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Protective association between JC polyoma viruria and kidney disease

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Abstract

Purpose of review—The presence of viruses in urine (urine virome) typically reflects infection in the kidneys and urinary tract. The urinary virome is associated with HIV-associated nephropathy and chronic glomerulosclerosis. There are many associations of this microbiome with human diseases that remain to be described. This manuscript reviews emerging data on relationships between kidney disease and urinary tract infection/colonization with JC polyomavirus (JCPyV).

Recent findings—Approximately 30% of the adult population sheds JCPyV in the urine. Further, urinary tract infection with one polyomavirus strain appears to inhibit secondary infections. The presence of urinary JCPyV and BK polyomavirus (BKPyV) replication were measured with polymerase chain reaction in African Americans to assess relationships with *apolipoprotein* L1 gene (*APOL1*)-associated nephropathy. Urinary JCPyV was associated with paradoxically lower rates of nephropathy in those with *APOL1* high-risk genotypes. Subsequent studies revealed African Americans with JCPyV viruria had lower rates of nondiabetic nephropathy independent from *APOL1*.

Summary—Urinary tract JCPyV replication is common and associates with lower rates of nephropathy. This relationship is observed in diverse settings. Results support a host immune system that fails to eradicate nonnephropathic viruses and is also less likely to manifest renal parenchymal inflammation resulting in glomerulosclerosis.

Keywords

African American; *apolipoprotein L1* ; chronic kidney disease; focal segmental glomerulosclerosis; HIV-associated nephropathy; JC polyomavirus

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The long-held tenet that urine is sterile has proven incorrect. Viruses frequently infect or colonize the kidneys and lower urinary tract [1,2▪▪]. This active viral replication produces viruria. There are many associations of the urinary virome with human diseases, whereas others remain to be described [3▪]. Next-generation sequencing has identified known and novel viruses in stool and sputum. In contrast, urine has been less well studied in large numbers of individuals. Although viral infections of the kidney have been proposed to be causes of acute and chronic forms of nephropathy, it is often difficult to accurately determine the timeline of infection as it relates to nephropathy onset [3▪].

HIV is an example of a virus with renal reservoirs of infection. HIV is a major mediator of *apolipoprotein L1* gene (*APOL1*)-associated collapsing glomerulopathy, referred to as HIV-associated nephropathy or HIVAN [4]. Fifty percentage of individuals with HIV infection and *APOL1* renal-risk genotypes, defined as having two copies of the *APOL1* G1 and/or G2 renal-risk alleles, developed HIVAN prior to availability of antiretroviral therapies [5]. Remarkably, HIVAN proved to be a treatable disease. Institution of highly active antiretroviral therapy prevents nephropathy in individuals who are at genetic risk for kidney disease based on *APOL1*. This striking observation led to the search for other viruses having properties like HIV, namely, lymphotropism and maintenance of renal reservoirs of infection, to determine whether they were potential mediators of chronic kidney disease (CKD) [1]. This manuscript reviews the evidence of whether the nephrotropic member of the polyomavirus family JC polyomavirus (JCPyV) is associated with CKD, as seen with BK polyomavirus replication (BKPyV; JC and BK are initials of patients in whom these viruses were first identified). Paradoxically, evidence linking JCPyV replication in the urinary tract supports lower risk for CKD [1,2▪▪,6,7]. Potential mechanisms underlying the protective association are discussed.

OVERVIEW OF THE POLYOMAVIRUS FAMILY

JCPyV and BKPyV are members of the polyomavirus family (*Polyomaviridae*), which is a family of small, icosahedral viruses that lack a membrane (envelope) and have a circular double-stranded DNA genome [8]. Infection with polyomaviruses is widespread in human populations but rarely causes disease. Instead, these viruses typically establish asymptomatic persistent or latent infections in individuals with healthy immune systems, and cause disease primarily as a result of immunosuppression [9]. JCPyV and BKPyV are notable for their tropism for the kidney, where they remain in a latent state but undergo periodic reactivation leading to shedding of virus in the urine [9]. In various studies, 60–80% of adults are seropositive for these viruses, and 20–40% are shedding virus in urine at any point in time [10,11].

Control of virus replication by the immune system appears to be critical for the asymptomatic nature of most polyomavirus infections. However, in patients with HIV/AIDS or undergoing treatment with immunosuppressive drugs, high levels of virus replication can lead to cell death and disease in key organ systems. For example, approximately 10% of renal transplant recipients suffer from polyomavirus-associated nephropathy caused by

BKPyV; this complication of over immunosuppression can result in graft loss [9]. Similarly, BKPyV replication is associated with kidney function decline in recipients of allogeneic hematopoietic stem cell transplants [12,13].

In contrast to BKPyV, in which disease in immunosuppressed patients is associated with virus replication in the kidney, disease caused by JCPyV occurs primarily in the central nervous system, namely, the demyelinating disease progressive multifocal leukoencephalopathy (PML). PML results from lytic infection of oligodendrocytes, resulting in demyelinating lesions in multiple areas of the brain [14]. The incidence of PML is much higher in individuals with HIV/AIDS (1–5%) than in those with other types of immunosuppression; therefore, it is considered one of the AIDS-defining illnesses [14]. Whether this reflects the importance of a particular type of immunodeficiency or represents an interaction between HIV and JCPyV remains an open question. With the advent of highly active antiretroviral therapy, the incidence of HIV/AIDS-associated PML has declined. However, a new source of PML cases was discovered in patients with multiple sclerosis (MS) receiving therapy with natalizumab, an anti-integrin antibody that inhibits extravasation of lymphocytes into the brain and consequently reduces lesions of MS [15,16]. These cases were striking because of the presence of two different demyelinating diseases in the same patient. There is evidence that JCPyV in these patients originates from a latent reservoir in hematopoietic stem cells and B lymphocytes, which are mobilized by natalizumab treatment and presumably enter the brain by hematogenous spread [16].

The presence of both JCPyV and BKPyV in the kidney made them candidates as potential mediators of CKD. Based on the spectrum of diseases present in immunosuppressed individuals, it seemed more likely that CKD would be associated with BKPyV than JCPyV. However, mounting evidence indicates that there is an association of CKD with JCPyV. As discussed below, it is in the opposite direction from that initially expected.

JC POLYOMAVIRUS IN AFRICAN AMERICANS WITH NONDIABETIC NEPHROPATHY

Complex interactions between host and pathogen genomes are well documented with significant evidence of coadaptation in both genomes in response to environmental changes, emergence of new mutations, and pharmacological treatments [17,18]. The rise in frequency of the *APOL1* G1 and G2 renal-risk variants, primarily in West Africa, appears to be the result of positive selection from the trypanolytic effect of APOL1 in serum that confers resistance to the parasite *Trypanosoma brucei rhodesiense*. This pathogen is transmitted by infected tsetse flies and can cause African sleeping sickness [19,20]. The *APOL1* renal-risk variants are also strongly associated with HIVAN and appear to play a direct role in the regulation of HIV-1 and its persistence in human podocytes [21–24].

We hypothesized that other (non-HIV) viral infections, especially those with similarity to HIV based on either lymphotropism [e.g., cytomegalovirus (CMV) and human herpes virus 6 (HHV6)] or maintaining renal reservoirs of infection (e.g., JCPyV and BKPyV) would be more prevalent in individuals with *APOL1* who had renal-risk variants and developed CKD [1]. We tested whether infections by these four viruses modified the association between

APOL1 and nephropathy. Urine (JCPyV and BKPyV) and plasma samples (HHV6 and CMV) were assessed in 300 first-degree relatives of African Americans with nondiabetic end-stage renal disease using quantitative PCR analysis. This sample from the Natural History of APOL1-associated Nephropathy Study (NHAANS) is enriched for *APOL1* renal-risk variants with a prevalence of 22%, relative to the 13% observed in the general African American population. The breakdown of these 300 individuals was 170 with 0 or 1 *APOL1* renal-risk variants (83 with CKD), and 130 with 2 *APOL1* renal-risk variants (43 with kidney disease). Urine JCPyV and BKPyV were detected in 90 and 29 of NHAANS participants, respectively, whereas HHV6 and CMV were too rare to be analyzed. There was no association between *APOL1* genotype and presence of JCPyV [odds ratio (OR) 95% confidence interval (CI) 1.3 (0.8, 2.2)]. However, after adjusting for the age at end-stage renal disease in each family based upon the age of affected probands, sex, and African ancestry proportion, presence of genomic DNA from JCPyV in urine and *APOL1* risk alleles were significantly (negatively) associated with elevated serum cystatin C, albuminuria (albumin to creatinine ratio >30 mg/g), and presence of CKD defined by an estimated glomerular filtration rate less than 60 ml/min per 1.73 m^2 and/or albuminuria in an additive (*APOL1* and JCPyV) model. BKPyV viruria was not associated with kidney disease. These analyses suggested a JCPyV protective effect among African Americans with two *APOL1* renal-risk variants.

A replication analysis was performed in an independent and newly recruited sample of 200 African Americans, 80 CKD cases (39 with 2 *APOL1* renal-risk variants and 41 with 0/1 *APOL1* renal-risk variants), and 120 non-nephropathy controls (40 with 2 *APOL1* renal-risk variants and 80 with 0/1 *APOL1* renal-risk variants) supported by the United States–Israel Binational Science Foundation (BSF) [2▪▪]. This analysis focused on potential protective effects of JCPyV on CKD, independently from *APOL1* genotype. CKD cases were selected for viral analysis by balancing between those with mild and severe kidney disease to prevent possible confounding effects of reduced nephron mass or urinary excretion of detectable viral shedding. Presence of JCPyV and BKPyV were again assessed using quantitative PCR. JCPyV frequencies were 40% in controls versus 5.1% in CKD cases ($P = 2 \times 10^{-4}$) among the *APOL1* renal-risk genotype carriers, and 48.8% in the controls versus 12.2% in CKD cases ($P = 8 \times 10^{-5}$) among the non-*APOL1*-risk genotype carriers. The combined prevalence of JCPyV, combining cases and controls regardless of *APOL1* renal-risk genotype status, was 8.75% in CKD cases versus 45.8% in non-nephropathy controls. This finding demonstrated a strong CKD protective effect of JCPyV [OR (95% CI), 0.15 (0.06, 0.42)]. A meta-analysis combining the results of the two independent samples (NHAANS and BSF, $N = 500$) showed an overall protective association between JCPyV and CKD [OR (95% CI), 0.37 (0.25, 0.57)]. In summary, evidence for replication of a protective association between urinary JCPyV and nondiabetic nephropathy was observed in African Americans.

These somewhat paradoxical results of protective association are supported by lower rates of advanced kidney disease in Brazilians with JCPyV viruria [6]. JCPyV viruria is also associated with lower rates of acute rejection and allograft failure in recipients of a kidney transplant [7].

POTENTIAL GENE–VIRUS INTERACTIONS IN AUTOIMMUNE FORMS OF CHRONIC KIDNEY DISEASE

More than 80 recognized autoimmune diseases exist. Many of these disorders can involve the kidneys and the majority are driven by a combination of genetic susceptibility and environmental factors. Among the leading hypothesized environmental triggers are viral and bacterial infections. This hypothesis has gained further traction with the recognition that the human body is predominately nonsterile and contains numerous microbial ecosystems. Many of these viruses and bacteria are capable of acting as pathogens when these ecosystems become out of balance or the individual is immunosuppressed. As an example, the connection of JCPyV and its role in PML and MS, an autoimmune disease, has been discussed.

Several mechanisms may lead viral infections to trigger autoimmune dysregulation. Molecular mimicry, high sequence similarity between foreign and self-peptide, is common and can result in autoreactive T and B cells producing autoimmune disease. Altindis *et al.* [25▪▪] identified 16 different human peptide hormones or growth factors with homologous sequences in viruses. Hepatitis C virus has sequences very similar to the human proteome [26]. Recently, there is growing experimental evidence in support of a hypothesis that Epstein–Barr virus (EBV)-induced molecular mimicry is important in the development of Parkinson's disease, moving Parkinson's diseases into the realm of autoimmunity [27].

Genome-wide association studies of various autoimmune diseases have implicated hundreds of genomic regions, many shared across several autoimmune diseases. The vast majority of associated regions are not in coding regions of the genome but in presumed regulatory regions of unknown mechanism. Data support strong association between EBV infection with autoimmune mechanisms of systemic lupus erythematosus (SLE) [28–30], including up to a 50-fold increased risk of disease in children [31]. Harley *et al.* [32▪▪] assessed whether any of the DNA-interacting proteins encoded by EBV preferentially bind to SLE risk loci. They identified the EBV gene product, EBNA2, and associated transcription factors (TFs) or cofactors bind to regions of the genome known to be risk loci not only for SLE, but also MS, rheumatoid arthritis, juvenile idiopathic arthritis, type 1 diabetes, inflammatory bowel disease, and celiac disease. Although recognizing that B cells are more heavily studied, they report data suggesting that the EBV-infected B cells are a plausible site for several risk loci in multiple autoimmune diseases. For what B-cell subtypes this hold and what other cells types might exhibit other unique EBNA2-TF patterns requires further study.

Endogenous retroviruses are viral elements embedded in the host genome resulting from past infection and they represent at least 1% of the human genome. They are transposons and play important roles in gene regulation and expression. Two human endogenous retroviruses, HERV-k13 on chromosome 13 and HERV-Fc1 on chromosome X, are associated with MS and may influence risk in type 1 diabetes and rheumatoid arthritis [33,34]. This intriguing hypothesis requires further investigation.

CONCLUSION

Multiple lines of evidence support relationships between presence of nephropathy and viral infections involving the kidneys and urinary tract. It was initially felt that these associations were likely to be pathologic, as with HIV in HIVAN. However, relationships between innate immune system activation and development of glomerulosclerosis and other autoimmune etiologies of CKD exist. The protective relationships between urine JCPyV infection with *APOL1* and non-*APOL1*-associated forms of glomerulosclerosis in African Americans, Brazilians with CKD, and postkidney transplant outcomes remain largely unexplained. Rather than a direct nephroprotective effect of JCPyV, we favor the hypothesis that an individuals' immune system may be permissive for urinary tract replication with the nonnephropathic JCPyV. This immune effect likely translates to a down-regulated systemic immune response, one less likely to promote renal inflammation with resultant glomerular and/or tubulointerstitial scarring. Assessment of the immune system in nonimmune suppressed individuals with and without JCPyV viruria remains to be performed. These studies will likely shed light on the paradoxical protective relationship between kidney disease and JCPyV. In addition, studies of the urine virome in patients with diabetic forms of kidney disease and in non-African American cohorts remain to be performed. The urine virome will likely hold clues to an individual's risk for development of nephropathy. It may also serve as a useful biomarker for risk of kidney disease.

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KEY POINTS

- Approximately 30% of individuals in the general US and Brazilian populations have evidence of active JCPyV replication in the urine.
- Urinary tract JCPyV infection is reproducibly associated with lower rates of nondiabetic CKD, including African Americans with *APOL1* and non-*APOL1*-associated glomerulosclerosis, CKD in Brazilians, and lower rates of acute rejection with improved kidney function in recipients of a kidney transplant.
- JCPyV viruria is postulated to be a marker for host immune systems that fail to eradicate nonnephropathic viral infections and are less likely to develop renal parenchymal inflammation resulting in glomerulosclerosis and CKD.