

## Impact of Hepatitis C Virus Infection on Kidney Transplantation

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### Abstract

Hepatitis C virus (HCV) infection increases morbimortality in renal transplantation. Hepatitis C virus positive kidney transplant candidates who remain on the waiting list show a greater risk of mortality than those who are transplanted. The aim of this study was to examine the impact of HCV infection on patient and allograft survival after kidney transplantation. Eighty two patients with end stage renal disease underwent kidney transplantation were included in this study. The patients were classified into group I including 46 HCV negative patients (HCV-) and group II including 36 HCV antibody and HCV-RNA positive patients (HCV+). The immunosuppressive protocols were similar in both groups. All recipients were followed up for 3years. Results: There were statistically insignificant differences ( $P>0.05$ ) between both groups as regard age, gender and donor type (living related or unrelated). Hemodialysis duration before transplantation was highly significant ( $P<0.01$ ) longer among HCV+ group ( $4.9\pm 3.7$  years) compared to HCV- patients ( $2.4\pm 4.3$  years). One patient died from each group showing insignificant difference ( $P>0.05$ ); 2 grafts (4.3%) lost in HCV- group and 3 (8.3%) in HCV+ group with also insignificant difference ( $P>0.05$ ). Five recipients (10.9%) in group I experienced delayed graft function compared to 2 (5.6%) recipients in group II with statistically insignificant difference. There was a significantly ( $P<0.05$ ) more number of acute rejection episodes among HCV+ patients (11=30.6%) than HCV- patients (5=10.9%). New onset diabetes mellitus occurred more among HCV+ (19.4%) than HCV- (8.7%) recipients, however the difference was insignificant. There was a significant ( $P<0.05$ ) higher incidence of cytomegalovirus disease among HCV+ (11.1%) than HCV- (2.2%) recipients. Conclusion: This study suggested that HCV positivity does not significantly affect patient and graft survival despite the significant increased incidence of acute rejection episodes and cytomegalovirus disease. Lastly, all measures should be taken to prevent HCV transmission in dialysis population.

### Introduction

Since hepatitis C virus (HCV) was identified in 1989 by Choo et al, as a main cause of non-A non-B hepatitis, HCV infection has achieved a great relevance in nephrology on the basis of its high prevalence among dialysis patients, renal allograft recipients as well as in essential mixed cryoglobulinemia with associated membranoproliferative glomerulonephritis<sup>(1,2,3)</sup>. Renal transplantation confers an overall survival benefit in HCV + hemodialysis patients with similar 5-year patients and graft survival to those without HCV infection<sup>(4)</sup>. Unfortunately, there is no safe treatment for HCV infection after renal transplantation. It has been reported recently that ribavirin monotherapy impr-

oved liver enzymes levels, had no effect on HCV viremia, but seems also not to have a beneficial effect on liver fibrosis<sup>(5)</sup>.

### Aim Of The Work

The aim of this study was to evaluate the effect of HCV infection among end stage renal disease (ESRD) patients after undergoing kidney transplantation.

### Patients And Methods

This prospective study included 82 patients with ESRD. All were receiving their first living kidney transplants at Naser Institute, and Ain Shams University

Specialized Hospital. The patients were classified according to HCV status into 2 groups. Group I: included 46 HBs Ag, and HCV antibody negative (HCV-) patients, 28 (60.9%) males and 18 (39.1%) females; 31 (82.6%) patients received living related grafts and the rest 14(17.4) were unrelated. Eight patients of group I were preemptive transplantation. Group II: Included 36 HBs Ag negative HCV antibody and RNA positive patients, 20 (55.6%) males and 16 (44.4%) females, 30 (83.3%) patients received related and 6 (16.7) unrelated grafts.

All patients were exposed to history taking including the etiology of renal failure, duration on hemodialysis, blood transfusion, and antiviral treatment (in group II). All patients underwent blood testing for serum alanine transferase (ALT), aspartate transferase (AST), albumin, prothrombin time, creatinine, blood urea nitrogen (BUN), and blood glucose level. Anti-HCV antibodies were determined with a third generation enzyme linked immunoassay (Abbott-laboratories, Chicago, IL, USA).HCV-RNA was detected by qualitative polymerase chain reaction (PCR) using Amplicor Kits (Roche Diagnostic System, Indianapolis, USA).A liver biopsy was indicated for all HCV-RNA- positive patients, irrespective of transaminases levels. All recipients were having <4 HLA mismatch with their donors, and the immunosuppressive protocols were similar in both groups in the form of triple therapy with steroids, cyclosporine, and azathioprin. The patients were followed up for 3 years as regard renal function tests, liver function tests, occurrence of delayed graft function (DGF)-defined as the transient requirement for dialysis beginning in the first week after the transplant operation<sup>(6)</sup>-, acute rejection, new onset diabetes mellitus (DM), and cytomegalovirus disease.

### Statistical Methods

SPSS statistical software package, v.9.02, Echosoftware Corp, USA, 1998 was used for data analyze. Dates were expressed as Mean  $\pm$ SD for quantitative measures and

both number and percentage for categorized data. Wilcoxon Rank sum test was used for comparison between two independent mean groups for non parametric data. Lastly, Chi-square test was used for correlation between each 2 independent techniques. The probability of error at 0.05 was considered significant, while at 0.01 highly significant.

### Results

Table-1 shows the characteristics of patients in group I (HCV-) and group II (HCV+). The mean age in group I was (42.4  $\pm$  11.2 years) with non significant difference (P>0.05) from group II (44  $\pm$  10.5 years). Also, there was non significant difference between both groups as regard gender (P> 0.05). Though 30.4% of patients in group I received kidneys from unrelated donors compared to 16.7% only in group II, the difference was insignificant (P>0.05). There was a highly significant (P<0.01) longer duration of hemodialysis before transplantation in group II than group I (4.9  $\pm$  3.7 & 2.4  $\pm$  4.3 years respectively).

Table-2 Shows non significant (P>0.05) difference between group I and group II as regard serum creatinine level during the follow up period, while a highly significant (P<0.001) higher level of BUW in group II (38.2  $\pm$ 11.7 mg/dl ) compared to group I ( 21  $\pm$  13.1 mg/dl ).One patient died in each group (both from infection) resulting in non significant difference (P>0.05) in patient survival between the two groups after 3 years, and the relative risk was 1.3 with HCV positivity. Also, there was insignificant difference (P>0.05) as regard three years graft survival between HCV - (95.7%) and HCV + (91.7 %) and the relative risk of graft loss is 1.9 with HCV positivity. Five recipients (10.9%) experienced delayed graft function in group I compared to 11 recipients (5.6%) in group II but the difference was insignificant (P>0.05).There was a significant (P<0.05) higher incidence of acute rejection episodes (all were steroid sensitive) in group II (30.6%) than group I (10.9%) with a relative risk of 2.8. There was a higher

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incidence of new onset DM in group II (19.4%) than group I (8.7%), however the difference was insignificant and the relative risk of developing DM with HCV positively was 2.2. There was a significantly

( $P < 0.05$ ) higher incidence of cytomegalovirus disease in HCV+ group II (11.1%) in comparison to group I (2.2%) with 5.1 relative risk.

**Table 1: Patients Demographic Characteristics, and clinical metrics in group I (HCV-) and group II (HCV+).**

Parameter	Group I N = 46	Group II N = 36	Z	P-Value	Significance	
Age (Years) mean $\pm$ SD	42.4 $\pm$ 11.2	44 $\pm$ 10.5	-0.7	>0.05	NS	
Gender	Male	28 (60.9 %)	20 (55.6 %)	0.63	>0.05	NS
	Female	18 (39.1 %)	16 (44.4 %)			
Donor Type	LR	32 (69.6 %)	30 (83.3%)	1.44	>0.05	NS
	LUR	14 (30.4 %)	6 (16.7%)			
Hemodialysis Duration (Years) mean $\pm$ SD	2.4 $\pm$ 4.3	4.9 $\pm$ 3.7	-2.8	<0.01	HS	

SD : Standard deviation  
LR : Living related .  
LUR : Living unrelated

NS : Non significant.  
HS : Highly significant.

**Table 2: Patients and Graft survival during the follow up period (3 years)**

Parameter	Group I N = 46	Group II N = 36	Z	P-Value	Significance	RR
BUN (mg\dl) mean $\pm$ SD	21 $\pm$ 13.1	38.2 $\pm$ 11.7	-6.2	<0.001	HS	
S. Creatinine (mg\dl) mean $\pm$ SD	1.7 $\pm$ 1.1	1.8 $\pm$ 1.4	-0.4	>0.05	NS	
Death n ( % )	1(2.2%)	1(2.8%)	-0.2	>0.05	NS	1.3
Graft Failure n ( % )	2(4.3%)	3(8.3%)	-0.8	>0.05	NS	1.9
Delayed Graft Function n ( % )	5(10.9%)	2(5.6%)	0.85	>0.05	NS	2
Acute Rejection n ( % )	5(10.9 %)	11(30.6%)	-2.2	<0.05	S	2.8
Diabetes Mellitus n ( % )	4(8.7 %)	7(19.4%)	-1.4	>0.05	NS	2.2
Cytomegalovirus Disease n ( % )	1(2.2 %)	4(11.1 %)	-1.7	<0.05	S	5.1

SD : Standard deviation  
RR : Relative risk

HS : Highly significant  
NS : Non significant

## Discussion

This study showed no significant difference between both groups as regard age, gender, and donor type. There was a significant longer duration of hemodialysis

before transplantation in group II (HCV+) implicating hemodialysis in the prevalence of HCV among ESRD patients. A similar finding was reported by Bruchfeld et al<sup>(7)</sup>.

The present study showed a slightly increased incidence of patient mortality and graft loss in HCV+ group compared to HCV- group during the 3 years follow up period, however the differences were insignificant. Pereira study showed that graft and patient survival were not significantly different after 3.5 years between HCV+ and HCV- kidney transplant recipients<sup>(8)</sup>. Also, Lee *et al*, reported that graft losses and death rates were not significantly different between HCV+ and HCV- kidney recipients<sup>(9)</sup>. In contrast, Legendre *et al*, Gentil *et al*, and Bruchfeld *et al*, observed a significantly higher percentage of graft loss among HCV+ than HCV- renal recipients<sup>(10,11,7)</sup>. Batty *et al*, claimed a 13% mortality rate in HCV+ and 8.5% in HCV- patients<sup>(12)</sup>. Nevertheless, Bezar-Behbahani *et al*, evaluated the impact of HCV infection occurring after kidney transplantation, and they suggested that HCV infection (in a previously HCV- recipient before transplantation) did not cause or contribute to renal dysfunction during the one year follow-up period of the study<sup>(13)</sup>. The frequency of new onset DM was significantly higher in HCV+ (19.4%) than HCV- (8.7%) patients. A similar finding was observed by Stehman - Breen *et al*, resulting in 18% prevalence of DM in an HCV infection cohort<sup>(14)</sup>. There was unexplained statistically insignificant higher incidence of delayed graft function among HCV- than HCV+ group. On the other hand, there was a significant ( $P < 0.05$ ) increased number of acute rejection episodes among HCV+ (11=30.6%) compared to HCV- (5=10.9%) recipients. This study showed a significantly increased incidence of cytomegalovirus disease in group II (11.1%) with a RR 5.1 in comparison to HCV- group. Till publishing this work, there were no trials in the literature correlating HCV status and cytomegalovirus disease after kidney transplantation.

### Conclusion & Recommendations

This study suggested that HCV infection among ESRD patients does not

affect significantly patient and renal allograft survival after kidney transplantation despite the significant increased incidence of acute rejection episodes and cytomegalovirus disease during the first 3 years following transplantation. A more extended study is advisable to identify the impact of HCV infection on the long term patient and graft survival. Lastly, all measures should be taken to prevent HCV transmission in dialysis population.

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## اثر عدوى فيروس التهاب الكبدى (سى) على زراعة الكلى ياسر سليمان قسم الباطنة – كلية الطب - جامعة عين شمس

ان الإصابة بالتهاب الكبدى الفيروسي (سى) يزيد من معدلات الوفيات والإعاقة فى مرضى زراعة الكلى . ان المرضى المصابون بالفيروس لكبدى (سى) يكونون أكثر عرضة للوفاه من المرضى الذين لهم زرع الكلى . ان الهدف من هذه الدراسة هو دراسة تأثير الإصابة بالفيروس (سى) على المرضى وعلى الكلى المنقولة بعد عملية الزرع . تتضمن هذه الدراسة 28 مريضاً مصاباً بفشل الكلى المزمن والذين تم لهم عملية زراعة الكلى . وقد تم تقسيم المرضى الى مجموعتين :-

**المجموعة الاولى :-** تتضمن 46 مريضاً غير مصابين بالفيروس الكبدى (سى)  
**المجموعة الثانية :-** تتضمن 36 مريضاً مصابين بالفيروس (سى) واستدل على ذلك باجابة الاجسام المضادة والإر ان ايه . وكان البروتوكول الدوائى المثبط للمناعة متماثل فى المجموعتين وقد تم متابعة المرضى لمدة 3 سنوات .

أظهرت الدراسة فرق ليس له دلالة إحصائية بين المجموعتين بالنسبة للعمر والجنس ونوع المتبرع ( قريب للمرضى او غير ذلك . وأظهرت النتائج دلالة إحصائية عالية القيمة بالنسبة لمدة الاستشفاء الدموى قبل عملية الزرع ، حيث وجد ان مدة الاستشفاء الدموى اطول (  $4.9 \pm 3.7$  ) فى المرضى المصابين بالفيروس (سى) مقارنة بالمرضى الغير مصابين بالفيروس (سى) (  $2.4 \pm 4.3$  ) . لم تظهر نتائج ذو دلالة احصائية لوفاة احدى المرضى من كل مجموعة , أيضا لم تظهر نتائج ذو دلالة إحصائية لإثنين (4.3 %) من مرضى زراعة الكلى فى المجموعة المصابة بفيروس (سى) و ثلاثة (8.3 %) فى المجموعة المصابة بفيروس (سى) و ذلك لفقدان العضو المزروع 0 و قد أصيب خمسة من المرضى الذين تم لهم عملية الزرع بتأخر فى وظيفة الكلى المزروعة من المجموعة الأولى (10.9 %) و ذلك بالمقارنة بإثنين (5.6 %) من المجموعة الثانية ولكن الفرق ليس له دلالة إحصائية . أظهرت النتائج وجود عدد اكبر من عمليات الرفض الحاد للكلى المزروعة للمرضى المصابين بالفيروس الكبدى (سى) (  $11 = 30.6$  %) وذلك بالمقارنة بالمرضى الغير مصابين بالفيروس (سى) (  $5 = 10.9$  %) وهذا الفرق ذو دلالة احصائية عالية القيمة وقد ظهرت حالات مرض البول السكرى حديث بين المرضى المصابين بالتهاب الكبدى الفيروسي (سى) (  $19.4$  %) والذين يتم لهم عملية الاستشفاء الدموى فى انتظار عملية زراع الكلى ولكن الفرق ليس له دلالة إحصائية . أظهرت النتائج ايضا وجود فرق ذو دلالة امانة بالنسبة لاصابة بمرض فيروس السيتومجالو وذلك بوجود نسبة اعلى فى المرضى المصابين بالفروس (سى) (  $11.1$  %) بالمقارنة بالمرضى الغير مصابين بالفيروس (سى) (  $2.2$  %) والذين تم لهم عملية الزرع

**التوصيات :-** أظهرت النتائج ان الإصابة بالفيروس (سى) لا يؤثر بشكل واضح على كل من نجاح المرضى والعضو المزروع بعد عملية زراعة الكلى وذلك على الرغم من وجود زيادة فى معدل حالات الرفض الحاد للكلى المزروعة والإصابة بمرض فيروس السيتومجالو .

و أخيرا يجب اتخاذ كل الإجراءات لمنع انتشار مرضى الفيروس الكبدى (سى) بين مرضى الاستشفاء الدموى