The Neglected fact: Anticoagulation-Related Nephropathy

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Dear Editor,

Anticoagulation-related nephropathy may be a frequently overlooked diagnosis. Previously known as warfarin-induced nephropathy, the disease has been found in other anticoagulants and extends to anticoagulation-related nephropathy. For this kind of disease, if not recognized and diagnosed in time, it will be a potentially devastating disease with extremely serious consequences for patients. Therefore, we need to know which factors are more likely to cause patients with anticoagulation-related nephropathy. Through understanding this extremely neglected disease, we can predict potential patients. Currently, there are no specific guidelines for the identification and management of anticoagulation-related nephropathy, but this is an urgent matter because of the increasing number of diseases and patients requiring anticoagulant therapy.

The use of anticoagulant therapy for atrial fibrillation and venous thromboembolism is on the rise. By 2050, the prevalence of atrial fibrillation in the United States is expected to reach 12 million. As a result, the number of patients receiving long-term anticoagulant therapy is also increasing. Therefore, it is important to understand the potential consequences of anticoagulant therapy for specific and vulnerable patients. In the United States, the prevalence of chronic kidney disease is about 14%,[1] and hypertension and diabetes are important risk factors for chronic kidney disease. In addition, acute kidney injury is one of the common complications in hospitalized patients. One study reported that in patients without chronic kidney disease, the incidence of acute kidney injury was 2.2% in intensive care patients, 0.72% in surgical patients, and 0.54% in general medical wards.[2] In clinical practice, the widespread use of anticoagulant drugs, the high prevalence of chronic kidney disease and the prevalence of risk factors and the frequent occurrence of acute kidney damage in hospitalized patients makes us realize that anticoagulation-related nephropathy is not accidental.

Warfarin, as a classic anticoagulant drug, has been widely used in clinical practice. Later, warfarin associated nephropathy was reported, and anticoagulation-associated nephropathy has appeared until now. Brodsky *et al.* first described the concept of warfarin-associated nephropathy in 2009. They described a population of warfarin-treated patients with acute kidney injury associated with a biopsy confirmed tubular type of obstructive tubular erythrocytes.[3] Another study specifically analyzed the relationship between warfarin overdose and the development of chronic kidney disease. Over a five-year period from 2005 to 2010, serum samples from the subjects showed that at least one in 49 patients had an INR greater than 3.0. There was also a significant rise in creatinine levels, and this study was the first to point to the need for routine renal function monitoring during warfarin administration in patients with chronic kidney disease.[3]

In 2011, a retrospective study of more than 15,000 patients treated with warfarin showed that 33% of patients with known chronic kidney disease and 16% of patients without chronic kidney disease had INR levels greater than 3, meeting the criteria for warfarin-related kidney disease. The most striking feature of these figures was a 65% increase in one-year mortality.[4] The results were confirmed in animal studies, which Ware *et al.* used mice that underwent 5/6 nephrectomy by ablation. The rats were then compared with healthy kidney controls. Both groups were given the same dose of warfarin. They found no difference in prothrombin time before treatment began between the two groups. The rats were then given different doses of warfarin within three weeks. The study showed varying degrees of elevation of prothrombin time in all subjects. The increase in prothrombin time in the control group was not associated with an increase in serum creatinine, however, the increase in prothrombin time was

associated with an increase in serum creatinine in rats undergoing partial nephrectomy.[5]

In fact, the pathogenesis of anticoagulation-related nephropathy is a complex mechanism of multiple factors, including excessive glomerular proliferation and glomerular hypertension, complex interaction of heme molecules, which cause oxidative stress and activate cascade of inflammation of renal tubular epithelium and surrounding stroma.[6-8] Thus warfarin is not the only anticoagulant involved in impaired kidney function. A study of the effect of dabigatran on renal function in 2013 reported that dabigatran resulted in a dose-dependent increase in serum creatinine and hematuria in the control group and in 5/6 nephrectomized rats, which was the first animal study of a novel oral anticoagulant and anticoagulation-associated nephropathy.[9] At the same time, this study was an important turning point in the expansion of warfarin-associated nephropathy to anticoagulation-associated nephropathy. The same conclusion was reached in another case report of acute kidney injury caused by the Xa inhibitor apixaban. Direct oral administration of anticoagulants has been established to cause anticoagulation-associated nephropathy.[10] Safety data from patients randomized to apixaban in ARISTOTLE's trial showed that the observed worsening of glomerular filtration rate was more than 20% in 16,869 patients.[11] The results were consistent with those obtained by Brodsky *et al.* in 2011. Another retrospective study conducted on 20,727 patients with atrial fibrillation who received at least one anticoagulant (dabigatran, rivaroxaban, apixaban, or warfarin). The study found that the overall risk of acute kidney injury was 22% lower in patients taking oral anticoagulants compared with those taking warfarin. There was no statistically significant association between direct oral anticoagulants and acute kidney injury in general, however, eGFR < 30 mL/min was associated with a higher risk of acute kidney injury compared with warfarin.[12]

It is important to understand the factors that put patients at higher risk for anticoagulation-related nephropathy. First, although the incidence is higher in patients with chronic kidney disease, the incidence of acute kidney injury in patients without chronic kidney disease is reported to be 20%. In the case of warfarin, the use of overdose therapy further increases the risk of anticoagulation-related nephropathy. INR > 3 showed accelerated progression of renal disease, confirmed by elevated serum creatinine and pathological evidence. In eGFR > 30 mL/min patients, compared with warfarin, direct oral administration of anticoagulant has a lower rate of acute kidney injury. Therefore, it is reasonable to speculate that there may be a lower incidence of anticoagulation-related nephropathy. But again, a prospective study will be challenging because the use of direct oral anticoagulants is limited to chronic kidney disease and is not generally used in populations with GFR < 30mL/min. This left patients with chronic kidney disease taking warfarin as the only available drug; we know that one agent may be associated with a higher inherent risk of anticoagulation-related nephropathy.

Prospective studies of this disease have been very difficult to design due to the confounding variables and current diagnostic approaches. Until now, we have had to rely on retrospective studies to guide our clinical decisions. By better understanding this neglected disease, we can diagnose and predict potential patients accurately and discuss alternative therapies for anticoagulation therapy. Currently, there are no specific guidelines for the diagnosis and management of anticoagulation-related nephropathy, but it is an important research direction, especially considering the increasing number of patients requiring anticoagulant therapy.

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