Proteinuria After Kidney Transplantation
Its Relation to Hepatitis C Virus and Graft Outcome

Alaa Sabry,[1] Rashad Hassan,[1] Ihab Mahmoud,[1] Magdy Hamed,[2] Mohamed Sobh[1]

[1]Department of Nephrology, Mansoura Urology and Nephrology Center, Mansoura University, Mansoura, Egypt
[2]Department of Internal Medicine, Mansoura Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

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Introduction. Chronic Hepatitis C Virus (HCV) infection has been associated with glomerular disease in native and transplanted kidneys. We evaluated the presence of HCV infection at the time of transplantation and occurrence of proteinuria in Egyptian kidney transplant patients and their link with graft survival.
Materials and Methods. This retrospective study was done on 273 patients with end-stage renal disease transplanted in Mansoura Urology and Nephrology Center Between 1993 and 1996. Their sera were routinely assayed for anti-HCV antibodies at the time of transplantation. The relationship between the HCV and the development of posttransplantation proteinuria was evaluated, along with the possible effects of proteinuria on long-term graft survival.
Results. A total of 169 kidney recipients (61.9%) were positive for anti-HCV antibodies. The mean durations of post-transplant follow-ups were 87.73 ± 26.79 months (range, 19 to 123 months) and 84.29 ± 28.55 months (range, 11 to 123 months) for the patients with and without anti-HCV antibodies, respectively. The patients in these groups were comparable regarding the incidence of proteinuria (33% and 32%, respectively) and its quantity (median, 0.6 g/d and 0.4 g/d, respectively). Irrespective of the HCV infection, patients with nephrotic-range proteinuria showed a worse graft survival ($P < .001$) and a higher frequency of chronic allograft nephropathy ($P = .03$) compared with nonproteinuric patients.
Conclusions. There is a high prevalence of HCV infection in our patients with end-stage renal disease awaiting kidney transplantation. The incidence and quantity of proteinuria do not increase by HCV infection, and nephrotic-range proteinuria is independently associated with chronic allograft nephropathy and a poorer graft outcome.

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INTRODUCTION

Proteinuria resulting from increase in glomerular permeability to large plasma proteins is a common finding in kidney transplant recipients.[1] Persistent proteinuria following kidney transplantation is attributed to many causes encompassing recurrent or de novo glomerulonephritis, allograft glomerulopathy, chronic rejection, nephrosclerosis, renal vein thrombosis, and reflux nephropathy.[2] It has been shown that proteinuria may directly damage the kidneys by different potential mechanisms.[3] The timing of posttransplant proteinuria is important; in the early posttransplant period, it commonly decreases, and neither its amount nor its duration is of prognostic value. However, a poor prognosis has been described in kidney transplant patients

with persistent proteinuria in long-term.[4]

The prevalence of antibodies against hepatitis C virus (HCV) in kidney transplant patients varies from 6% to 64% depending on the geographic area.[5] The HCV infection is responsible for extrahepatic diseases in immunocompetent individuals, especially glomerulonephritis.[6] However, little is known about its effect on kidney transplantation. Some reports suggest that HCV-infected kidney recipients may develop recurrent or de novo glomerulonephritis (due to cryoglobulinemia) or deposition of complexes containing viral antigen and anti-HCV antibodies.[7] Other reports indicate that similar extrahepatic syndromes associated with hepatitis C can also occur after organ transplantation.[8]

In Egypt, the HCV infection has reached epidemic proportions with up to 21.9% of the general population affected. This has been partly attributed to the routine parenteral administration of antischistosomal drugs during the 1960s.[9] The current study was therefore carried out to estimate the prevalence of HCV among our kidney transplant recipients, to investigate any association between pretransplant anti-HCV antibodies and the occurrence of posttransplant proteinuria, and finally to clarify any effect of the HCV and proteinuria on patient and graft survival.

MATERIALS AND METHODS

Patients

We enrolled 317 patients with end-stage renal disease who fulfilled our inclusion criteria (older than 18 years and negative for hepatitis B surface antigen [HBsAg]) in our study. All of them received kidney transplants in Mansoura Urology and Nephrology Center in Mansoura, Egypt, between April 1993 and January 1996. Patients living with a functioning graft for 6 months posttransplantation were assessed and 44 were excluded due to a positive result for HBsAg (n = 11), death or graft failure within 6 months posttransplant (n = 10), and lost to follow up (n = 23). Results of pretransplant anti-HCV antibodies assessment (using third generation enzyme-linked immunosorbent assay [ELISA]) was available for all of the patients.

Pretransplant Workup

During their regular hemodialysis, all of the patients were screened monthly for serum creatinine before and after dialysis sessions, Kt/V, serum electrolytes, prothrombin time, fasting and postprandial blood glucose, serum uric acid, complete blood count, and liver function tests including serum levels of bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransaminase, alkaline phosphatase.

Screenings for anti-HCV antibodies (Murex, Dartford, UK), hepatitis B virus markers (ELISA technique, Behring, Marburg, Germany), cytomegalovirus (CMV) IgM antibody (microparticle enzyme immunoassay, Abbot, Abbott Park, Illinois, USA), and antihuman immunodeficiency virus (HIV) 1 and 2 antibodies (Murex HIV-1 and HIV-2 enzyme immunoassay tests, Murex, Dartford, UK) were carried out every 3 months.

Cryoglobulin Assay

Cryoglobulin assay was done for 163 patients out of the 273 patients included in the study after a mean period 86.4 ± 27.4 months (range, 11 to 123 months) posttransplant. Blood sample (10 mL of whole blood) was brought to the laboratory immediately after obtaining. The specimen was not refrigerated before the test. Tubes for collection were not anticoagulated since the use of plasma might result in development of cold precipitable fibrinogen, cryofibrinogen, or heparin-precipitable protein. The specimen was incubated for at least 30 minutes to 1 hour at 37°C in a heat block or water bath prior to centrifugation. Thereafter, it was centrifuged at room temperature and the fresh serum was placed into an appropriately labeled tube. One tube was preserved in the refrigerator for a minimum of 4 days and another was left at room temperature.

Posttransplant Workup

Following kidney transplantation, all the recipients were immunosuppressed with triple-drug regimen (prednisolone, cyclosporine, and azathioprine) according to the standard protocol described by Ghoniem and coworkers.[10] Azathioprine dose was reduced by 50% whenever the blood leukocyte count fell below 3.0×10^9/L. They were evaluated for graft function (serum creatinine, creatinine clearance, urinalysis, graft ultrasonography, and radioisotope renography). After discharge from the hospital, they were subjected to thorough clinical examination and laboratory investigation.

In addition to the routine urinalyses, a 24-hour urinary protein was measured 12 months after transplantation by a timed end-point method,[11] which was corrected to urinary protein in mg/h/m^2. Proteinuria was defined as urinary protein above 300 mg/d at 2 successive assays. Nephrotic-range proteinuria was defined as daily protein excretion greater than 3.5 g/d/1.73 m^2 surface area, whilst persistent proteinuria was defined as urinary protein remaining above 300 mg/d over 3 months after the onset. Transient proteinuria was not considered for the analysis.

Liver function tests were checked daily during hospitalization, and then monthly for patients with normal liver function and upon each visit for those with hepatic dysfunction. Chronic hepatitis was defined as 2-fold or greater elevation of serum transaminases for 6 months or more. Before the introduction of myclophenolate mofetil into our immunosuppressive protocol, doubling of serum transaminases and/or rising of serum bilirubin were managed by replacing azathioprine with cyclophosphamide (1 mg/kg/d). Azathioprine was reintroduced 1 month after normalization of the liver function tests. It was permanently discontinued if this reintroduction was associated with hepatic dysfunction. Since the administration of myclophenolate mofetil, cyclophosphamide has no longer been used, and instead, patients with hepatic dysfunction received myclophenolate mofetil (1.5 g/d).

Liver biopsy was performed for the patients who developed a 2-fold or greater elevation of serum transaminases during the 6 months posttransplant. Biopsy specimens were evaluated by a pathologist blind to the study protocol and scored according to Knodell and colleagues' classification.[12]

Rejection of the graft (acute or chronic allograft nephropathy) was diagnosed and graded by kidney biopsy using the Banff 97 working classification of renal allograft pathology.[13] Glomerulopathy in the kidney allograft was defined as mesangial matrix expansion, mesangial proliferation, basement membrane thickening with double contours, and peripheral mesangial interposition, sometimes accompanied by focal segmental sclerosis. Screening for viral infections was carried out at 6-month intervals and whenever indicated (HBsAg, CMV, anti-HIV-1 and anti-HIV-2, and anti-HCV antibodies). Finally, serum levels of C3 complement (reference range, 0.79 g/L to 1.06 g/L) and C4 complement (reference range, 0.23 g/L to 0.30 g/L), rheumatoid factor reactivity, and administration of angiotensin converting enzyme inhibitors were determined.

Statistical Analyses

Quantitative data were displayed in terms of mean ± standard deviation for normally distributed variables and median and range for skewed variables. The unpaired *t* test and the Mann-Whitney test were used for comparisons. Qualitative data were described in cross tabulation with the chi-square and Fischer exact tests used for the comparison of frequencies. Graft and patients survival rates were assessed using the Kaplan-Meier method and the long-rank test. All the analyses were carried out using the SPSS software for Windows (Statistical Package for the Social Sciences, version 10.0, SPSS Inc, Chicago, Illinois, USA). A *P* value less than .05 was considered significant.

RESULTS

Frequency of Hepatitis C Virus among Kidney Transplant Patients

A total of 317 patients were transplanted during the study period. We excluded 44 patients due to a positive result for HBsAg (n = 11), death or graft failure within 6 months posttransplant (n = 10), and lost to follow up (n = 23). The remaining 273 recipients were living with functioning grafts for at least 6 months. The mean follow-up period of the patients was 86.4 ± 27.4 months. The pretransplant anti-HCV antibody test was positive for 169 patients (61.9%).

The two groups of kidney allograft recipients with and without anti-HCV antibodies were comparable with respect to age, sex, donor source, human leukocyte antibodies (HLA) mismatches, and the primary kidney disease. Anti-HCV-positive recipients (group 1) received significantly more blood transfusions and had a significantly longer duration of hemodialysis than the anti-HCV-negative recipients (group 2; Table 1). The mean follow-up period for the patients in groups 1 and 2 was 87.73 ± 26.79 months (range, 19 to 123 months) and 84.29 ± 28.55 months (range, 11 to 123 months), respectively.

The patients of the two groups were comparable with regard to the incidence and quantity of

Table 1. Pretransplant Characteristics of 273 Patients With End-stage Renal Disease*

Characteristics	Kidney Allograft Recipients		*P*
	Anti-HCV Positives (n = 169)	Anti-HCV Negatives (n = 104)	
Mean age, y	30.7 ± 10.5	29.6 ± 11.2	.40
Sex			.85
Male	122 (72.2)	74 (71.2)	
Female	47 (27.8)	30 (28.8)	
Mean donor age, y	34.4 ± 10.0	36.1 ± 10.6	.17
Donor sex			.33
Male	84 (49.7)	58 (55.8)	
Female	85 (50.3)	46 (44.2)	
Number of HLA mismatches			.66
0 to 2	44 (26.0)	24 (23.1)	
2 to 4	112 (60.4)	69 (66.3)	
> 4	13 (7.7)	11 (10.6)	
Mean duration of hemodialysis, mo	21.8 ± 18.8	8.4 ± 7.5	< .001
Mean pretransplant blood transfusions, U	5.6 ± 6.9	2.5 ± 4.0	< .001
Primary kidney disease			.50
Unknown	99 (58.6)	67 (64.4)	
Hypertension	5 (3.0)	5 (4.8)	
FSGS	6 (3.6)	8 (7.7)	
MPGN	4 (2.4)	2 (1.9)	
MN	1 (0.6)	0	
Crescentic GN	4 (2.4)	2 (1.9)	
Amyloidosis	1 (0.6)	1 (1.0)	
Chronic pyelonephritis	27 (16.0)	7 (6.7)	
Obstructive uropathy	9 (5.3)	3 (2.8)	
PCKD	9 (5.3)	6 (5.8)	
Hereditary nephritis	4 (2.4)	3 (2.8)	

*Values in parentheses are percents. HCV indicates hepatitis C virus; HLA, human leukocyte antibodies; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; MN, membranous nephropathy; GN, glomerulonephritis; and PCKD, polycystic kidney disease.

proteinuria, serum level of C3 complement, reactivity of rheumatoid factor, incidence of acute and chronic allograft glomerulopathy, incidence of de novo and recurrent glomerulonephritis, and serum levels of creatinine at the start and the end of the study. Acute transplant glomerulopathy and a positive cryoglubulin assay were not seen in any of the patients. In group 1, the recipients had a significantly lower serum level of C4 complement and a higher incidence of posttransplant chronic hepatitis (Table 2).

Heptitis C Virus and Proteinuria

Ninety patients (33.0%) showed persistent proteinuria (by dipstick examination), of whom 56 (62.2%) were in group 1 and (37.8%) were in group 2. Forty-seven patients (17.2%) displayed nephrotic-range proteinuria, 28 (59.6%) being in group 1 and 19 (40.4%) in group 2.

When the patients with nephrotic-range proteinuria in each group were compared, there were no significant differences regarding the primary kidney disease, number of acute rejection episodes, serum levels of C3 and C4 complements, reactivity of rheumatoid factor, incidence of posttransplant chronic hepatitis, de novo and recurrent glomerulonephritis, and serum creatinine at the start and the end of the study. Despite being greater in the patients of group 1, the frequency of chronic allograft nephropathy did not reach a statistically significant level (Table 3).

When the patients with and without nephrotic-range proteinuria were compared in group 1, it was found that the frequencies of acute cellular rejection episodes, recurrent and de novo glomerulonephritis, chronic allograft nephropathy, and graft failure were statistically greater and serum levels of creatinine at the end of the study was higher in the patients with nephrotic-range proteinuria (Table 4). Similar findings were observed in group 2 concerning the comparison between the patients with nephrotic-range proteinuria and the nonproteinuric patients;

Table 2. Posttransplant Clinical Characteristics of Patients With and Without Anti-HCV Antibody*

Characteristics	Kidney Allograft Recipients		*P*
	Anti-HCV Positives (n = 169)	Anti-HCV Negatives (n = 104)	
Proteinuria positives	56 (33.1)	34 (32.7)	.94
Median 24-hour urine protein (range), mg/d	0.6 (19.96)	0.4 (10.25)	.09
C3 Complement			.40
Normal	119 (70.4)	67 (64.4)	
Low	7 (4.1)	2 (1.9)	
C4 Complement			< .001
Normal	79 (46.7)	60 (57.7)	
Low	47 (27.8)	9 (8.7)	
Positive rheumatoid factor	9 (5.3)	3 (2.8)	.40
Receivers of ACE inhibitors	104 (61.5)	35 (33.7)	.07
De novo GN	2 (1.2)	3 (2.8)	.31
Recurrent GN	2 (1.2)	2 (1.9)	.62
Posttransplant chronic hepatitis	72 (42.6)	19 (18.3)	< .001
Initial serum creatinine, mg/dL	1.37 ± 0.54	1.44 ± 0.75	.36
Last serum creatinine, mg/dL	3.16 ± 2.81	3.69 ± 3.15	.22
Chronic transplant glomerulopathy	5 (3.0)	3 (2.8)	
Chronic allograft nephropathy	80 (47.3)	48 (46.2)	.85
Graft failure	49 (29.0)	37 (35.6)	.26
Patient death	15 (8.9)	10 (9.6)	.84

*Values in parentheses are percents. HCV indicates hepatitis C virus; ACE, angiotensin converting enzyme; and GN, glomerulonephritis.

Table 3. Posttransplant Clinical Characteristics of Patients With Nephrotic-range Proteinuria in Groups With and Without Anti-HCV Antibody*

Characteristics	Patients With Nephrotic-range Proteinuria		*P*
	Anti-HCV Positives (n = 28)	Anti-HCV Negatives (n = 19)	
Primary kidney disease			.73
Unknown	17 (60.7)	10 (52.6)	
FSGS	3 (10.7)	4 (21.1)	
MPGN	1 (3.6)	1 (5.3)	
Crescentic GN	1 (3.6)	0	
Chronic pyelonephritis	3 (10.7)	1 (5.3)	
Obstructive uropathy	2 (7.1)	2 (10.6)	
PCKD	0	1 (5.3)	
Hereditary nephritis	1 (3.6)	0	
C3 Complement			.12
Normal	9 (32.1)	10 (52.6)	
Low	5 (17.9)	1 (5.3)	
C4 Complement			.42
Normal	8 (28.6)	8 (42.1)	
Low	6 (21.4)	3 (15.8)	
Positive rheumatoid factor	0	1 (5.3)	.28
Acute cellular rejection episodes	1.5 ± 1.3	1.6 ± 1.4	.81
De novo GN	2 (7.1)	3 (15.8)	.35
Recurrent GN	2 (7.1)	2 (10.6)	.68
Posttransplant chronic hepatitis	12 (42.9)	4 (21.1)	.12
Initial serum creatinine, mg/dL	1.47 ± 0.53	1.47 ± 0.46	.99
Last serum creatinine, mg/dL	4.98 ± 3.11	6.08 ± 3.54	.27
Chronic allograft nephropathy	25 (89.3)	13 (68.4)	.07
Graft failure	18 (64.3)	12 (63.1)	.94
Patient death	3 (10.7)	3 (15.8)	.61

*Values in parentheses are percents. HCV indicates hepatitis C virus; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; GN, glomerulonephritis; and PCKD, polycystic kidney disease.

Table 4. Posttransplant Clinical Characteristics of Patients With a Positive Anti-HCV Antibody in Groups With and Without Nephrotic-range Proteinuria*

Characteristics	Patients With a Positive Anti-HCV Antibody		*P*
	Nephrotic-range proteinuria (n = 28)	No Proteinuria (n = 141)	
C3 Complement			
Normal	9 (32.1)	91 (65.5)	< .001
Low	5 (17.9)	2 (1.4)	
C4 Complement			
Normal	8 (28.6)	63 (44.7)	.43
Low	6 (21.4)	30 (21.3)	
Positive rheumatoid factor	0	8 (5.7)	.27
Acute cellular rejection episodes	1.53 ± 1.26	0.93 ± 1.13	.02
De novo GN	2 (7.1)	0	.004
Recurrent GN	2 (7.1)	0	.004
Posttransplant chronic hepatitis	12 (42.9)	49 (34.8)	.96
Initial serum creatinine, mg/dL	1.47 ± 0.53	1.26 ± 0.44	.27
Last serum creatinine, mg/dL	4.98 ± 3.11	2.51 ± 2.50	< .001
Chronic allograft nephropathy	25 (89.3)	36 (25.5)	< .001
Graft failure	18 (64.3)	22 (15.6)	< .001
Patient death	3 (10.7)	8 (5.7)	.52

*Values in parentheses are percents. HCV indicates hepatitis C virus and GN, glomerulonephritis.

serum creatinine level was significantly higher at the end of the study in proteinuric patients (6.08 ± 3.54 mg/dL versus 3.60 ± 3.02 mg/dL, $P = .04$), and a significant difference in the frequency of graft failure was observed between these two groups (12 out of 19 versus 19 out of 85, $P = .003$).

Graft Survival

There was no significant difference regarding graft survival between the kidney allograft recipients in groups 1 and 2 ($P = .25$) as shown in Figure 1. Irrespective of the HCV infection, the patients with nephrotic-range proteinuria showed a worse graft survival ($P < .001$; Figure 2) and a higher frequency of chronic allograft nephropathy compared with nonproteinuric patients (38 out of 47 versus 64 out of 183, $P = .03$).

DISCUSSION

The HCV infection is the main cause of chronic liver disease among kidney allograft recipients, being the fourth most prevalent cause of mortality.[14] The proportion of HCV-infected patients in kidney transplant patients varies from 6% to 64% depending

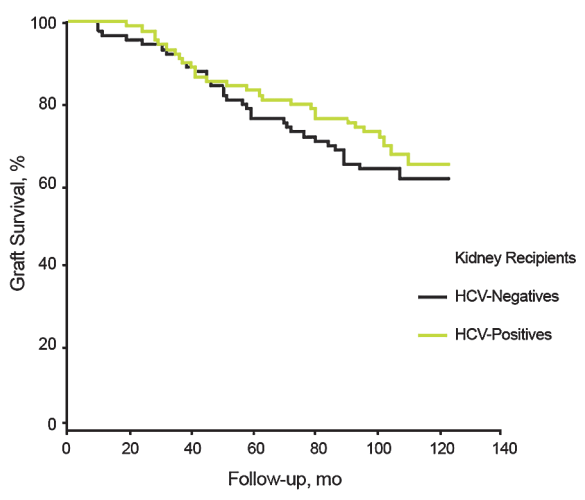

Figure 1. Graft survival rate was not significantly different between the kidney recipients with and without anti-HCV antibodies.

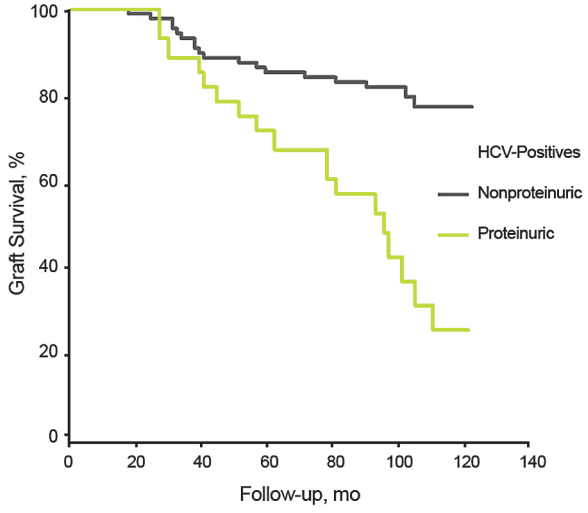

Figure 2. Graft survival rate in the HCV-infected kidney allograft recipients was lower in the presence of nephrotic-range proteinuria.

on geographic areas.[5] In Egypt, infection by the HCV has reached epidemic proportion with up to 21.9% of the population affected.[9] To our knowledge, there is no clear data about the prevalence of HCV among Egyptian kidney transplant recipients.

The present study was a single-center investigation of a homogenous group of living kidney transplant recipients with a mean duration of 86.4 ± 27.4 months follow-up period. Our first aim was to determine the frequency of the anti-HCV antibody-positives among the kidney transplant recipients. One of the most striking findings of our study is the inordinately high frequency of HCV infection in our patients with ESRD awaiting kidney transplantation. Sixty percent of them tested positive for anti-HCV antibodies by third generation ELISA. Hestin and colleagues[15] described a lower prevalence (9.6 %) in kidney transplant patients, which can be explained as follows: firstly, there is a low prevalence of HCV in Europe (antibodies range from 0.1% to 1.5% with a north-to-south gradient)[16] compared to the high prevalence in the general population in Egypt. Secondly, we previously reported a higher prevalence of HCV infection among patients with glomeruloapthy (up to 38%) compared to the general population.[17] Thirdly, other factors may increase the prevalence such as duration of hemodialysis and frequency of blood transfusions. In our study, we found a positive correlation between blood transfusions during maintenance hemodialysis and the risk of HCV infection as patients positive for anti-HCV antibodies received significantly more blood units and significantly longer duration of hemodialysis compared to those negative for the antibodies. Finally, some other factors are specific to the Egyptian population including routine antischistosomal therapy.[9]

Hepatitis C infection has been linked to distinct histologic patterns of immune complex glomerulonephritis. The association with mesangial proliferative glomerulonephritis, de novo or recurrent (with or without cryoglobulinemia), has now been extensively documented in recipients of kidney transplants,[8] membranous nephropathy, and acute and chronic transplant glomerulopathy.[8,18-20] The HCV-infected allograft can display a recurrence of the primary HCV-related glomerulonephritis.[21] Unfortunately, there are no data on this subject, since transplanted patients may also suffer from acute or chronic rejection. In some cases, primary glomerulonephritis remains undiagnosed, and sometimes an allograft biopsy is not carried out or is misdiagnosed due to the absence of immunohistological studies.

In our study, we did not find a significant difference regarding the frequency of de novo, recurrent, acute and chronic transplant glomerulopathy between the HCV-positive and HCV-negative kidney transplant recipients, even when we compared those with nephrotic-range proteinuria in both groups. Chronic allograft nephropathy did not reach statistical significance despite being higher in the HCV-positive recipients with nephrotic-range proteinuria. We did not find any case of acute transplant glomerulopathy in either group, which may be, in part, due to the lack of immunofluoresence and electron microscopic examination in our study.

The HCV infection may have a significant negative impact on graft survival of kidney transplant recipients,[5] but some authors have reported no impact at all.[22,23] Lower graft survival results from lowered patient survival, HCV-related glomerulonephritis, acute rejection, or chronic allograft nephropathy. We found no significant difference in graft survival between the HCV-positive and HCV-negative groups after a long follow-up period. We do believe, however, that longer duration of follow-up is necessary for comprehensive conclusions to be drawn.

Persistent proteinuria was reported to develop in up to 30% of all kidney allograft recipients in long-term, and it frequently progresses to nephrotic syndrome.[23,24] There is increasing evidence suggesting that proteinuria may be directly damaging to the kidney by different potential mechanisms, including direct mesangial and tubular toxicity.[24] A single kidney is already exposed to other insults, so the kidney allograft could be particularly sensitive to this type of damage. Several studies have provided evidence that proteinuria is associated with an increased risk of kidney allograft dysfunction or transplant failure.[25] In agreement with our results, Peddi and associates found that posttransplantation persistent proteinuria was detected in 194 (36.4%) of the 532 transplant recipients.[1] Five- and 10-year graft survival rates were lower in the proteinuric group (60% and 25%) than in the nonproteinuric patients (90% and 80%), and the main cause

of graft loss was chronic rejection for those in the proteinuric group (64%) and death with a functioning kidney among the nonproteinuric recipients (69%). Kidney function at the moment of the analysis was worse in the proteinuric group than in the nonproteinuric group.[1]

The underlying cause of proteinuria, not the proteinuria per se, could be the factor contributing to transplant dysfunction and failure. Persistent proteinuria is almost invariably a sign of structural kidney disease, even when the kidney function is intact. Perez Fontan and coworkers observed that when proteinuria was categorized according to its persistence, persistent but not transient proteinuria was associated with poor patient survival.[2] Roodnat and colleagues also found a negative influence of proteinuria on death risk and cardiovascular risk was particularly increased when proteinuria was present.[26]

Our second aim in the current study was to investigate whether there is an association between pretransplant HCV status and posttransplant proteinuria; no significant difference was observed regarding the quantity of proteinuria, serum level of C3 complement, rheumatoid factor positivity, or incidence of de novo and recurrent glomerulonephritis when the HCV-positive and HCV-negative proteinuric patients were compared. Chronic allograft glomerulopathy—despite of being higher in HCV-positive patients—did not reach a statistical significance.

The amount of protein excreted in the urine was previously shown to be a powerful predictor of graft outcome.[4] It has recently been discussed that the allograft is particularly vulnerable to the adverse effect of proteinuria for several reasons.[27] Protein-loaded epithelial cells express more major histocompatibility complex class II antigens, rendering them potentially susceptible to immune reactions. It has also been shown that proximal tubular cells of patients with cyclosporine nephrotoxicity express more endothelin-1, a potent agonist in the generation of renal fibrosis.[1] Our data is not in agreement with that described by Hestin and colleagues[15] who reported a significant difference in the cumulative probability of posttransplant proteinuria between recipients with and without anti-HCV antibodies (45.1% versus 13.1 %, respectively, at 5 years). The histology of biopsies from 26 out of 44 recipients with proteinuria, in their study, showed that de novo glomerular lesions were more frequent in HCV-positive patients. This inconsistency between Hestin and colleagues'[15] results and ours may be due to factors related to the viral titer, differences in viral genotyping, and the different sources of the kidney allograft cadaveric allograft recipients have a significantly higher incidence of rejection episodes and received more profound immunosuppressives during the posttransplant course compared to patients receiving living donor transplants).

Our third aim was to clarify the influence of the HCV and proteinuria on both patient and graft survivals. Our kidney transplant recipients with nephrotic-range proteinuria, irrespective of their serology, had significantly more frequent de novo and recurrent glomerlonephritis and chronic allograft nephropathy when compared with nonproteinuric patients, which suggests that proteinuria per se is a marker of underlying graft damage. Our findings are supported by what was reported previously by Roodnat and colleagues[26] where a relative risk of graft failure was found to be elevated in proteinuric patients (2.03) as compared to nonproteinuric patients. Interestingly, the risk of patient death was also higher in graft recipients with proteinuria as compared to nonproteinuric patients.

In correlation with our results, Hohage and coworkers[25] examined 327 patients transplanted between 1980 and 1990. Proteinuria at 6 months after transplantation was noted in 25.5% of the patients. Nonproteinuric patients had a 5-year graft survival of 85.6%, much higher as compared to 58.9% in proteinuric patients. No correlation was found with regard to sex or age of the recipient, duration of haemodialysis, age of the donor, cold ischaemia time, or HLA mismatches. It appears that mild proteinuria at 6 months after transplantation is a predictor of decreased long-term graft function.

In our study, we did not find a significant influence of HCV infection on patient and graft survivals that is in agreement with some earlier reports[28-30]; however, we feel that more long-term follow-up is needed to confirm or disprove this observation.

The association between the HCV infection and essential mixed cryoglobulinemia has been known very early.[6] We previously reported an incidence of 54% in patients with HCV-associated nephropathy.[17]

Surprisingly, none of our patients in this study had cryoglobulins. Possible explanations for our failure to detect cryoglobulins—which is consistent with some reports about cases of mesangial proliferative glomerulonephritis in patients with replicative HCV in which cryoglobulinemia was absent[7,19,31]: first, by the fact that cryoglobulins appear only many years after chronic HCV infection, owing to continued exposure to the antigen,[32] we can speculate that long-term follow-up for these patients is needed for possible development of cryoglobulins. Second, perhaps in immunosuppressed transplant patients, the HCV can produce glomerular disease in the absence of cryoglobulins. Third, it was reported previously that immunosuppression increases HCV viremia and decreases immunoglobulin synthesis.[33]

Indeed, our study has certain limitations, being a retrospective study with all the limitations of such type of studies—namely methodological deficiencies compared to controlled trials, imprecise and incomplete data gathering, and lack of randomization—is the main drawback. Hopefully, these limitations will be avoided in a future work.

CONCLUSIONS

There is a high prevalence of HCV infection in our patients with ESRD in Egypt awaiting kidney transplantation. We found no significant difference regarding the incidence and quantity of proteinuria in our HCV-positive and HCV-negative kidney transplant recipients. Nephrotic-range proteinuria is significantly associated with a high incidence of chronic allograft nephropathy and a poor graft outcome.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Alaa Sabry, MD
Department of Nephrology, Urology and Nephrology Center, Mansoura University, Mansoura, Egypt
Tel: +20 50 226 2222
Fax: +20 50 2263717
E-mail: asabry20@yahoo.com

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