinary albumin was shown to predict end-stage renal disease (ESRD) and death⁷⁷.

As many patients with renal dysfunction have microalbuminuria, it is of importance to study to what extent the increased cardiovascular and mortality risk is related to either the lower GFR or the increased albuminuria. While some investigators advocate the use of

urinary albumin excretion as an alternative to total protein measurement, and others suggest that the profile of proteins excreted has differential diagnostic and prognostic value, the National Kidney Foundation recommended that an increase in protein excretion be used as a screening tool in patients at risk of developing renal disease⁷⁸.

Previous evidence of worse cardiovascular events in subjects with microalbuminuria was derived from data in patients with type 1 and type 2 diabetes. Shortly thereafter, similar data were published for the presence of microalbuminuria in hypertension as well as in the older and general population. In addition, the level of eGFR and the evolution to chronic kidney disease (CKD) has also been found associated with an increased risk for cardiovascular events^{77,79}.

It has been recommended, for screening and prevention of developing renal failure in all clinical fields including renal transplantation, not to only pay attention to eGFR, but to focus more on assessing their albuminuria status. Recent studies have shown that higher levels of albuminuria predict the occurrence of renal function loss and cardiovascular events, and that moderately impaired renal function (KDOQI stage 3 CKD) is not such a risk factor when albuminuria is absent⁶¹.

Recently, Halimi, et al. retrospectively analyzed the impact of urinary albumin excretion and non-albumin proteins on ESRD and death in 616 kidney graft recipients. The authors observed that in subjects with low proteinuria < 0.25 g/day, 76% of urine proteins were non-albumin proteins, and in those with >1 g/day, 44% of the urine proteins were non-albumin proteins. Non-albumin proteins expressed as a continuous or a categorical variable and urinary albumin excretion (per g/day) were highly significant risk factors for graft loss. The presence of

non-albumin proteins and macroalbuminuria also were significant risk factors for death. This study suggests that urinary albumin excretion is a valuable prognosis factor for graft survival and that prospective studies are required to evaluate if systematic screening of microalbuminuria might be helpful for clinical and pathology diagnostic assays in the follow-up of renal transplantation⁸.

Therapeutic interventions

The relationship between proteinuria, patient and allograft survival, as well as the increased risk of cardiovascular events is well established and the importance of its early detection have been previously highlighted by numerous studies.

Consequently, several authors have analyzed the possible relationship between early diagnosis and strategies to protect the renal graft. On this issue, many studies concerning the use of ACEI/ARB have investigated their action primarily as anti-proteinuric and antihypertensive drugs^{13,80-84}.

Therefore, a review of the current status of this not yet well defined policy might be of interest.

Randomized trials in proteinuric chronic kidney disease in the non-transplant setting have confirmed that blockade of the renin-angiotensin-aldosterone system (RAAS) is associated with reduction of proteinuria and consequently delayed progression of chronic renal failure. Nevertheless, the effect of ACEI/ARB, or their combined administration, to reduce proteinuria in renal transplantation remains uncertain⁸⁵.

Knoll maintains that treatment with ACEI or ARB can decrease proteinuria, but taking into account that there is no evidence from

randomized trials that this strategy improves patient or graft survival, its generalized use requires statistical confirmation from randomized trials⁷⁶.

It had been shown that the RAAS blockade in kidney transplantation is associated with some potentially relevant adverse events, such as hyperkalemia, anemia, and even an acute and hemodynamically-mediated decline in renal function⁸⁶.

Consequently, for several authors up to now there is not convincing evidence supporting that RAAS blockade has further benefit on the progression of chronic allograft injury in comparison with other antihypertensive interventions^{87,89}.

On the other hand, several studies had evaluated and supported the use of ACEI and ARB in renal transplantation. The RAAS is viewed as an additional mechanism in the development and progression of chronic allograft injury. The RAAS-blocking agents efficiently improve posttransplant hypertension and are useful in reducing proteinuria and for treating posttransplant erythrocytosis⁸⁴. In addition, some clinical studies have shown that RAAS blockade reduces transforming growth factor- β 1 and other markers of fibrosis⁹⁰.

It has also been mentioned that RAAS blockade may also improve cardiovascular disease, which constitutes the main cause of mortality and morbidity in renal allograft recipients⁸⁷. In a study comprising 2,031 kidney graft recipients, Heinze, et al. compared graft and patient survival with and without ACEI/ARB therapy. Ten-year survival rates were 74% in the ACEI/ARB group, but only 53% in the non-ACEI/ARB group ($p < 0.001$). Ten-year actual graft survival rate was 59% in ACEI/ARB patients, but only 41% in those without RAAS blockade ($p = 0.002$). Ten-year unadjusted functional graft survival rates were 76% among ACEI/ARB patients and

71% in non-ACEI/ARB recipients ($p = 0.57$). The authors consider that more frequent use of these drugs may reduce the high incidence of death and renal allograft failure in these patients²⁷.

In a systematic review of the evidence, Hiremath, et al. remarked that ACEI and ARB slow the progression of renal disease. However, the authors mentioned the need for randomized trials of sufficient power and duration to confirm this reno-protective action and its benefits for patients and kidney graft survival⁸⁸.

A search of the literature performed by Jennings, et al. complemented this controversial subject by evaluating seven studies. One study examined only plasma levels of a common marker for tissue fibrosis, and one included only patients who had early graft dysfunction. Of the other five studies, three primarily reported safety endpoints and two reported clinical efficacy endpoints. Safety data in patients with functioning grafts (SC from < 2.5 to 3.0 mg/d) show that early therapy with RAAS inhibitors did not result in appreciable increases in SC or potassium levels after up to nine months of therapy. This study suggested that the early initiation of RAAS inhibitors is safe in posttransplant patients with functioning grafts, and that it is reasonable to consider these agents as first-line pharmacotherapy in patients with hypertension and compelling indications (i.e. diabetes or heart failure) in the first 12 weeks following transplant⁸⁹.

Kunz, et al., in a meta-analysis of 49 studies involving 6,181 patients, showed that the results in reducing proteinuria are comparable with ACEI or ARB. The author considers that the combination of both drugs is more effective than either drug administered alone. It is also recommended to consider the potential side effects associated to the use of ACEI or ARB⁹¹.

Other authors also estimate that the combination of ARB and ACEI further reduced proteinuria more than either agent alone^{27,92}, and recent evidences suggest that adding aldosterone antagonist therapy may further increase renal protection, but may also enhance the risk of hyperkalemia⁸⁶.

The conclusion of these different studies and the analysis of evidence suggest that ongoing and future trials will be needed to determine if ACEI/ARB, related with their action on proteinuria, hypertension, and/or cardiovascular diseases, and with strict control of side effects, should be a recommended strategy to improve the outcome for patients having received kidney transplantation.

Discussion and Conclusion

This review aims to point out the importance of proteinuria as an individual risk factor in the prognosis of graft and patient survival in kidney transplantation.

Correct evaluation of urine protein excretion and the feasibility of screening techniques has been a matter of research interest. In general, the review performed, analyzing different trials, concluded that a random urine PCR correlates with 24-hour estimation and reliably predicts the presence of significant proteinuria^{28,34-36}.

The different studies reviewed have categorized the range of urine protein excretion using diverse terminology, e.g. significant, heavy or persistent (> 1 g/day)^{49,51}, high (> 0.5 g/day)⁹, early, minimal and low (0.25-1 g/day)^{8,43,46,52} and others. Concerning urinary albumin excretion, the lowest detectable level evaluated was 2 mg/l, with 7.4% as coefficient of variation⁸.

It was shown that 23.4% of patients with heavy proteinuria by the end of one year

cannot maintain good renal function, with the majority of grafts being lost. Also, transplant glomerulopathy, *de novo* glomerulonephritis, and chronic rejection have been demonstrated as main causes of significant or heavy proteinuria^{38,41,49,69,70}.

The risks of mortality, myocardial infarction, and progression to kidney failure associated with a given level of eGFR are independently increased in patients with higher levels of proteinuria⁶¹. It was mentioned that adjusted mortality rates were more than two-fold higher among individuals with heavy proteinuria, 56.3% in patients with proteinuria > 1 g/day, and 88.1% in patients with proteinuria < 1 g/day ($p = 0.01$).

With regard to early and/or low proteinuria levels related to the use of ECD, it was observed that this grade of proteinuria was also an early predictor of worse graft survival in the first year posttransplantation^{7,42,43,52,53}.

In addition, low-grade proteinuria was correlated with other risk factors such as donor characteristics (age and cause of death), prolonged ischemia times, and acute rejection. It was also suggested that short-term proteinuria reduction is associated with improved long-term graft survival⁷. This effect of early proteinuria as a strong predictor of poor patient and graft survival was directly related to the intensity and persistence of the disorder⁴⁴.

Concerning the value of minimal proteinuria as risk and prognostic factor, it was shown that five-year graft survival in recipients presenting minimal proteinuria was 83% in contrast to 97.1% in the non-proteinuric cohort. Even minimal proteinuria one year posttransplantation was associated with poor graft outcome⁴⁶.

It was also mentioned that lower levels of proteinuria are generally associated with non-glomerular, nonspecific histological changes⁴⁵.

Table 1. Low proteinuria

Low proteinuria (< 0.5 g/day)	Patients (n)	Graft survival	Patient survival
Amer, et al. ⁷⁵	613	Yes	Not mentioned
Roodnat, et al. ⁴⁸	722	Yes	Yes
Kang, et al. ⁴⁶	272	Yes	Not mentioned
Martínez, et al. ⁵²	180	Yes	Not mentioned
Djamali, et al. ⁵³	925	Yes	Yes
McLaren, et al. ⁵⁴	862	Yes	Not mentioned
Total	3,574	Yes: 6	Yes: 2 Not mentioned: 4

Proteinuria was also evaluated as a categorical variable (presence vs. absence) and as a continuous variable one year after transplantation and both were independent variables, with no interaction with any of the other clinical variables. On the contrary, interaction with the original disease was confirmed. This analysis showed that death risk was almost twice as high for patients with proteinuria at one year⁴⁸.

Conversely, in two studies in patients with proteinuria > 0.5 g/day, no impact was observed in patient mortality^{17,59}.

Aiming at simplifying the diverse information and taking into account the association between results, graft and patient outcome, and degree of urinary protein excretion, we categorized three levels of proteinuria: low, middle, and high levels.

In 3,574 patients even low level proteinuria predicts high risk for allograft dysfunction. With regard to its significance as a risk factor for patient survival, only two studies analyzed this issue, showing the presence of proteinuria as a mortality risk factor (Table 1).

Middle proteinuria was observed in the posttransplant period of 6,488 kidney recipients.

In 10 studies, proteinuria has been reported as a risk factor and predictor of graft survival. Concerning patient mortality, five studies did not mention the analysis of the issue. Three of the remaining five mentioned proteinuria as a significant prognostic factor of mortality. In two others, no difference was seen in patient survival between proteinuric and non-proteinuric patients (Table 2).

High proteinuria (> 1 g/day) was investigated in five studies with 7,501 patients. In three of the studies, proteinuria was found as a significant individual risk factor for graft survival. Concerning patient mortality, proteinuria was a major risk factor in the two trials that analyzed this factor (Table 3).

Proteinuria as a prognostic factor for graft and patient survival has been evaluated in 22 studies comprising 18,179 patients considering two groups: in 14,839 patients as an independent risk factor unrelated to post-transplant events either immunological or non immunological, and in 2,724 patients related with posttransplant events. In another 616 patients, albuminuria was also analyzed as a risk factor for graft and patient outcome.

From the 22 studies evaluated (21 concerning proteinuria and one albuminuria) 19 categorized proteinuria/albuminuria as an

Table 2. Middle proteinuria

Middle proteinuria (> 0.5 < 1 g/day)	Patients (n)	Graft survival	Patient survival
Hohage, et al. ⁴¹	357	Yes	Not mentioned
Arias, et al. ³⁷	485	Yes	Not mentioned
Ibis, et al. ⁴³	130	Yes	Not mentioned
Sancho, et al. ¹⁷	337	Yes	No
Ibis, et al. ⁵⁹	126	Yes	No
Cherukuri, et al. ⁴²	477	Yes	Yes
Cantarovich, et al. ⁹	454	Yes	Yes
Halimi, et al. ⁷	484	Yes	Not mentioned
Sabry ⁵⁷	273	Yes	Not mentioned
Fernández-Fresnedo, et al. ⁵¹	3,365	Yes	Yes
Total	6,488	Yes: 10	Yes: 3 No: 2 Not mentioned: 5

independent risk factor for outcome of kidney transplantation in 16,821 patients (Tables 4-9).

As regards its relevance in the prognosis of graft survival, this subject was mentioned in 20 studies and was significant in analyzing proteinuria/albuminuria renal recipients from a cohort of 12,647 patients.

Concerning patient mortality, this issue is mentioned to have been analyzed in 10 out of the 21 studies. Eight of them analyzed

the outcome of 12,091 patients and confirmed that proteinuria is a significant predictor of mortality. On the contrary, in 463 patients no difference in patient mortality was found between proteinuric and non-proteinuric patients.

This controversial result merits some comments. One of the trials⁵⁹ involved a small number of patients, which could be statistically limiting to evaluate the multifaceted mortality risk factors in kidney transplantation. In the other

Table 3. High proteinuria

High proteinuria (> 1 g/day)	Patients (n)	Graft survival	Patient survival
Cusumano, et al. ³⁸	288	Yes	Not mentioned
Park, et al. ⁵	884	Yes	Not mentioned
Kim, et al. ⁴⁹	797	Yes	Not mentioned
van Ree, et al. ⁴⁷	604	Not mentioned	Yes
Hernández, et al. ⁶⁶	4,928	Not mentioned	Yes
Total	7,501	Yes: 3 Not mentioned: 2	Yes: 2 Not mentioned: 3

Table 4. Proteinuria, unrelated to posttransplant events either immunologic or nonimmunologic

Author	Patients (n = 14839)	Proteinuria screening	Proteinuria grade	Study period
Cusumano, et al. ³⁸	288	Following 3 months	> 1 g/day	Not mentioned
Hohage, et al. ⁴¹	357	6 months	0.25-1 g/day	5 years
Park, et al. ⁵	884	6 months	> 1 g/day	60.2 ± 30.8 months
Kim, et al. ⁴⁹	797	6 months	> 1 g/day	Mean 3.7 years
Roodnat, et al. ⁴⁸	722	1 year	2 successive values > 0.20 g/l	5 years
Fernández-Fresnedo, et al. ⁵¹	3,365	1 year	Categorical variable > 0.5 to >1 g/day	8 years
Arias, et al. ³⁷	485	3 months	> 0.5 g/day	6.41 ± 3.6 years
Ibis, et al. ⁴³	130	3 months	> 0.3 g/day	60 months
Amer, et al. ⁷⁵	613	1 year	> 0.15 to < 0.5 g/day	46 ± 21 months
Sancho, et al. ¹⁷	337	6 months	> 0.5 g/day	53.35 ± 52.63 months
Van Ree, et al. ⁴⁷	604	> 1 year	> 0.3 g to > 1 g/day	5.3 years (4.7-5.7)
Hernández, et al. ⁶⁶	4,928	1 year	> 1 g/l at the first year	Median 82 months
Ibis, et al. ⁵⁹	126	> 6 months	≥ 0.5 g/day	63.2 ± 19.9 months
Kang, et al. ⁴⁶	272	1 year	< 0.5 g/day	6.41 ± 3.6 years
Cherukuri, et al. ⁴²	477	3 months	4 groups: PCR < 0.15 to > 1	Mean 122 months
Cantarovich, et al. ⁹	454	3 months, 2 and 5 years	≥ 0.5 g/day	100 ± 3.2 months

study¹⁷, ACEI/ARB have been given post-transplantation to all recipients. Taking into account the anti-proteinuric effect of ACEI/ARB and the noted improvement on graft and patient survival suggested in several clinical studies^{67,80-82}, we may speculate on the potential role of this therapeutic measure. Wilmer, et al. remarked that therapeutic measures to reduce the amount of proteinuria might be useful to improve patient outcome as long as they are introduced within the first two years posttransplantation¹⁴.

Several authors in this review have also considered the significance of the association between graft histopathology, urine protein excretion and its relation as risk prognostic factor with the different grades of proteinuria.

Some decades ago, Petersen, et al., based on clinical findings, pathophysiological features and renal lesions, observed that the main histopathological etiology of graft dysfunction was glomerular (glomerular transplant disease). The urine protein excretion presented in the study was heavy grade proteinuria⁶⁹. Different authors also showed that the main causes of persistent heavy proteinuria were transplant glomerulopathy, allograft glomerulonephritis, and chronic rejection^{38,70}. Recent data revealed that 80% of patients with proteinuria > 1.5 g/day had glomerular pathology. It was also observed that proteinuria was significantly associated with reduced graft survival independent of other risk factors, including glomerular pathology, graft function, recipient age, and acute rejection.

Table 5. Proteinuria unrelated to posttransplant events either immunologic or nonimmunologic as independent risk factor of graft and patient survival

Author	Independent risk factor	< Graft survival	< Patient survival	Clinical data
Cusumano, et al. ³⁸	Not mentioned	Yes	Not mentioned	Significant Pr > 1 g/day for 3 consecutive months observed in 28.4% of 288 grafts. Pr associated with chronic rejection and transplant glomerulopathy. Graft survival lower with significant Pr.
Hohage, et al. ⁴¹	Yes	Yes	Not mentioned	357 patients followed for 5 years. Early Pr (0.25-1.0 g/day). Graft survival at 5 years: 58.9 vs. 85.6% in non-proteinuric.
Park, et al. ⁵	Yes	Yes	Not mentioned	Pr > 1 g/d for 6 months. Diagnosis 54.3% chronic rejection, 27.2% glomerulonephritis. 5-year graft survival: 69.4% in patients with Pr, 86.5% without (p < 0.01).
Kim, et al. ⁴⁹	Not mentioned	Yes	Not mentioned	797 patients, 6.7% Pr > 1 g/d, ≥ 6 months. Diagnosis: acute or chronic vascular rejection, transplant glomerulopathy, glomerulonephritis. Five-year graft survival with Pr > 1 g was 56.3% and 88.1% with Pr < 1 g.
Roodnat, et al. ⁴⁸	Yes	Yes	Yes	In 722 patients Pr independent variable, not interaction with any other variable. Death risk was almost twice as high for patients with Pr at 1 year.
Fernández-Fresnedo, et al. ⁵¹	Yes	Yes	Yes	In 3,365 pts, 1-year Pr as a categorical variable was detected in 15.3% patients. Graft failure and mortality was higher in proteinuric patients
Arias, et al. ³⁷	Yes	Yes	Not mentioned	485 pts with graft functioning at least 1 year. Group A: baseline SC < 1.5 mg/dl; group B: baseline SC 1.5-3 mg/dl. Pr > 0.5 g/day was a significant risk factor for graft survival. Only BP shows also independent risk factor, but lower than Pr.
Ibis, et al. ⁴³	Yes	Yes	Not mentioned	Pr (> 300 mg/d) 130 pts with Pr showed significantly lower graft survival: 54.17 vs. 82.62% (p < 0.002).
Amer, et al. ⁷⁵	Yes	Yes	Not mentioned	Proteinuria, pathology and survival were analyzed in 613 patients. 1 year Pr > 0.150 g/day in 276 patients (45%), in 182 was < 0.5 g/day. In > 84% patients low levels of were related with albuminuria. Pr > 1.5 g/day was linked with glomerular pathology and use of sirolimus. 80% of patients with Pr > 1.5 g/day had glomerular pathology. Lower levels of Pr were not related with specific pathologies at 1 year and related with low graft survival.
Sancho, et al. ¹⁷	Yes	Yes	No	337 patients with Pr > 0.5 g/day with ACEI/ARB. 68 patients (20.17%) had persistent Pr > 0.5 g/day. SC and systolic BP were higher from the early stages in the proteinuric group. Graft survival at 5 years was 69% in Pr patients and 93% in non-Pr patients (p = 0.000). No differences in patient survival.
Van Ree, et al. ⁴⁷	Yes	Not mentioned	Yes	In 604 patients Pr was correlated with markers of endothelial dysfunction. Patients with Pr > 1.0 g/day and high sICAM-1 or sVCAM-1 concentrations were at increased risk for death, patients with Pr > 1.0 g/day and low concentrations of endothelial dysfunction were not.

Continue

Table 5. Proteinuria unrelated to posttransplant events either immunologic or nonimmunologic as independent risk factor of graft and patient survival (continued)

Author	Independent risk factor	< Graft survival	< Patient survival	Clinical data
Hernández, et al. ⁶⁶	Yes	Not mentioned	Yes	4,928 patients randomly assigned to 2 groups: a modeling population (n = 2,452) used to create a new index and a testing population (n = 2,476) used to test this index. During the first posttransplant year Pr was predictor of cardiovascular disease and death.
Ibis, et al. ⁵⁹	Yes	Yes	No	Pr (≥ 0.5 g/day) was associated with cardiovascular disease (p = 001). Patients with Pr had less graft survival: 58.62 vs. 80.41% (p = 0.02). No association between Pr and patient survival.
Kang, et al. ⁴⁶	Yes	Yes	Not mentioned	272 patients in 2 groups: no Pr (< 0.2 g/day), minimal Pr (0.2-0.5 g/day), and overt Pr (≥ 0.5 g/day). 5-year graft survival: minimal Pr was 83.0%, and in the overt Pr was 70%, in contrast to 97.1% in the no Pr.
Cherukuri, et al. ⁴²	Yes	Yes	Yes	In 477 pts, low-grade Pr evaluated 3 months posttransplantation. 4 groups of patients based on median PCR. Even low-level Pr predicted graft loss (p = 0.001). Mortality only significant with high levels. Low-grade Pr identifies high-risk group of patients.
Cantarovich, et al. ⁹	Yes	Yes	Yes	454 first transplants Pr > 0.5 g/d (HP) and SC > 120 µmol/l (HSC) at 3 months, 2 and 5-years were compared. HSC prognostic factor of graft survival (p < 0.001) only at 5 years, but does not predict mortality at any period. HP at 3 months (p < 0.001) and at 2 years (p < 0.001) predicts graft failure and mortality.

Pr: proteinuria; BP: blood pressure; SC: serum creatinine; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; sICAM-1: soluble intercellular adhesion molecule type 1; sVCAM-1: soluble vascular cellular adhesion molecule type 1; HP: high proteinuria; HSC: high serum creatinine.

The predominant pathology presented in allograft loss was glomerular, particularly in patients who at one year had proteinuria > 0.5 g/day than in those with lower levels (66 vs. 25%; p = 0.030)⁷⁵.

The presence of proteinuria in kidney recipients with HCV was also evaluated and no significant difference was found regarding the incidence and quantity of proteinuria in both groups (HCV positive and negative).

Table 6. Proteinuria related to immunologic or nonimmunologic pre- or posttransplant events

Author	Patients (n = 2,724)	Proteinuria screening	Proteinuria grade	Study period
Halimi, et al. ⁷	484	1, 3 and 12 months	< 1 g/day	7.2 years
Martínez, et al. ⁵²	180	1, 3, 6 and 9 months	> 0.1 g/day	1 year
Sabry, ⁵⁷	273	Not mentioned	0.4 g/day	87 ± 26.79 months
Djamali, et al. ⁵³	925	1 month after late acute rejection	UPC ≥ 200	38.7 ± 2.6 months
McLaren, et al. ⁵⁴	862	1 year	>0.1 gl	10 years

Table 7. Proteinuria related to immunologic or nonimmunologic pre- or posttransplant events as an independent risk factor of graft and patient survival

Author	Proteinuria independent risk factor	< Graft survival Pr: yes Pr: no	< Patient survival Pr: yes Pr: no	Clinical data
Halimi, et al. ⁷	Yes	Yes	Not mentioned	In 484 patients, earlier low Pr (< 1 g/24-hours) was evaluated 1 and 3 month. Pr was correlated with other risk factors. Low-grade Pr was independent predictor of graft loss.
Martínez, et al. ⁵²	Yes	Yes	Not mentioned	In 180 recipients from ECD Pr values above the median (0.100 g/day) at 1 year posttransplantation significantly reduced the death-censored graft survival ($p < 0.0001$). GFR < 40 ml/min in the first year ($p = 0.007$) and Pr at 1 year > 0.100 g/day ($p = 0.002$) were independent risk factors for graft survival.
Sabry, ⁵⁷	Not mentioned	Yes	Not mentioned	In both HCV+ and HCV- groups (273 patients), those with nephrotic range Pr showed worse graft survival and higher frequency of chronic allograft nephropathy compared with non-proteinuric patients.
Djamali, et al. ⁵³	Yes	Yes	Yes	Proteinuria and patient/graft outcomes following AR in 925 patients. 80 patients identified with biopsy and UPC ratios at baseline. Mean time to AR 19 ± 2.3 months. 42 patients had $\Delta\text{UPC} \geq 200$ (high proteinuria group) and higher rates of graft loss (26 vs. 15%; $p = 0.01$) or combined graft loss or death (38 vs. 20%; $p = 0.002$ by log-rank).
McLaren, et al. ⁵⁴	Yes	Yes	Not mentioned	862 patients followed 10-years. Chronic allograft failure (CAF) in 9.2%. Pr, early and late AR, and serum triglycerides were risk factors. SC levels at 6 months were not predictive of CAF.

Pr: proteinuria; ECD: expanded criteria donors; GFR: glomerular filtration rate; AR: acute rejection; SC: serum creatinine.

Table 8. Albuminuria

Author	Patients (n = 616)	Albuminuria screening	Albuminuria grade	Study period
Halimi, et al. ⁶	616	31.4% = 12 months 68.6% means 60 months	Lowest 2 mg/l (coefficient of variations 7.4%)	40 months (3.7-99 months)

On the other hand, it was shown that in both groups, those patients with nephrotic-range proteinuria showed worse graft survival and higher frequency of chronic allograft nephropathy compared with non-proteinuric patients⁵⁷.

The severe impact in the outcome of kidney transplantation produced by proteinuria, and considering that experimental and

clinical research has supported the use of ACEI/ARB in diabetes, hypertension, and proteinuric nephropathy, has led to explore the possible benefit of this therapy in kidney transplantation. Nevertheless, the use of these drugs remains controversial^{76,85}.

However, different studies with large numbers of patients supported the use of

Table 9. Albuminuria as risk factor

Author	Albuminuria independent risk factor	< Graft survival Pr: yes Pr: no	< Patient survival Pr: yes Pr: no	Clinical data
Halimi, et al. ⁶	Yes	Yes	Yes	616 renal recipients to analyze the influence of UAE and non-albumin proteins (NAP), ESRD, and death. In individuals with proteinuria < 0.25 g/day, 76% of proteins were NAP; in those with >1 g/day, 44% of proteins were NAP. NAP expressed as a continuous (HR: per g/day: 4.00 [2.85-5.63]; p < 0.0001) or a categorical (presence vs. absence, HR: 29.09 [8.80-96.20]; p < 0.0001) parameter and UAE (per g/day, HR: 1.86 [1.24-2.78], p<0.0001) were risk factors for graft loss in univariate analyses. The presence of NAP (HR: 5.37 [2.55-11.34]; p < 0.0001) and macroalbuminuria (HR: 4.12 [1.65-10.29]; p = 0.0024) were risk factors for death.

UAE: urinary albumin excretion; ESRD: end-stage renal disease; NAP: non-albumin proteins;

ACEI and ARB in mono or combined therapy to slow the progression of renal disease. On the other hand, several trials comparing graft and patient survival (with and without ACEI/ARB therapy) showed that 10-year graft and patient survival rates significantly improved in the ACEI/ARB group. Some studies suggested that the early initiation of RAAS inhibitors is safe and it could be reasonable to consider these agents as first-line pharmacotherapy in patients in the first 12 weeks following transplantation. Nevertheless, data are still insufficient to recommend these drugs in patients with early graft dysfunction^{27,88-89}.

Recently, Kunz, et al. in a meta-analysis of 49 studies involving 6,181 patients showed that the therapeutic results concerning reduction in proteinuria are comparable with ARB or ACEI. In addition, the authors remarked that the combination of both drugs is more effective than either drug alone. This study also recommends that the potential side effects should be considered cautiously⁹¹.

In conclusion, the analysis performed in this review concerning the prognostic value of proteinuria in kidney transplantation

clearly suggests that proteinuria (and albuminuria) at any time and grade are significant prognostic risk factors of graft and patient survival.

On the other hand, the possible benefit of ACEI/ARB in renal transplantation still requires confirmation.

Systematic proteinuria screening during the follow-up of renal transplantation should be considered a mandatory rule that will render possible the early diagnosis of possible clinical and/or histopathological etiologies and opportune therapeutic prescription.

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References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32(Suppl 3):S112-9.
2. Solez K, Vicenti F, Filo RS. Histopathology from 2-years protocol biopsies from a U.S. multicenter kidney transplant

- trial-comparing tacrolimus versus cyclosporine: A report of the FK506 Kidney Transplant Study Group. *Transplantation*. 1998;66:1736-40.
3. Kang CM, Kim GH, Lee CH, Kwak JY, Kwon OJ. Analysis of allograft biopsy specimens in renal transplants with proteinuria: is proteinuria a culprit of graft loss? *Transplant Proc*. 2005;37:984-6.
 4. Wormer KL, Vella JP, Sayegh M. Chronic allograft dysfunction: mechanisms and new approaches to therapy. *Semin Nephrol*. 2000;20:126-47.
 5. Park JH, Park JH, Bok HJ, et al. Persistent proteinuria as a prognostic factor for determining long-term graft survival in renal transplant recipients. *Transplant Proc*. 2000;32:1924. **This trial analyzes graft and patient survival associated with the presence or not of persistent proteinuria as prognostic factor.*
 6. Paul LC, Sijpkens YW. Surrogate end points in chronic kidney graft rejection studies. *Transplant Proc*. 1999;31:1293-4.
 7. Halimi JM, Laouad I, Buchler M, et al. Early Low-grade proteinuria: causes, short-term evolution and long-term consequences in renal transplantation. *Am J Transplant*. 2005;5:2281-8. ***Considers the powerful predictor role of early low-grade proteinuria due to pretransplant renal lesions, ischemia-reperfusion and immunologic injuries. This study suggest that early especially low grade proteinuria may be an integrator of pre transplant immunologic and non-immunologic it is harmful and should not be neglected as predictor of graft loss.*
 8. Halimi JM, Buchler M, Al-Najjar A, et al. Urinary albumin excretion and the risk of graft loss and death in proteinuric and non-proteinuric renal transplant recipients. *Am J Transplant*. 2007;7:618-25. ***Microalbuminuria and macroalbuminuria are powerful independent predictors of ESRD and death. In addition, microalbuminuria is a risk factor for graft loss even in non-proteinuric patients.*
 9. Cantarovich F, Martinez F, Heguilen R, et al. Proteinuria >0.5 g/d, a prevalent prognostic factor for patient and graft survival in kidney transplantation. *Clin Transplant*. 2010;24:175-80.
 10. Kamar N, Frimat L, Blanco G, et al. Evaluation of the efficacy and safety of a slow conversion from calcineurin inhibitor -to sirolimus- based therapies in maintenance renal-transplant patients presenting with moderate renal insufficiency. *Transpl Int*. 2007;20:128-34.
 11. Burton C, Harris KP. The role of proteinuria in the progression of chronic renal failure. *Am J Kidney Dis*. 1996;27:765-75.
 12. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney Int*. 1996;49:518-24.
 13. Broekroelsofs J, Stegman CA, Navis, G et al. Risk factors for long-term renal survival after renal transplantation: a role for angiotensin-converting enzyme (insertion/deletion) polymorphism? *J Am Soc Nephrol*. 1998;9:2075-81.
 14. Wilmer WA, Rovin BH, Hebert CJ, et al. Management of glomerular proteinuria: a commentary. *J Am Soc Nephrol*. 2003;14:3217-32.
 15. Jafar TH, Schmidt CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med*. 2001;135:73-87.
 16. Ruggenenti P, Schieppati A, Remuzzi G. Progression, remission, regression of chronic renal diseases. *Lancet*. 2001;357:1601-8.
 17. Sancho A, Gavela E, Avila A, et al. Risks factors and prognosis for proteinuria in renal transplant recipients. *Transplant Proc*. 2007;39:2145-7.
 18. Barnas U, Schmidt A, Haas M, et al. Parameters associated with chronic renal transplant failure. *Nephrol Dial Transplant*. 1997;12:82-5.
 19. Fernandez-Fresnedo G, Escallada R, Rodrigo E, et al. The risk of cardiovascular disease associated with proteinuria in renal transplant patients. *Transplantation*. 2002;73:1345-8. ***This paper characterizes proteinuria as an independent risk factor for patient outcome in kidney transplantation.*
 20. Amer H, Cosio FG. Significance and management of proteinuria in kidney transplant recipients. *J Am Soc Nephrol*. 2009;20:2490-2.
 21. López V, Martin M, Cobelo C, et al. Renin-angiotensin system dual blockade using angiotensin receptor plus aliskiren decreases severe proteinuria in kidney transplant recipients. *Transplant Proc*. 2010;42:2883-5.
 22. Seeman T, Dusek J, Vondrák K, Janda J. Ramipril in the treatment of proteinuria in children after renal transplantation. *Pediatr Transplant*. 2010;14:283-7.
 23. Amara AB, Sharma A, Alexander JL, et al. Randomized controlled trial: lisinopril reduces proteinuria, ammonia, and renal polypeptide tubular catabolism in patients with chronic allograft nephropathy. *Transplantation*. 2010;89:104-14.
 24. Knoll GA. Proteinuria in kidney transplant recipients: prevalence, prognosis, and evidence-based management. *Am J Kidney Dis*. 2009;54:1131-44. **Interesting detailed review.*
 25. Geara AS, Azzi J, Jurewicz M, Abdi R. The renin-angiotensin system: an old, newly discovered player in immunoregulation. *Transplant Rev*. 2009;23:151-8.
 26. Tylicki L, Biedunkiewicz B, Chamienia A, et al. Renal allograft protection with angiotensin II type 1 receptor antagonists. *Am J Transplant*. 2007;7:243-8.
 27. Heinze G, Mitterbauer C, Regele H, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol*. 2006;17:889-99.
 28. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med*. 1983;309:1543-6.
 29. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney Int*. 1998;53:1209-16.
 30. Redon J. Renal protection by antihypertensive drugs: insights from microalbuminuria studies. *J Hypertens*. 1998;16:2091-100.
 31. Bianchi S, Bigazzi R, Campese VM. Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. *Am J Kidney Dis*. 1999;34:973-95.
 32. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. ACE Inhibitors in Diabetic Nephropathy Trialist Group. *Ann Intern Med*. 2001;134:370-9.
 33. Krishna KS, Pandey AP, Kirubakaran MG, Kanagasabapathy AS. Urinary protein/creatinine ratio as an indicator of allograft function following live related donor renal transplantation. *Clin Chim Acta*. 1987;163:51-61.
 34. Steinhäuslin F, Wauters JP. Quantitation of proteinuria in kidney transplant patients: accuracy of the urinary protein/creatinine ratio. *Clin Nephrol*. 1995;43:110-5.
 35. Torng S, Rigatto C, Rush DN, Nickerson P, Jeffery JR. The urine protein to creatinine ratio (P/C) as a predictor of 24-hour urine protein excretion in renal transplant patients. *Transplantation*. 2001;72:1453-6.
 36. Price CP, Newall RG, Boyd JC. Use of protein: creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. *Clin Chem*. 2005;51:1577-86. ***In this complete review the authors suggest that the use of a protein:creatinine ratio measurement might be more reliable than the protein concentration measurement when a random urine sample is used.*
 37. Arias M, Fernández-Fresnedo G, Rodrigo E, et al. Non-immunologic intervention in chronic allograft nephropathy. *Kidney Int Suppl*. 2005;99:S118-23.
 38. Cusumano AM, Iotti R, Turin M, Dávalos M, Jost L, Vilches A. Incidence, etiology and prognostic value of persistent significant proteinuria in kidney transplants. *Medicina (B Aires)*. 1996;56:346-52.
 39. Yildiz A, Erkoç R, Sever, MS, et al. The prognostic importance of severity and type of post-transplant proteinuria. *Clin Transplant*. 1999;133:241-4. **In this analysis the authors found a significant association between the characteristics of proteinuria (type and severity) and outcome of kidney transplantation.*
 40. Bear RA, Aprile M, Sweet J, Cole EH. Proteinuria in renal transplant recipients: Incidence, cause, prognostic importance. *Transplant Proc*. 1988;20:1235-6.

41. Hohage H, Kleyer U, Brückner D, August C, Zidek W, Spieker C. Influence of proteinuria on long-term transplant survival in kidney transplant recipients. *Nephron*. 1997;75:160-5. **This study gives clear evidence about the association between mild proteinuria and worse prognostic of transplant outcome.*
42. Cherukuri A, Welberry-Smith MP, Tattersall JE, et al. The clinical significance of early proteinuria after renal transplantation. *Transplantation*. 2010;89:200-7. **This analysis showed the significant role of low-grade proteinuria at 3 months to identify high-risk group of patients post kidney graft.*
43. Ibis A, Altunoglu A, Akgül A, et al. Early onset proteinuria after renal transplantation: a marker for allograft dysfunction. *Transplant Proc*. 2007;39:938-40.
44. Pérez Fontán M, Rodríguez-Carmon, A, García Falcón T, Valdés, F. Early proteinuria in renal transplant recipients treated with cyclosporin. *Transplantation*. 1999;67:561-8.
45. Amer H, Cosio FG. Significance and management of proteinuria in kidney transplant recipients. *J Am Soc Nephrol*. 2009;20:2490-2.
46. Kang NR, Lee JE, Huh W, et al. Minimal proteinuria one year after transplant is a risk factor for graft survival in kidney transplantation. *J Korean Med Sci*. 2009;(Suppl):S129-34.
47. van Ree RM, Oterdoom LH, de Vries AP, et al. Circulating markers of endothelial dysfunction interact with proteinuria in predicting mortality in renal transplant recipients. *Transplantation*. 2008;86:1713-9. ***This trial analyzes and remarks on the association of markers of endothelial dysfunction and proteinuria as independent predictors of mortality in kidney transplantation.*
48. Roodnat JI, Mulder PG, Rischen-Vos J, et al. Proteinuria after renal transplantation affects not only graft survival but also patient survival. *Transplantation*. 2001;72:438-44. ***This study found proteinuria as an independent predictor of graft failure and patient death.*
49. Kim SC, Kang CH, Kim SK, et al. Impact of heavy proteinuria (>1 g/d) following renal transplantation. *Transplant Proc*. 2000;32:1894-5.
50. Fernández-Fresnedo G, Rodrigo E, de Francisco AL, et al. Change in serum creatinine levels between 6 and 12 months and kidney graft survival: influence of proteinuria. *Transplant Proc*. 2005;37:1433-4.
51. Fernández-Fresnedo G, Plaza JJ, Sánchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. *Nephrol Dial Transplant*. 2004;(Suppl. 3):iii47-51. ***This study confirms the independent risk factor role of proteinuria on cardiovascular disease and mortality in kidney transplantation.*
52. Martínez Esteban D, Jironda Gallegos C, Cabello Diaz M, et al. Creatinine clearance and proteinuria as early markers of kidney graft survival. *Transplant Proc*. 2010;42:2880-2. **This trial shows the association one year posttransplant between limited renal function and low proteinuria with worse kidney graft survival among recipients from expanded criteria donors.*
53. Djamali A, Samaniego M, Torrealba J, Pirsch J, Muth BL. Increase in proteinuria >200 mg/g after late rejection is associated with poor graft survival. *Nephrol Dial Transplant*. 2010;25:1300-6.
54. McLaren AJ, Fuggle SV, Welsh KI, Gray DWR, Morris PJ. Chronic allograft failure in human renal transplantation. A multivariate risk factor analysis. *Ann Surg*. 2000;232:98-103. ***This study analyzes risk factors of biopsy proven chronic allograft failure.*
55. Mahmoud IM, Elhabashi AF, Elsayy E, El-Husseini AA, Sheha GE, Sobh MA. The impact of hepatitis c virus viremia on renal graft and patient survival: a 9-year prospective study. *Am J Kidney Dis*. 2004;43:131-9.
56. Morales JM, Marcén R, Andres A, et al. Renal transplantation in patients with hepatitis C virus antibody. A long national experience. *NDT Plus*. 2010;3(Suppl. 2):ii41-6.
57. Sabry A. Proteinuria among renal transplant patients and its relation to hepatitis c virus and graft outcome: a single center experience. *Exp Clin Transplant*. 2010;8:91-7.
58. Shi BY, Wang Z, Zheng HL, Qian YY, Han MX. Risk factors of long-term cardiovascular diseases and cerebrovascular diseases in kidney allograft recipients. *Acta Academiae Medicinae Sinicae*. 2009;31:284-7.
59. Ibis A, Akgül A, Ozdemir N, et al. Posttransplant proteinuria is associated with higher risk of cardiovascular disease and graft failure in renal transplant patients. *Transplant Proc*. 2009;41:1604-8.
60. Diaz JM, Sainz Z, Guirado LL, et al. Risk factors for cardiovascular disease after renal transplantation. *Transplant Proc*. 2003;35:1722-4.
61. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303:423-9. **The authors found that the outcome risks of death and graft failure were independently increased in individuals with higher levels of proteinuria.*
62. Schröppel B, Heeger PS. Gazing into a crystal ball to predict kidney transplant outcome. *J Clin Invest*. 2010;120:1803-6.
63. Sijpkens Y, Zwinderman A, Mallat M, Boom H, de Fijter H, Paul L. Intercept and slope analysis of risk factors in chronic renal allograft nephropathy. *Graft*. 2002;5:108-13.
64. Vella J. Risk factors for graft failure in kidney transplantation. UpToDate. 2010. <http://www.uptodate.com/contents/risk-factors-for-graft-failure-in-kidney-transplantation>.
65. Khalkhali HR, Ghafari A, Hajizadeh E, Kazemnejad A. Risk factors of long-term graft loss in renal transplant recipients with chronic allograft dysfunction. *Exp Clin Transplant*. 2010;8:277-82.
66. Hernández D, Sánchez-Frustoso A, González-Posada JM, et al. A novel risk score for mortality in renal transplant recipients beyond the first posttransplant year. *Transplantation*. 2009;88:803-9. ***This trial describes a comorbidity index useful to identify high risk renal transplant recipients.*
67. Reichel H, Zeier M, Ritz E. Proteinuria after renal transplantation: pathogenesis and management. *Nephrol Dial Transplant*. 2004;19:301-5. **Interesting and detailed review.*
68. Harlan WR Jr, Holden KR, Melville Williams G, Hume DM. Proteinuria and nephritic syndrome associated with chronic rejection of kidney transplants. *N Engl J Med*. 1967;277:769-76.
69. Petersen VP, Olsen TS, Kissmeyer-Nielsen F, et al. Late failure of human renal transplants. An analysis of transplant disease and graft failure among 125 recipients surviving for one to eight years. *Medicine (Baltimore)*. 1975;54:45-71.
70. First MR, Vaidya PN, Maryniak RK, et al. Proteinuria following transplantation. Correlation with histopathology and outcome. *Transplantation*. 1984;38:607-12.
71. Peddi VR, Dean DE, Hariharan S, Cavallo T, Schroeder TJ, First MR. Proteinuria following renal transplantation: correlation with histopathology and outcome. *Transplant Proc*. 1997;29:101-3.
72. Ramanathan V, Suki WN, Rosen D, Truong LD. Chronic allograft nephropathy and nephrotic range proteinuria. *Clin Transplant*. 2005;19:413-7.
73. Oberbauer R, Haas M, Regele H, Barnas U, Schmidt A, Mayer G. Glomerular permselectivity in proteinuric patients after kidney transplantation. *J Clin Invest*. 1995;96:22-9.
74. Barnas U, Mayer G. Glomerular proteinuria in renal transplant patients: mechanisms and treatment. *Kidney Int Suppl*. 1997;51:S78-80.
75. Amer H, Fidler ME, Myslak M, et al. Proteinuria after kidney transplantation, relationship to allograft histology and survival. *Am J Transplant*. 2007;7:2748-56. ***This study shows for the first time that proteinuria and graft histology are statistically independent predictors of graft survival.*
76. Knoll GA. Proteinuria in kidney transplant recipients: prevalence, prognosis, and evidence-based management. *Am J Kidney Dis*. 2009;54:1131-44. **Interesting and detailed review.*
77. Damsgaard EM, Frøland A, Jørgensen OD, Mogensen CE. Microalbuminuria as predictor of increase mortality in elderly people. *BMJ*. 1990;300:297-300.
78. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis*. 2002;39:S1-266.
79. de Jong PE, Gansevoort RT. Focus on microalbuminuria to improve cardiac and renal protection. *Nephron Clin Pract*. 2009;111:c204-11.
80. Martínez-Castelao A, Hueso M, Sanz V, Rejas J, Alsina J, Grinyó JM. Treatment of hypertension after renal transplantation: long-term efficacy of verapamil, enalapril, and doxazosin. *Kidney Int Suppl*. 1998;68:S130-4.

81. del Castillo D, Campistol JM, Guirado L, et al. Efficacy and safety of losartan in the treatment of hypertension in renal transplant recipients. *Kidney Int Suppl.* 1998;68: S135-9.
82. Hausberg M, Barenbrock M, Hohage H, Müller S, Heidenreich S, Rahn KH. ACE inhibitor versus beta-blocker for the treatment of hypertension in renal allograft recipients. *Hypertension.* 1999;33:862-8.
83. Muirhead N, House A, Hollomby DJ, Jevnikar AM. Effect of valsartan on urinary protein excretion and renal function in patients with chronic renal allograft nephropathy. *Transplant Proc.* 2003;35:2412-4.
84. Bravo P, Felgueiras J, Santos C, Oliveira C, Ponce P. Angiotensin-converting enzyme inhibitors after renal transplantation. *Transplant Proc.* 2008;40:740-2.
85. Thilly N, Bayat S, Alla F, Kessler M, Briangon S, Frimat L. Determinants and patterns of renin-angiotensin system inhibitors' prescription in the first year following kidney transplantation. *Clin Transplant.* 2008;22:439-46.
86. Remuzzi G, Perico N, Macia M, Ruggenenti P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int.* 2005;68:S57-65.
87. Cruzado JM, Rico J, Grinyó JM. The renin angiotensin system blockade in kidney transplantation: pros and cons. *Transplant Int.* 2008;21:304-13.
88. Hiremath S, Fergusson D, Doucette S, Mulay AV, Knoll GA. Renin angiotensin system blockade in kidney transplantation: a systematic review of the evidence. *Am J Transplant.* 2007; 7:2350-60.
89. Jennings DL, Taber DJ. Use of renin-angiotensin-aldosterone system inhibitors within the first eight to twelve weeks after renal transplantation. *Ann Pharmacother.* 2008; 42:116-20.
90. Campistol JM, Iñigo P, Larios S, Bescos M, Oppenheimer F. Role of transforming growth factor- β_1 in the progression of chronic allograft nephropathy. *Nephrol Dial Transplant.* 2001;16:114-6.
91. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med.* 2008;148:30-48.
92. Kumar S, Ram CVS. Angiotensin receptor blockers: Current status and future prospects ACEI and angiotensin II. *Indian Heart J.* 2007;59:443-53.