with a higher BMI. However, in this cohort, it turned out that urine volume also rose in tandem with BMI, offsetting the increase in solutes, such that overall calcium oxalate supersaturation did not increase. Notably, in this same study, urine pH was lower among those individuals with a greater BMI. This finding is consistent with emerging evidence that obesity and insulin resistance are associated with decreased ammoniagenesis, a lower urine pH, and increased risk for uric acid stones. Thus, the path from obesity to urine composition to stone might be more nuanced than initially expected.

In this issue of JASN, Sorensen et al. provide another interesting observation from the Women’s Health Initiative Observations Study that is relevant to our discussion. They observed in this prospective cohort of 84,225 postmenopausal women followed since 1993 that those with a greater BMI had a higher risk of stones, replicating findings from previous cohorts. In addition, they found that higher caloric intake and lower physical activity scores translated into more kidney stones. However, this association was not all about obesity because all three features (BMI, caloric intake, physical activity) were independent risk factors. Thus, something about being relatively sedentary increased the risk of one of these postmenopausal women forming a kidney stone. Importantly, the intensity of the activity was not important, because only mild to moderate weekly activity was enough to be protective against stones. As the authors point out, moderate exercise reduces the risk of many things that are associated with stones, such as hypertension and diabetes (discussed above). Exercise can also have a favorable effect on bone health, and nephrolithiasis has also long been associated with osteoporosis.

It is important to remember that this study only included postmenopausal women, and, thus, will need to be replicated in other populations. It is also possible that women who exercise regularly have other healthy lifestyle habits that decrease stone risk (dietary and otherwise). Nevertheless, conservative (nonpharmacologic) counseling for patients with stones often centers almost exclusively on diet, stressing increased fluid intake, normal dietary calcium, lower sodium, moderate protein, and reduced dietary oxalate. The results of Sorensen et al. suggest that a recommendation for moderate physical activity might reasonably be added to the mix.

ACKNOWLEDGMENTS

This work was supported by the Mayo Clinic O’Brian Urology Research Center (U54DK100227) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), as well as by the Rare Kidney Stone Consortium (U54DK083908), a member of the National Institutes of Health Rare Diseases Clinical Research Network funded by the NIDDK, the National Center for Advancing Translational Sciences, and the Mayo Foundation.

DISCLOSURES

None.

REFERENCES


Kidney Infection with HIV-1 Following Kidney Transplantation

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Published online ahead of print. Publication date available at www.jasn.org.

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As HIV has evolved to a chronic condition as a result of combination antiretroviral therapy (cART), an increasing number of HIV-infected patients with well-controlled disease are progressing to ESRD secondary to comorbidities associated with HIV. Reports from both the United States and Europe have demonstrated favorable outcomes after kidney transplantation in the HIV-infected recipient.1,2 Although early results in all of these studies demonstrate patient and graft survival rates that are comparable with HIV-negative kidney recipients, there was an unexpectedly higher incidence of rejection reported in a United States multicenter trial, which could affect long-term allograft survival. In this issue of JASN, Canaud et al. report findings that HIV-1 infected kidney allografts in a cohort of patients with undetectable systemic HIV who received effective antiretroviral therapy.3 Of equal importance, they report a new and noninvasive test for determining HIV-1 infection of the kidney allograft by measuring DNA and RNA levels in patients’ urine. Canaud et al. further hypothesize that unrecognized reinfection of the transplanted kidney by HIV-1 will compromise allograft function, and is associated with the higher rejection rates observed in kidney transplant recipients with HIV.

In the report by Canaud et al., 68% (13 of 19) of HIV-infected kidney recipients with undetectable plasma HIV-1 RNA had evidence of HIV infection within the kidney allograft.3 Two distinct types of infections were observed, affecting either podocytes (5 of 13) or tubular cells (8 of 13). The former type of infection had a more severe clinical effect, resulting in nephrotic-range proteinuria and disease progression. Although infection of the tubular cells with HIV-1 was not associated with a significant decrease in kidney function, the authors speculated that HIV infection may stimulate an immune response that is partly responsible for the higher rejection responses noted in the United States series. Regarding the development of HIV infection within the graft, it is important to note that in the United States prospective trial including 150 kidney transplant recipients with undetectable plasma HIV-1 RNA, there was no histologic evidence of recurrent or de novo FSGS on light microscopy, nor was there evidence of nephrotic-range proteinuria.1 However, electron microscopy was not performed on a routine basis as part of the National Institutes of Health (NIH)—funded United States multicenter prospective trial and light microscopy failed to demonstrate histologic changes in the report from Canaud et al.

Although recurrent HIV nephropathy was not a factor in early graft loss (within 3 years of transplant in the United States trial), the findings of HIV infection of the kidney allograft are important and need further attention. Even in this relatively small series of 19 patients, 5 of 19 had infection of the podocytes with serious clinical ramifications. Although the United States trial may not have observed HIV infection in the kidney allograft, it may potentially be recognized with more rigorous screening for proteinuria and electron microscopy. For that reason, the identification of a noninvasive urine screen (PCR for HIV-1 DNA and RNA levels) that correlates with reinfection will be a valuable tool. It is less clear what type of intervention would be helpful to prevent further progression of HIV-1 infection in the kidney allograft. With only 19 patients, Canaud et al. were not able to identify factors typically associated with infection of the podocytes or tubular cells. There was no correlation with G1 and/or G2 APOLI variants in either the donor or recipient, which are typically associated with HIV nephropathy in African Americans. Similarly, HIV coreceptor tropism with either C-C chemokine receptor type 5 or C-X-C chemokine receptor type 4 did not correlate with HIV infection of the podocytes or tubular cells, although this is consistent with the fact that neither the tubular cells nor podocytes carry the receptors for HIV.

In the United States prospective trial, there was a 2- to 3-fold higher incidence of acute rejection noted after both kidney (n = 150) and liver (n = 125) transplantation in the HIV-infected host.1,4 Canaud et al. speculate that the higher rejection rates observed in the United States series may be related to HIV-1 infection of the kidney allograft, although it is less clear how this would mechanistically occur. It is feasible that HIV infection would recruit inflammatory cells to the kidney and there would be some cross-reactivity with alloantigen in the inflammatory milieu.5,6 Alternatively, the inflammatory infiltrate associated with the HIV infection could be misinterpreted as rejection. This would be analogous to the challenges in differentiating poliovavirus-mediated inflammation from rejection of the kidney allograft, or differentiating rejection of the liver allograft from recurrent hepatitis C infection. In either case, it is important to know that the higher rejection rates in HIV-infected recipients were observed after both liver and kidney transplantation in the United States series. Fifty percent of the rejections in HIV-coinfected liver transplant recipients occurred within the first 3 weeks of transplantation. Rejection episodes were also early and aggressive in kidney transplant recipients, suggesting a dysregulated immune response rather than an inflammatory response to HIV infection of the podocytes and tubular cells. These kinetics are more suggestive of immunologic memory associated with early and aggressive rejection. A plausible explanation for a dysregulated and highly active immune response could relate to homeostatic expansion of a skewed population of memory T cells associated with immune reconstitution and antiviral therapy observed in HIV-1–infected recipients.

Unlike the United States trial, the French multicenter report on kidney transplantation (which includes the patients from Hospital Necker, Paris) showed similar rejection rates (15%) after kidney transplantation in HIV–infected recipients versus uninfected recipients.3 The investigators attribute the lower rejection rates in the French series to the use of raltegravir-based antiviral therapy. Raltegravir, an integrase inhibitor that does not affect the cytochrome P450 system, results in more consistent exposure to the calcineurin inhibitors required for effective immunosuppression.7 The French multicenter data suggest that the improvement in rejection rates corresponded to improved drug exposure in the absence of pharmacokinetic interactions negatively affecting exposure to immunosuppressive
agents. It is important to note that at the time of the United States trial, raltegravir-based therapy was used in only a few patients. In order to remove poor exposure to immunosuppressive medications as a mechanism leading to the higher rejection rates seen in the United States trial,8 most United States centers are switching to raltegravir-based regimens to avoid the problematic pharmacokinetic interactions between immunosuppression and cART. Nonetheless, there is a possibility that cART used in the United States trial was more effective in preventing kidney reinfec tion than the raltegravir-based regimens used in the series reported by Canaud et al. Alternatively, HIV infection of the allograft may have been present at a subclinical level in the 150 transplant recipients reported in the United States trial, and further investigation using in situ hybridization on paraffin blocks will be performed. Prospectively, electron microscopy as well as in situ hybridization should be performed to determine what factors, including cART, are associated with HIV infection of the kidney allograft. Along these lines, the urine test that Canaud et al. used to measure HIV-1 DNA and RNA levels will be an important noninvasive method for detecting HIV infection in the increasing number of HIV-positive transplant recipients.

The finding of HIV infection of the kidney allograft comes at a very important time in the evolution of transplanting HIV-infected recipients with kidneys from HIV-infected deceased donors. This novel strategy was utilized by Muller et al. in Capetown, South Africa, to facilitate kidney transplantation in an increasing population of HIV-infected individuals with renal insufficiency using kidneys procured from HIV-negative deceased donors.9 In the report by Muller et al., donor kidneys from HIV-infected deceased donors were used as long as there was a normal kidney biopsy and there was no evidence of proteinuria. Early results were excellent and the program in South Africa has grown, with ongoing early success in terms of patient and allograft survival. On the basis of the encouraging early results in Capetown, efforts are ongoing to change United States law (National Organ Transplant Act) prohibiting the use of organs isolated from the HIV-positive donor. Boyarsky et al. estimate the potential for up to 500 HIV-positive deceased donors.10 Although the main concern in utilizing organs isolated from the HIV-positive donor. Boyarsky et al. estimate the potential for up to 500 HIV-positive deceased donors per year, which could potentially benefit the increasing number of HIV patients in the United States who are awaiting heart, lung, pancreas, liver, and kidney transplants.10 Although the main concern in utilizing organs isolated from HIV-infected donors relates to superinfection with a potentially more virulent HIV strain, the report of reinfec tion of the transplanted kidneys with HIV will be important in determining the ultimate safety and efficacy of transplanting organs isolated from the HIV-infected donor.

In summary, Canaud et al. demonstrated reinfec tion of the kidney allograft with HIV-1 after transplantation in the HIV-infected recipient with well controlled (undetectable) viral disease. The identification of a noninvasive urine test to detect early reinfec tion that correlates with allograft HIV-1 infection will facilitate the identification of donor and recipient factors associated with recurrent HIV renal disease. It is less clear what intervention may control the reinfec tion, although identifi cation of donor and/or recipient factors associated with early reinfec tion may provide some clues. Potential strategies include tapering immunosuppression or providing more effective cART. Kidney transplantation in HIV-infected recipients has provided the opportunity to safely obtain tissue as part of routine protocols after transplantation. Although the findings reported by Canaud et al. will have important implications for the HIV-infected transplant recipient, the opportunity to identify factors associated with HIV infection/HIV nephropa thy could have a significant impact on the increasing numbers of HIV-infected individuals with well controlled disease who are progressing to ESRD.

ACKNOWLEDGMENTS

The author thanks Rodney Rogers from the University of California, San Francisco, for his expert coordination of the NIH-funded (Grant AI052748) United States multicenter trial and his help in preparing this editorial. The author also thanks all of the Solid Organ Transplantation in HIV: Multi-Site Study investigators, coordinators, and participants.

DISCLOSURES

None.

REFERENCES


See related article, “The Kidney as a Reservoir for HIV-1 after Renal Transplantation,” on pages 407–419.