EDITORIAL COMMENT

Do we really need more evidence to use hepatitis C positive donor kidney more liberally?

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Abstract

The number of patients listed active for kidney transplantation has continued to rise over the last 10 years, leading to significantly increased wait-list time for patients awaiting kidney transplantation in the USA. This increased demand has led to a supply–demand mismatch and should prompt clinicians to seek timely solutions to improve access to available organs. Hepatitis C virus positive [HCV(+)] kidneys continue to be discarded without clear evidence that they lead to poor outcomes in the current era of highly efficacious HCV treatment with direct-acting antiviral agents (DAAs). Increased utilization of HCV(+) donor kidneys will decrease wait-list time and improve availability of donor organs. Emerging data suggests that HCV can be successfully treated with DAAs after kidney transplantation with 100% sustained virologic response rates and no significant changes from baseline kidney function. Utilization of HCV(+) donor kidneys should be considered more liberally in the era of highly effective HCV treatment. Further studies are warranted to assess the long-term effect of HCV(+) donor kidneys in transplant recipients in the new era of DAAs.

Key words: graft failure, hepatitis C, kidney donor, kidney transplantation, outcome

According to the 2015 Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTS) annual data report, a total of 18 597 adult and pediatric kidney transplants were performed in the USA in 2015 [1]. Despite the best efforts of the new kidney allocation system targeted to ameliorate organ allocation efficiency, significant mismatch of supply and demand remains evident. A 10-year trend shows an increase in the number of patients listed active on the wait list from 47 000 in 2005 to 61 234 in 2015, with increasing wait time until transplantation [1]. The percentage of patients awaiting kidney transplant for >5 years increased from 11.4% to 15.7% over this time frame, with roughly 12.8% requiring dialysis for at least 11 years before receiving transplant [1].

Despite the alarming trend over the years, thousands of donor kidneys continue to be discarded, with ~17% being rejected in the year 2013 [2]. In particular, the number of disposed hepatitis C virus positive [HCV(+)] donor kidneys remains a staggering problem with over 4000 HCV(+) donor kidneys being discarded between the years 2005 and 2014 [3].

Rising wait-list time and increasing supply–demand mismatch of kidneys should prompt clinicians to seek solutions to improve access to available organs. Significant reductions in

wait times have been noted with utilization of HCV(+) donor kidneys. HCV(+) recipients waited on average 10 months less at their institutions to receive HCV(+) donor kidneys and an average of 13 months less to receive an HCV(−) donor kidney [4]. All efforts should be made to perform transplantation to reduce the widening discrepancy between demand and supply. One solution is to use HCV(+) donor kidneys. In the current issue of *CKJ*, Cohen *et al.* present data to show the outcomes of HCV (+) donor kidneys' transplantation in HCV(+) recipients [5].

Effect of HCV infection on kidney function

Figure 1 illustrates three different HCV-mediated pathophysiological pathways that lead to kidney damage and chronic kidney failure: (i) HCV-associated glomerulopathy/glomerulonephritis; (ii) the effect of the immune response to HCV; and (iii) HCV-related direct and indirect effect on kidney fibrosis.

The most common form of renal disease associated with HCV infection is Type I membranoproliferative glomerulonephritis (MPGN) associated with Type II mixed cryoglobulinemia [6]. Less frequently described lesions include MPGN without cryoglobulinemia as well as membranous nephropathy. Occasional cases of focal segmental glomerular sclerosis (FSGS), thrombotic microangiopathy and fibrillary or immunotactoid glomerulopathies have been also reported [6]. Moreover, the presence of HCV is also associated with albuminuria, amyloid deposition, tubule-interstitial nephritis or HCV–antibody immune complexes, which can be responsible for kidney injury due to systemic immune response to HCV infection [7–9].

The adaptive immune system's response to HCV infection also contributes to the development of chronic kidney disease (CKD). There are some common immune system responses seen in people who control the infection, as compared with those who develop chronic infection. In those who control HCV, gamma-interferon is preferentially expressed in liver by T-lymphocytes several weeks after infection [10]. This induces the expression of chemokines to attract T cells and proteins associated with antigen processing and presentation [10].

It is also believed that HCV has the potential for entry into and replication within renal tissue, which has direct cytopathic and immunologic effects [8, 11]. Furthermore, insulin resistance can be a very important host factor in patients with chronic HCV infection [12]. Insulin resistance and hyperinsulinemia causes excess intra-renal production of insulin-like growth factor 1 and transforming growth factor β, thus triggering proliferation of renal cells and upregulating the expression of angiotensin II Type 1 receptors in mesangial cells, which in turn enhances the harmful effects of angiotensin II in the kidney [13]. The efficacy of the previous HCV treatment was low, but newer treatments of HCV may decelerate the progression of CKD.

Direct-acting antiviral therapy for HCV and the effect on kidney function

The advent of direct-acting antiviral agents (DAAs) and the subsequent reduction of interferon-based regimens has paved the pathway for well-tolerated and efficacious treatment of HCV [14]. The 2015 American Association for the Study of Liver Diseases (AASLD) guidelines for HCV treatment state that some of the newer approved DAAs can be safely dosed in patients with renal impairment. However, data remain sparse for patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2) and for patients with end-stage renal disease [15].

Treatment of HCV with DAAs in kidney transplant recipients has shown significant promise for the future. In a cohort of 25 patients, Kamar *et al.* demonstrated 100% HCV cure rate in post-kidney transplant recipients with no significant change in glomerular filtration rate from baseline [16]. Similar studies have also resulted in high cure rates and intact serum creatinine levels pre- and post-treatment in kidney transplant recipients [17–19]. While these data are extremely promising, long-term studies evaluating kidney function with larger cohorts are needed.

Kidney transplantation from HCV(+) donor to HCV(−) recipients

In a paper published in the current issue of *CKJ*, Cohen *et al.* performed an elegant analysis comparing renal allograft outcomes in HCV(+) recipients who received HCV(−) versus HCV(+) donor kidney [5]. Although this is not the first study conducted [20–22] to answer the important clinical question of whether HCV status of the donor has any effect on an HCV(+) recipient's outcome, this is the first study that uses a sophisticated methodological approach to balance measured confounders. The ideal study to answer this clinically important question would be a blinded randomized clinical trial. However, in real
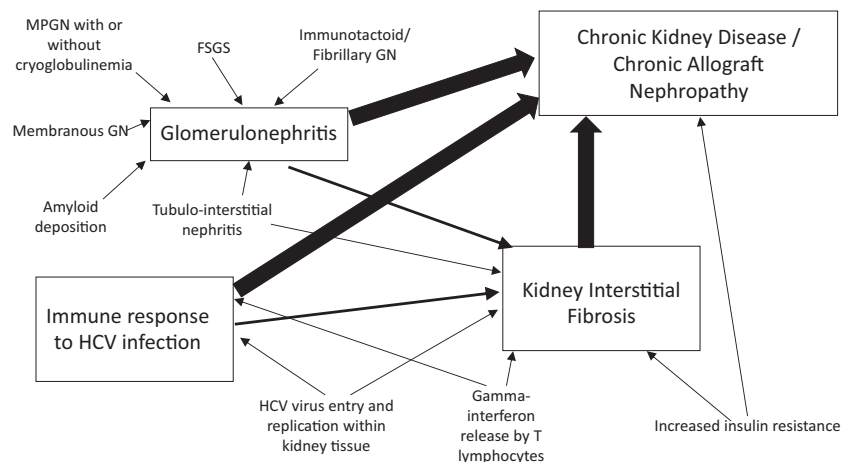

Fig. 1. Pathophysiological pathways explain association between hepatitis C infection and CKD. GN, glomerulonephritis.

life, this would be extremely difficult to perform, especially in the era of highly effective HCV treatment. In this case, the best available evidence should come from well designed and carefully performed analysis of observational data. Cohen *et al.* [5] utilize a propensity score-matched approach, which is able to balance the measured confounders between HCV(+) and HCV(−) donor groups. They performed a retrospective registry data analysis using United Network for Organ Sharing (UNOS) available until March 2016. This US database includes information of all recipients and donors in the USA. This is another major advantage of this analysis compared with a potential clinical trial. In this analysis, all recipient and donor data are available, whereas in a clinical trial usually very selected patient data can be analyzed. The primary outcome of the study was all-cause mortality. They defined the secondary outcomes as an all-cause allograft failure and treated rejection within the first year of transplantation. After well-balanced propensity score matching, the authors performed time-to-event analyses, namely Cox regression and competing risk regression analyses. The examined population consisted mainly of Caucasian, middle-aged, male recipients. Compared with HCV(−) donors, HCV(+) donor transplantation was associated with approximately 40% higher all-cause mortality and an all-cause graft failure risk. However, there was no difference between acute rejection rate between the two groups [5].

Although the results are not unexpected and are similar to previous studies [20–22], they still require some explanation. Given the relatively low treatment rate of HCV in dialysis patients [23], we can assume ∼75% of the recipients have already had ongoing active infection [24]. Donation from an HCV seropositive person should not result in a new infection in these HCV seropositive recipients in the following theoretical situations: (i) donor was cleared from the virus and only seropositive status remained positive; and (ii) the genotype and the load of the virus is the same in the donor and the recipient. In all other situations, there will be a new viral burden or infection will develop during the transplantation. Therefore, further studies need to be performed where the genotype and the viral load of the donors and recipients are available.

Nevertheless, we should inform all HCV(+) recipients that an HCV(+) donor organ would increase the risk of death and graft loss. In addition, we should also discuss that HCV treatment is available and highly effective after transplantation and that there are currently no long-term data available on whether treated recipients have an increased risk of death and graft loss. Further studies are highly warranted to assess HCV treatment on graft function, risk of death and graft loss. It is also very important to emphasize that accepting an HCV(+) organ will significantly decrease the wait-list time [4]. If the recipient is willing to accept an HCV(+) kidney and the center is willing to perform HCV(+) donor transplantation, the waiting time can be reduced by >1 year [4]. Further studies are needed to compare the survival of dialysis patients refusing HCV(+) donor kidney, consequently remaining on dialysis, and their counterparts who accept an HCV(+) donor graft.

In summary, this article confirms the increased risk of graft loss and death associated with HCV(+) donation, but individual clinical situations, such as HCV viral load negative donor, same genotype, etc., might modify this observed risk. Nevertheless, using HCV(+) kidneys is associated with decreased waiting time and HCV can be safely treated after kidney transplantation. Because of these benefits, HCV(+) donor transplantation should be encouraged as an option.

Future use of HCV(+) donor for HCV(−) recipients

An exciting pilot study recently published in the *New England Journal of Medicine* by Goldberg *et al.* offers a valuable glimpse into the future of kidney transplantation and will hopefully ameliorate the strain created by organ supply–demand inconsistency [25]. In this informed consent study, 10 HCV(−) recipients who had a long anticipated wait-list time and who were currently undergoing dialysis were transplanted with HCV genotype 1-infected kidneys. All the recipients had detectable viral load by the third day of post-transplant and were subsequently started on DAAs therapy with elbasvir–grazoprevir. All the recipients were cured of HCV and achieved a sustained virologic response 12 weeks after the end of treatment while maintaining intact allograft function [25].

These data and the data presented by Cohen *et al.* illustrate a promising future for the use of HCV(+) donor kidneys [5]. If confirmed in long-term studies, a significant improvement will be noted in the availability of organs, as well as a reduction in the wait times for kidney transplantation.

Conflict of interest statement

MMZ has received honoraria from Merck.

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