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Weekly Assessment of Proteinuria After Renal Transplantation: A Possible Clinical Relevance

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ABSTRACT

Aim of the study: Presence of protein in urine is negatively associated with kidney function. In order to evaluate the contribution of proteinuria from native kidney to post renal transplant urine protein content, we estimated protein urea before and weekly after kidney transplantation. The relation of proteinuria and serum biochemical parameters in clouding serum creatinine, fasting blood sugar, cholesterol level and immunosuppressive drugs used is also investigated.

Methods: Proteinuria was evaluated according to definition of >300 mg/24 hours. Patients were classified into three groups, group (A)< 300 mg/24hours. Group (B) 300-1000 mg/24hours and group (C)> 1 gm/24 hours. All Patients were treated with immune suppressive drugs; tacrolimus, my co phenol late mo fetil and prednisone. Anti-hypertensive drugs (ACEI and ARB) that might reduce protein urea were not used.

We tested the association between level of protein urea and serum creatinine, fasting blood glucose, HBA1C and Cholesterol. Moreover, we also investigated the association with hypertension, diabetes mellitus and immunosuppressive drugs used.

Results: A total of 68 renal transplants recipients were included in our study with mean age of 40.4 years and 57.4% were male. The prevalence of proteinuria in post renal transplant patients based on the average of recorded protein urea during first eight weeks, was27.9 % compared with98.3% in pre-transplant patients. Based on resolution of proteinuria in our study, in pre-

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transplant patients, group A was 1.6%, group B 25.8% while group C was 72.5%. However, in post-transplant patients, group A was 72%, group B23.5%, and group C 4.4%. Weekly assessment of protein urea for two months indicated significant amelioration in proteinuria level and a remarkable reduction in serum creatinine levels. The prevalence of protein urea during week 8 was (95.2%, 2.9%, and 1.4%) in group A, B and C, respectively. In addition, patients with non-detectable level increased to 82%. No correlation between fasting blood sugar, HBA1C, cholesterol land protein uria were observed.

Conclusion: There was a dramatic decrease in proteinuria after renal transplantation. Moreover, a gradual decrease in renal proteinuria during first eight weeks was positively associated with remarkable melioration in kidney function.

Keywords: Proteinuria, Renal Transplant, Allograft Survival.

Introduction

Proteinurea is highly prevalent after kidney transplant. It has been reported that after renal transplantation protein urea is immediately and frequently detected. The source of proteinuria may be from the native kidneys or from the allograft [1], probably as a consequence of the glomerular or tubular dysfunction. Differential diagnosis may be difficult. However, after successful kidney transplantation, protein urea tends to fall rapidly reaching almost normal levels within few weeks [1, 2, 3]. The persistence of protein urea or a late appearance, on the other hand, represents a sign of injury to allograft [4].

Based on the threshold used to define proteinuria, the prevalence of proteinuria in kidney transplant recipients differs considerably from 11 to 45 % [5, 6, and 7]. This large variation in proteinuria prevalence depends on threshold and criteria used to define proteinuria. Several studies used a threshold just above the normal limit >150 mg/24h, with the highest prevalence of proteinuria between 31 and 45% [6, 8, 9]. Other studies used a cut off level >1 g/d; the average prevalence was 19% [5, 10, 11]. Using a high threshold to define proteinuria (>2 to 3 g/d) a much lower prevalence of proteinuria with an average of 13% has been shown [5, 12, 7]. These data suggest that post-renal transplant proteinuria is a common condition and a predictor of the renal allograft injury. It constitutes a major risk factor for renal allograft and patient survival. [13,14].

Ponticelli and Graziani [15] showed that proteinuria may be tubular or glomerular, induced by failure in tubular reabsorption or defective in glomerular barrier. They also reported the different causes and diseases behind tubular or glomerular proteinuria. However, the pathogenesis of the post-renal transplant proteinuria is multi factorial. Rood Nat et al., [8] reported that transplant recipients with glomerul one phritis, systemic disease, or arterial hypertension as original renal disease are more susceptible to proteinuria. Moreover, other investigators showed that degree of proteinuria are more frequently associated with allograft histological characteristic [16-19]. However, Chung et al., [20] disputed these results and showed that there was negative correlation between proteinuria and allograft histological characteristic. In addition, other investigators [10, 21] reported that incidence of proteinuria was significantly higher in patients who received the

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kidney from donors positive for hepatitis C virus. These reports were also disputed by other studies including Khedr et al., [16] where no significant correlation was found. These discrepancies may be due to the different definitions of proteinuria accounted in these studies. Delineation of the origin of post renal transplant proteinuria is highly important for the appropriate management.

The association of proteinuria and the use of immunosuppressive drugs by allograft recipients posed a particular problem. A higher rate of proteinuria has been reported in post-transplant renal patients who switched from a CNI-based immunosuppressive regimen to inhibitors of mammalian target of rape my in (m TOR inhibitors), Sirolimus [22-27]. Stephan yet al., [28] studied the effect of Sirolimus on proteinuria and concluded that proteinuria was significantly associated with use of Sirolimus at 1 year. Therefore, Sirolimus use should be considered as a potentially reversible cause of proteinuria in the kidney transplant population.

The mechanisms behind proteinuria are still under investigation. In addition, the evidence-based therapies for the management of proteinuria in kidney transplant recipients from most causes are lacking and limited. The use of the blockade RAAS with ACEIs and ARBs may reduce proteinuria, but the long-term effect of these medications on patient and graft survival remains unknown.

It has been reported that post-renal transplant proteinuria is commonly associated with graft and patient survival [6]. Rood Nat et al. [8] confirmed previous results and showed that proteinuria doubled the risk of graft failure in comparison with non proteinuric transplant patients. In addition, Fernadez-Fresnedo et al. [14] studied the effect of proteinuria in patients with glomerulonephritis, hypertension, or systemic diseases at 1 year on graft survival and concluded that there was an inverse relationship between graft survival and proteinuria. Moreover, there was a parallel relationship between increasing amounts of proteinuria and relative risk of graft failure, as being 2.33 for proteinuria 0.5–1 g/day and 3.46 for proteinuria >1 g/ day.

Any increase of proteinuria by 1 g/day increased the risk of graft loss by 27%. Even proteinuria detected just above normal value whatever the cause (low-grade), has been reported to be a potent predictor of graft loss [10]. These data have been confirmed by Cherekun et al., [29] using a multivariate analysis indicating that low grade of proteinuria at three months predicted death-censored graft failure.

There has been only one report that attempted to evaluate the prevalence and risk factors of proteinuria in post-transplant in Saudi patients between January 1979 and November 1998 [30]. To date and up to our knowledge, there have been no reports that investigated the contribution of proteinuria from native kidney followed weekly in Saudi kidney transplant patients. Therefore, the main aim of this study is to assess the contribution of proteinuria from native kidney and weekly follow up after kidney transplantation in Saudi transplant recipients.

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Materials and Methods

The study population consisted of Saudi kidney transplant recipients in King Abdul-Aziz Medical City (KAMC), National Guard, aged 30-75 years, from January 2015 to January 2017 with at least 8 weeks follow up after kidney transplantation. The research proposal was submitted to and approved by research Ethics Committee and IRB of King Abdullah International Medical Research Centre (KAIMRC) number SP16/158.

It is a retrospective study, carried out by reviewing medical records of post renal transplant Saudi patients. The following parameters were collected from patient's medical records; age and gender and weight of the recipient. Hypertension before and after kidney transplant, diabetes and other diseases are recorded. Patients should be under medical treatment with immunosuppressive drugs for the first time. Based on the presence of proteinuria, patients were classified into three groups depending on resolution of proteinuria. Group A patients from < 300 mg/24hours, group B patients from 300-1000mg/24hours, group C from>1gm/24hours [30]. Date, types of immunosuppressive medications used besides the complete medical history and the detailed clinical examination were collected as well as possible etiology and risk factors involved in the induction of proteinuria.

Data of proteinuria were collected before and after kidney transplant. In addition, data of laboratory investigations including complete blood count, lipid profile, and kidney function tests, fasting blood sugar and HBA1C were obtained from medical records.

Immunosuppression

The immunosuppressive regimen consisted of different doses of tacrolimus ranged from (0.5-7 mg BID), mycophenolate of etil (250 -1000 mg BID) and/or prednisone (5-15 mg OD). Three patients had tacrolimus and mycophenolate only and only one patient treated with tacrolimus together with prednisolone.

Statistical Analysis: Descriptive statistical analyses were performed on the data for the study sample. Continuous variables were summarized using mean and standard deviation (SD), and proportions were used for categorical variables. Statistical comparisons between different various data were made. The distribution of all continuous data were examined. For continuous variables with normal distribution, a t-test were used for comparisons, Statistical significance were considered at $p<0.05$. All statistical analyses were performed using SPSS 21.0 [Release 21.0.0.0].

Results

A total of 68patients were included in this study. Demographic characteristics of patients included in the present study are depicted in (Table 1). Average age was 40.72 (SD = 16.4) years, with 54% males. Average weight was 73.2KG (SD = 20.6) KG. Seventy-two percent of patients had hypertension (HTN)38% diabetes, 27.9 % had additional medical problems. (Table 1).Forty nine patients (72%) were treated with antihypertensive medications (calcium channel blocker; CCBs and beta1 antagonist and received ant diabetic medications mainly insulin.

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An important finding in this study is that there was a significant reduction of proteinuria during the follow up period in kidney recipient (8 weeks) as compared with proteinuria level before. This was confirmed by a parallel significant reduction in serum creatinineindicatingremarkable improvement in kidney function. As there was a dramatic decrease in serum creatinine level during follow up as compared with pre-transplant creatinine level (Table2).

Table 3 show results for proteinuria before kidney transplant (week 0) and in the first 8 weeks after transplantation. There was a gradual significant decrease in proteinuria compared with proteinuria level before kidney transplant. A parallel significant reduction in serum creatinine was also observed.

Table 1: Profile of Subjects. N = 68.

Factor	
Gender n (%)	
Male	39 (57.4%)
Female	29 (42.6%)
Age (years) mean ± SD	40.72± 16.4
median (IQR)	41.5 (26.5 - 56)
Weight (KG) mean ± SD	73.2± 20.6
median (IQR)	73.4 (57.9–87.9)
Height (cm)	159.3 ±12.7
BMI	28.4± 6.6
Marital Status Married (%)	23 (33.8%)
Smoking	4 (5.8%)
Graft Type n (%)	
Living	44 (64.7%)
Cadaveric	24 (35.3%)
HTN	49 (72.1%)
DM	26 (38.2%)
Other Medical Problems	19 (27.9%)

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An association between level of proteinuria and serum creatinine was detected. Amelioration of proteinuria was associated with attenuation of serum creatinine which may indicate promotion in kidney function (Table 4). However, there were no significant co-relationship between various laboratory parameters (serum fasting blood sugar, HBA1C and serum cholesterol) and proteinuria.

Results from paired comparisons between baseline and follow up measures are displayed in Table 2. The results showed highly significant reductions in proteinuria and creatinine levels ($p<0.001$ for both measures)

Table2: Descriptive Statistics and Comparison between before kidney transplant and after (Follow-Up) Proteinuria and Creatinine.

		Before	After (Follow UP)	p-value
Proteinuria **(gm/l)**N=62	mean ± SD	2.62 ± 1.83	0.17± 0.23	<0.001*
Creatinine **(µmol/l)** N=68	mean ± SD	878.4 ± 287.6	190.8 ± 70.75	<0.001*

* Based on ANOVA single factor

Table3: Descriptive Statistics and Comparison of Proteinuria and Creatinine between Week 0 (before kidney transplant) and Week 1 through Week 8 (after kidney transplant).

	Mean (SEM)	
	Proteinuria (g/l)	**Creatinine (µmol/l)**
	N=62	**N=68**
Week 0	2.62 (0.23)	878.7 (34.9)
Week 1	0.37 (0.05)*	480.3 (21.7)*
Week 2	0.18 (0.04)*	309.7 (19.1)*
Week 3	0.12 (0.02)*	196.6 (13.7)*
Week 4	0.16 (0.05)*	145.7 (9.9)*

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Week 5	0.11 (0.03)*	113.5 (8.8)*
Week 6	0.18 (0.05)*	94.5 (5.3)*
Week 7	0.13 (0.04)*	95.4 (6.8)*
Week 8	0.08 (0.03)*	90.5 (4.8)*

*p<0.001 compared to week 0 (baseline) ANOVA single Factor. SEM = Standard Error of the mean

Results in Table 3 showed that proteinuria and creatinine levels were significantly decreased post-transplant compared to pre-transplant (week 0) at all follow up points (week 1- week 8); p<0.001.

Table 4: Descriptive Statistics and Comparison of Creatinine, Cholesterol, FBG and HBA1C by Proteinuria Level. N = 68.

	Proteinuria Group				
Factor	**Negative (n = 3)**	**>0-0.3 Group A (n = 46)**	**>0.3-1 Group B (n = 16)**	**>1 Group C (n=3)**	**p-value***
Creatinine mean ± SD	118.8 ± 28.7	187.9 ± 69.1	198.9 ± 63.6	264.0 ±111.2	0.08
Cholesterol mean ± SD	4.5 ± 0.2	4.4 ± 0.3	4.5 ± 0.2	4.5 ± 0.2	0.22
FBG mean ± SD	7.4 ± 1.3	6.5 ± 2.7[a]	9.6 ± 4.3	6.7 ± 2.4	0.01*

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HgA1c	mean ± SD	6.2 ± 1.3	6.2 ± 1.4[b]	7.0 ± 1.5[d]	5.8 ± 1.6	0.24

* Based on the one-way ANOVA

[a] N=45, [b]N=39, [d]N=15

Table 4 shows results of descriptive statistics and comparison of Creatinine, cholesterol, FBG and HgA1c by proteinuria level. FB Glevels were significantly different among patients with highest proteinuria levels at group B (p = 0.01). However, no statistically significant differences were observed between proteinuria groups in terms of creatinine, cholesterol, or HgA1c (p = 0.08, 0.22, and 0.24 respectively).

There were no statistical correlation between proteinuria levels after transplantation and any of the followed measures of creatinine, fasting blood glucose, HgA1c, and cholesterol.

Table 5: Descriptive Statistics and Comparison of Proteinuria, Creatinine, Cholesterol, FBG and HBA1C by Graft Type.

Factor	**Graft Type**		
	Living	**Cadaveric**	**p-value***
Proteinuria mean ±SD (n)	0.30 ± 0.29 (42)	0.36 ± 0.33 (23)	0.43
Creatinine mean ± SD (n)	202.4 ± 77.8 (44)	169.4 ± 50.23 (24)	0.07
Cholesterol mean ± SD (n)	4.61 ± 0.93 (41)	4.28 ± 0.87 (23)	0.17
FBG mean ± SD (n)	8.5 ± 3.6 (43)	5.1 ± 0.35 (24)	<0.001*

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HgA1c	mean ± SD (n)	6.9 ± 1.5 (40)	5.4 ± 0.3 (20)	<0.001*

* Based on the one-way ANOVA

Table 5 results showed interestingly, that FBG as well as HgA1c are significantly different between the cadaveric type and living donor renal transplant (p-value <0.001). While proteinuria, cretonne and cholesterol levels were not (p-value= 0.43, 0.07, and 0.17 respectively). The difference may be confounded by existing diabetes, however 18 patients (40%) of total 44 living donor transplant were diabetics while 7 patients (55%) out of total 24 cadaveric transplant were diabetic.

Table 6: Descriptive Statistics and Comparison of Proteinuria, Creatinine, Cholesterol, FBG and HBA1C by disease state.

Factor	**Hypertension**	**Diabetes Mellitus**	**Both**
Proteinuria mean ±SD (n)	0.34 ± 0.33 (46)	0.37 ± 0.28 (24)	0.39 ± 0.29 (22)
Creatinine mean ± SD (n)	196.9± 68.2 (48)	208.6 ± 77.04 (25)	210.3 ± 75.5 (23)
Cholesterol mean ± SD (n)	4.5 ± 0.97 (45)	4.7 ± 1.0 (25)	4.61 ± 1.0 (23)
FBG mean ± SD (n)	7.9 ± 3.7* (46)	10.7 ± 3.12* (25)	10.91 ± 3.1* (23)

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HgA1c	mean ± SD (n)	6.7 ± 1.5 *(43)	7.9 ± 0.9* (25)	7.93 ± 0.9* (23)

* P-value < 0.001 Based on the one-way ANOVA

Table 6 compared the proteinuria, creatinine, cholesterol, FBG, and HgA1c according to disease state. All measurements were not significant except for FBG and HgA1c in patients with hypertension, diabetes or both disease states.

The results showed that there were no statistically significant difference in proteinuria between patients on calcium channel blockers CCB (n=35) when compared to patients who are not using CCB (n=35); p-value=0.58. Most of the CCB group were on am lodipine (83%) and the rest were on nifidipine (17%). The subgroup analysis showed no statistically significant difference in proteinuria between amlodipine and nifidipine groups; p-value=0.98.

Discussion

Proteinuria is positively associated with deterioration of kidney function. Therefore, it must be periodically investigated especially in kidney transplant recipients and if it is present, the aetiology should also studied [12]. Previous study indicated that proteinuria after kidney transplant is a predictor of graft and patients survival [8]. Thus, discrimination of the source of post-transplant proteinuria (native kidney or allograft) is an important factor for these patients to increase graft and patients survival.

The prevalence of proteinuria in post renal transplant patients described previously in the literature differ considerably because of different definitions used for proteinuria and different period evaluated after kidney transplantations. A mar et al., [6] found prevalence greater than 45% with proteinuria greater than 150 mg/day. However the prevalence was sharply reduced to 15.3% and 20.2% when the cut-off point for proteinuria had raised to 500 mg/day [14,31] respectively. Proteinuria is associated negatively with both native and allograft kidney function, and it has a significant effect on the risk of failure of allograft kidney. Therefore, assessment of proteinuria for 12 months after kidney transplantation is feasible, confirmed its role as a prognostic factor even at level below 500 mg/day.

In our study, we selected resolution of proteinuria values more than 300 mg/day, the prevalence of proteinuria in pre-renal was 98.5% while in post-transplant patients was 8.5%. However, if the proteinuria cut-off point was less than or equal to 1 gm/day, the prevalence was 74% and 1.4% in pre and post renal transplant recipients respectively, as we have only one patient have more than 1gm/day after kidney transplantation. The distribution of the patients in the present study based on the degree of proteinuria was largely different than that in previous study Souqiyyeh et al., [31]

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which used cut off proteinuria of less than 300 mg/24hrs and reported prevalence proteinuria of 38.5%, and 11.5% above 1000 mg/24hr. The reason of discrepancy may be the difference in the evaluation of follow up period after kidney transplantation or difference in the technique used in proteinuria estimation.

The results of the present study clearly demonstrate that successful kidney transplantation associated with rapidly graft function significantly resolves proteinuria gradually within the first eight weeks. As the highest level of proteinuria was noticed in the first week after renal transplant parallel with highest level of creatinine, then there was a significant gradual decrease in follow-up until week 8 as compared with proteinuria level before transplant (week0). Therefore, the present study indicated that deterioration in renal function measured by creatinine, positively associated with higher proteinuria >0.3 gm/day as in first week after transplantation and gradually ameliorated until week 8, as the level of proteinuria was < 0.1 gm/l. This confirms the value of regular measurement of proteinuria during first months after transplantations proteinuria is an indicator of renal damage and subsequent decline in renal function. Thus we could assume that beyond the first two months post-transplant period, the source of proteinuria appears to be of allograft origin exclusively in kidney transplant patients.

Opelz et al., [32] evaluated the effect of RAAS inhibitors on patient and graft survival and concluded that there was no significant improvement in proteinuria after kidney transplantation in 17,209 recipients, suggesting that control of blood pressure is more important than type of antihypertensive drugs used. This finding was disputed by He inze et al., [33] who demonstrated that patients using antihypertensive as ACE inhibitors or an ARB showed a highly improvement in graft survival. In our study we noticed that there was an improvement in kidney function as reflected by the significant reduction in weekly serum creatinine although antihypertensive drugs used were calcium channel blockers or beta1 antagonist.

Hire math et al., [34] and Knoll et al., [35] claimed that the prime target to be achieved after renal transplantation is the reduction of proteinuria for nephron-protection. Therefore weekly assessment of proteinuria can be considered an important measure to follow-up kidney function and allograft survival. Therefore, it is highly important to stress that evaluation of proteinuria should be a systematic request by the nephrologists and be performed by the kidney recipient annually. It is noteworthy that the neither type of graft (living vs. cadaveric) nor the disease state (hypertension or diabetes) were associated with post-transplant proteinuria as well as other measurements with the exception of fasting blood glucose and the HgA1c levels. Both FBG and HgA1c were significantly higher in living donor transplant, patients with hypertension and/or diabetes. The significance of this finding need to be further investigated. The use of calcium channel blockers is reported to have a beneficial effect on proteinuria; however, our results showed no statistical differences between CCB-users vs. non-users and further comparison also showed no difference between amlodipine and nifedipine. The proteinuria reduction is associated with the non-dihydropyridine CCB and all subjects were using dihydropyridine CCBs which are known for neutral effect on proteinuria [36]. Nevertheless, further studies are highly needed to investigate renal histology to better understand etiology and management of proteinuria. A major

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limitation of our study is the small sample size. Hopefully a future investigation will be conducted including a larger and more representative sample with more variant demographic and clinical characteristics.

Conclusion

In this study, significant reductions in proteinuria and creatinine levels were weekly observed post renal transplantation. Further studies are highly warranted to confirm this finding and explore other patient and transplant related factors.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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