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
respect to risk. This retrospectively studied cohort of adult patients was assembled from two North American tertiary care centers with large populations of glomerular patients and represented only idiopathic membranous nephropathy. There were some baseline differences in the two cohorts reflecting the populations and practices of the respective institutions. About one-half of the patients were on antiplatelet agents at the time of VTE (suggesting that these agents might not provide protection). The good news is that VTE did not adversely affect renal survival, and no patient died as a consequence of VTE (actual patient survival data with and without VTE are not shown).

In this study, the diagnosis of VTE was made with the appropriate screening technique, which was performed when there was a clinical suspicion (i.e., routine screening was not performed). This likely led to the lower incidence of VTE (7.2%) compared with previous studies where VRT could be seen in up to 50% of patients and pulmonary emboli in 22% of patients who underwent prospective screening. However, there are no randomized trials looking at whether prospective screening leads to a better outcome.

The authors report that the risk of VTE begins at a threshold albumin of 2.8 g/dl and becomes higher as the albumin levels drop further. What was surprising was that VTE appeared early in the course of disease and was not related to the duration of hypoalbuminemia but to the level of serum albumin. This implies that there are as-yet unidentified patient-specific factors that, in addition to low albumin levels, confer the VTE risk.

There are several strengths to this study. The major strength of the study is that this is the largest such cohort assembled as a consequence of collaboration between two major institutions in North America—the Glomerular Disease Collaborative Networks (from the University of North Carolina, Chapel Hill, NC) and the Toronto Glomerulonephritis Registry (from the University of Toronto, Toronto, Canada). The authors have done an admirable job in collecting and analyzing VTE episodes and risk factors in a diverse group of patients. The VTE rate of 7%–8% was remarkably similar in the two cohorts, supporting the validity of their results. However, there are several limitations to the study. This study being of retrospective design, it is possible that all cases of VTE were not captured and that all risk factors were not systematically investigated. For example, likely due to small sample sizes and possible under-reporting, protection from antiplatelet agents and risk from malignancies and smoking do not seem to be significant factors. Furthermore, recurrent VTE rates and response to anticoagulation are not mentioned. It is surprising that RVT was the predominant form of VTE (because these are clinically silent in the majority), which suggests that both clinical diagnosis and screening were used to define the patients with VTE (only 10 patients had VTE in at least one site).

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.