Venous Thromboembolism and Membranous Nephropathy: So What’s New?

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The association of venous thromboembolism (VTE) with the nephrotic syndrome, particularly deep vein and renal vein thrombosis (DVT and RVT, respectively) is firmly established (1–3). In a retrospective study of 298 nephrotic patients followed for a mean period of 10 years (4), the annual incidence of VTE was 1.02%/yr, and the absolute risk of arterial thrombosis was 1.48%/yr. The risk of both venous and arterial thrombosis was particularly high within the first 6 months of diagnosis (with annual incidences of 9.85% and 5.52%, respectively) (4). In children with the nephrotic syndrome, 9.2% of 326 patients experienced 38 thromboembolic episodes over a median period of 3.7 years (5). This risk is particularly high in patients with idiopathic membranous nephropathy.

Deep vein thrombosis (DVT) of the lower extremities is the most commonly observed site of thrombosis. In review of hospital discharges from 1979 to 2005, of 925,000 patients with a diagnosis of nephrotic syndrome, 14,000 (1.5%) were diagnosed with DVT; <5000 had RVT (6). Pulmonary embolism (PE) has been previously described in nephrotic patients with or without an evident DVT or RVT (1,7). In a study of 89 nephrotic patients with a serum albumin <2.0 g/dl (20 g/L), 19 (21%) patients had a high probability V/Q scan, and, in patients with low or intermediate probability scans, pulmonary angiograms demonstrated PE in another 10 patients (8,9). The renal vein is a classic site for thrombosis in nephrotic patients, being unusual in healthy subjects, and the prevalence of RVT can vary from 22% to 52% (2,7,10). Acute RVT is uncommon, with chronic RVT being predominant. Chronic RVT is insidious, usually discovered incidentally or when a workup for the source of pulmonary embolism reveals it. Although it has been suggested that a chronic RVT may lead to worsening proteinuria or kidney function, this has never been clearly documented (10). In a single case report of a patient with unilateral RVT and nephrotic syndrome due to membranous nephropathy, bilateral ureteral catheterization studies showed no difference in protein excretion or creatinine clearance between the two kidneys (11).

The reason(s) underlying the hypercoagulable state in nephrotic patients are not clearly understood. There is evidence of ongoing subclinical coagulation using measures of hemostasis activation, such as the plasma level of fibrinopeptide A (9) and D-dimer. Multiple hemostatic abnormalities have been described, including decreased levels of antithrombin and plasminogen (due to urinary losses), increased platelet activation, hyperfibrinogenemia, inhibition of plasminogen activation, and the presence of high-molecular-weight circulating fibrinogen moieties (9). The possibility of immune complex injury in the glomerulus resulting in systemic effects on clotting has also been evoked (9).

The risk of thrombosis seems to be related to the severity and duration of the nephrotic state and seems to be particularly increased with serum albumin concentrations <2.0 g/dl (20 g/L) (9). Furthermore, among the causes of nephrotic syndrome, the risk is highest with membranous nephropathy, followed by membranoproliferative GN and minimal change disease (9).

The diagnosis of thrombotic complications is usually based on clinical suspicion and confirmed by the appropriate imaging study (CT angiogram, nuclear scans, and ultrasound/Doppler scans). Whether asymptomatic patients should be screened is not clear because there is an absence of studies that show clinical benefit from screening. Besides, if there is an initially negative study, patients could conceivably develop thrombosis at a later stage.

The role of prophylactic anticoagulation (especially in patients with membranous nephropathy with severe nephrosis) has been debated (12). Using Markov modeling, Sarasin and Schifferli (13) have calculated that the mortality benefit of prophylactic anticoagulation outweighs the risk. In the authors’ opinion, prophylactic anticoagulation is suggested in patients with massive proteinuria, a serum albumin <2.0 g/dl (20 g/L), and an additional risk factor for thrombosis (e.g., a prior idiopathic thromboembolic event; immobilization; severe heart failure; morbid obesity; or abdominal, orthopedic, or gynecologic surgery). Patients who achieve remission of nephrotic syndrome should have anticoagulation discontinued 6 months after remission if there is no other indication for anticoagulation (9).

In the article by Lionaki et al in this issue of CJASN (14), the largest ever reported cohort (n=898) of patients with membranous nephropathy was analyzed for the incidence of thromboembolic events and predisposing factors contributing to this risk. The main messages from this paper were the relatively low(er) risk for VTE of 7.2% compared with some earlier studies, the fact that most episodes occur within the first 2 years (median time, 3.8 months from diagnosis of nephrosis), and the serum albumin supersedes urinary protein with
In summary, although not much novel information is provided in the paper by Lionaki et al, due to the large sample size, it does serve to provide a better estimate and time of diagnosis of clinically manifest VTE events in patients with idiopathic membranous nephropathy. The serum albumin levels appear to be the pre-eminent risk factor. However, the single most important question in these patients is whether to anticoagulate prophylactically or not, and disappointingly, this was not addressed by the paper (but the authors promise this decision analysis is underway!).

Disclosures
None.

References

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See related article, “Venous Thromboembolism in Patients with Membranous Nephropathy,” on pages 43–51.