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Hypercoagulability and Nephrotic Syndrome

Antonietta Gigante[1], Biagio Barbano[1,*], Liborio Sardo[2], Paola Martina[1], Maria L. Gasperini[2], Raffaella Labbadia[1], Marta Liberatori[2], Antonio Amoroso[2] and Rosario Cianci[1]

Department of Nephrology[1] and Department of Clinical Medicine[2], Sapienza University of Rome, Rome, Italy

Abstract: Patients with nephrotic syndrome are at increased risk for thromboembolic events such as deep venous and arterial thrombosis, renal vein thrombosis and pulmonary embolism. This thrombophilic phenomenon has been attributed to a "hypercoagulable" state in which an imbalance between naturally occurring pro-coagulant/pro-thrombotic factors and anti-coagulant/antithrombotic factors promotes *in situ* thrombosis in deep veins or arteries. Management of thromboembolic events may be divided in prophylactic and therapeutic strategies. Hypoalbuminemia is the most significant independent predictor factor of thrombotic risk, especially for values <2 g/dL. However, the most important question in these patients is whether to anticoagulate prophylactically or not. The decision depends on type of glomerulonephritis, proteinuria severity, other predisposing factors and prior history of thrombosis. Reviewing the recent literature, we suggest the best therapeutic management of anticoagulation for patients with nephrotic syndrome, focusing on prophylactic strategies.

Keywords: Arterial thrombosis, deep venous thrombosis, nephrotic syndrome, proteinuria, renal venous thrombosis, venous thromboembolism.

INTRODUCTION

Nephrotic syndrome (NS) is characterized by heavy proteinuria (3.5 g/24 h per 1.73 m^2 surface area or greater), edema, hypoalbuminemia and hyperlipidemia. Several glomerular diseases, either primary or secondary, can cause NS. Complications of NS are divided into 2 categories: disease-associated and drug-related complications (especially infections due to immunosuppressive therapy) [1].

The main mechanism of disease-associated complications is due to urinary protein loss and the risk of developing venous thromboembolism (VTE) and arterial thromboembolism (ATE) is considered among the most serious complications [2]. Thromboembolic episodes are more frequent in adults (26.7%) than in children (3%) and the percentage increases considering the type of underlying glomerulonephritis [3]. In fact membranous nephropathy, membranoproliferative glomerulonephritis and minimal change disease are associated with a higher risk of thromboembolism than other nephropathies [4]. The frequency of VTE and ATE is difficult to establish because the majority of studies investigated renal vein thrombosis (RVT). However, deep venous thrombosis (DVT) seems to develop in approximately 15% of NS patients, while unilateral or bilateral RVT has been reported in about 30% of patients with greatest incidence in membranous glomerulonephritis (37%), membranoproliferative glomerulonephritis (26%) and minimal change disease (24%) [4-8]. Moreover, a characteristic difference of RVT presentation in relation to age has been observed. Young patients (mean age of 20 years) have a more acute RVT onset, presenting also one or more symptoms as flank pain, macroscopic hematuria and impairment of renal function, while older adults (mean age of 38 years) develop most frequently chronic RVT [5,6]. Some studies revealed a high risk of VTE and ATE within the first 6 months of NS diagnosis in adults [9]. In a recent study of childhood NS, median time to the first thromboembolism was 70.5 days after diagnosis of NS; DVT was more frequent than ATE and occurred in 76% of cases and was frequently associated with the use of a central venous catheter (45%) [10]. In relation to drug administration, steroid-resistant NS had a higher risk of thromboembolism than steroid-sensitive NS [11].

PATHOPHYSIOLOGY OF "HYPERCOAGULABLE" STATE IN NEPHROTIC SYNDROME

Multiple factors contribute to the dysregulated coagulation state of NS, though all the reasons are not clearly understood. The pathogenesis of hypercoagulability in the NS results from an imbalance between anti-coagulant/antithrombotic factors (antithrombin III, active protein C and S, tissue factor pathway inhibitor) and naturally occurring pro-coagulant/pro-thrombotic factors (fibrinogen, factor V, factor VIII, platelets, Von Willebrand factor, fibrinolytic system, plasminogen activator inhibitor fibrinogen) with associated abnormalities in platelet activation that promote *in situ* thrombosis in deep veins or arteries [12]. Because of a breakdown in the permselectivity barrier of the glomerular capillary wall, the main defect of NS results in the leakage of high molecular mass proteins, at least the size of albumin (approximately 69 kD) [13].

The hypoalbuminaemia of the NS is a consequence of an excessive loss of albumin in the urine.

*Address correspondence to this author at the Department of Nephrology, "Sapienza" University of Rome, Viale del Policlinico 155, Rome, Italy; Tel: +390649972074; Fax: +39064453677; E-mail: biagionet@hotmail.com

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Table 1. Risk Factors of Nephrotic Syndrome.

Risk factors	
Genetic predispositions	Membranous nephropathy
Obesity	Elevated lipoprotein (a)
Prior idiopathic thromboembolic events	Anthiphospolipid autoantibodies
Severe heart failure	Central venous catheter
Serum albumin <20 g/L	Intravascular volume depletion
Abdominal, orthopedic, or gynecologic surgery	Use of diuretics or steroids
Intercurrent illness or immobilisation	Steroid-resistant nephrotic syndrome

The NS may be considered as a model for the study of low albumin effects on platelets. In fact, platelet aggregation may be mediated by several mechanisms linked to the inhibitory effects of albumin as the decreased conversion of arachidonic acid to thromboxane A_2 and the increased conversion of endoperoxides (PGH_2) to prostaglandins (PGD_2) [14]. Several indices of platelet function as platelet aggregation ratio, platelet half-life, circulating beta-thromboglobulin concentrations and aggregation suggest an activation of platelets in these patients.

Furthermore, platelet activity usually inversely correlate with serum albumin levels (e.g.in course of remission or relapse), and is potentially reversible by adding albumin *in vitro* or following albumin infusions [15]. Moreover, several studies have shown that low serum albumin is associated with increased cardiovascular mortality [14, 16].

Thus, many other important hemostatic proteins of similar size are also pathologically excreted in the urine [17]. Loss of antithrombotic factors in the urine due to NS, is counterbalanced by an increase in plasma pro-coagulant cofactors, as factor V, factor VIII and fibrinogen [18]. Other risk factors [3, 5, 19] are also involved in the pathophysiology of this "hypercoagulable" state in NS and are summarized in Table **1**.

ENDOGENOUS ANTITHROMBOTIC FACTORS

Antithrombin III (65 kD)

In NS, antithrombin III (AT III) deficiency occurs in 40 to 80% of patients, with higher incidence of thromboembolic complications when serum albumin levels is below 20 g/L and AT III levels are 75% below normal [20]. DVT and pulmonary embolism have been often observed in childhood in patients with very low AT III levels [20, 21].

Protein C (62 kD)

Although slightly smaller than albumin, plasma concentrations of protein C are preserved and/or upregulated to the point that the levels are generally increased. Some studies investigated the hypercoagulability risk in NS childhood and the authors found a significant increase in Protein C activity, as one of the protective mechanism against thrombosis [22].

Protein S (69 kD)

Protein S is an important co-factor required for the efficient activity of protein C; it is found in 2 forms in plasma as free and functionally active protein S (approximately 30-40% of total circulating protein S) and complexed to C4b-binding protein (C4BP, 570 kD). In NS, because of the protein S molecular mass (69 kD), free protein S is lost in the urine whereas C4BP is preserved or elevated, binding up any remaining protein S. Thus, the total protein S plasma content may remain normal or even increase, while the free and functionally active protein S should be reduced contributing to the risk for the development of thromboembolic events [3, 23].

Tissue Factor Pathway Inhibitor (TFPI) (34-41 kD)

TFPI originates from vascular endothelium and is the major physiological inhibitor to the tissue factor mediated extrinsic pathway of blood coagulation. TFPI binds to factor Xa and, in this combination, binds to and inhibits tissue factor/factor VIIa complex. TFPI appears to be increased in patients especially in nephrosis relapses and this phenomen could be compensation for its loss in urine. Al-Mugeiren *et al.* monitored TFPI levels in childhood NS. They concluded that the elevated levels of both total and free TFPI in various phases of NS add another natural anticoagulant mechanism, which will attenuate the hypercoagulability of childhood NS [24].

PRO-COAGULANT/PRO-THROMBOTIC FACTORS

Fibrinogen (340 kD)

Fibrinogen is a 340 kD protein not filtered by the altered glomeruli of NS patients because of its size. In NS patients, elevated plasma fibrinogen levels are secondary to amplified hepatic synthesis and the consequent increase in its circulating levels and total intravascular pool may contribute to the hypercoagulability by providing more substrate for fibrin formation and promoting hyperviscosity, platelet hyperaggregability and red blood cell aggregation [25]. Serum albumin and fibrinogen levels are inversely correlated in NS, with only a slight compensatory increase in albumin synthesis, whereas fibrinogen, factors V and factor VIII synthesis are increased out of proportion to urinary losses [26-31].

Fibrinogen is an independent predictor of vascular pathology in myocardial infarction, stroke and progression of carotid or peripheral arterial disease [32-34], even in case of subclinical atherosclerosis [35].

Factor V (330 kD), Factor VIII (>200 kD)

Because of high molecular weight, plasma levels of factors V and VIII are increased. Particularly, the latter is typically increased as much as 2- to 3-fold compared with controls. Anyway, increased factor VIII represents a risk factor for VTE in the general population [36-38].

Platelet Reactivity

Platelet hyperreactivity and increased blood viscosity may contribute to the thrombotic diathesis. In NS, conditions such as thrombocytosis, decreased red blood cell deformability and increased von Willebrand factor levels may promote both transport towards the vessel wall and increased adhesion of platelets [5]. The pathogenesis of platelet hyperaggregability is multifactorial and associated with hypoalbuminemia, hypercholesterolemia, high levels of low density lipoprotein (LDL) and hyperfibrinogenemia [39-42].

NS may be particularly dangerous in adults with atherosclerotic disease, in whom the thrombocytosis, hyperaggregability and hyperlipidemia may increase their risk for arterial thrombotic disease [9].

Von Willebrand Factor (250 kD)

Increased von Willebrand factor levels, which promote platelet transport towards the vessel wall, and increased platelet adhesion are observed in NS [43].

Fibrinolitytic System and Plasminogen Activator Inhibitor

In NS, the fibrinolytic system is slightly changed. Several studies have focused on plasminogen (92 kD) and its mild decrease correlating with the degree of proteinuria [44, 45].

The other regulators of plasmin formation are tissue-type plasminogen activator (tPA; 72 kD) and plasminogen activator inhibitor (PAI-l) (52 kD) [46, 47]. Yoshida *et al.* showed a greater urinary excretion of tPA and PAI-1 in NS patients than in controls [48]. Conversely, important inhibitors of fibrinolysis with high molecular weight such as α_2-macroglobulin (725 kD) and lipoprotein (a) (500 kD) are increased in concentration. Thus, in NS fibrinolytic activity is reduced, resulting in prothrombotic activity [3].

Lipoprotein (a) plays a pro-inflammatory role by triggering chemotaxis of macrophages and it is colocalized with them within atherosclerotic plaques [49]. Lipoprotein (a) is associated with vascular disease as showed by prospective studies in the general population [50, 51].

LOCAL ACTIVATION OF THE GLOMERULAR HEMOSTASIS SYSTEM

In NS, elevated fibrinogen levels were found in renal vein blood, correlating with intraglomerular fibrin deposition and contributing to glomerular injury development [47]. During active phases of glomerulonephritis associated with NS, thrombin formation may arise in glomeruli, following activation of the glomerular hemostasis system [49]. In the kidney, tPA and PAI-1 are thought to be secreted by endothelial, glomerular epithelial and mesangial cells and a disproportionate increase in PAI-1 expression in glomeruli compared with t-PA has been demonstrated suggesting diminished fibrinolytic activity [48].

THROMBOSIS

Venous and arterial thromboses are observed in the NS with different features and frequencies. The most dangerous complication of VTE is pulmonary embolism (PE), unusual and described in nephrotic patients with or without evidence of DVT or RVT [35]; the estimated prevalence of asymptomatic PE ranges from 12 to > 30% [6].

Nephrotic Syndrome and Venous Thrombosis

DVT of the lower extremities is the most commonly observed site of thrombosis, even if RVT, inferior cava vein, hepatic vein and cerebral venous system may be involved [53-55]. In a large series of 898 patients with membranous glomerulonephritis, thrombotic events were seen in 7.2% of patients and serum albumin levels were the only marker of risk, with the threshold level being 28 g/L and the risk increasing by approximately two-fold for every 10 g/L of albumin decrease below this threshold [56]. Indeed, the risk of thrombosis seems to be related to the severity and duration of the NS, particularly increased with serum albumin concentrations ≤20 g/L.

Predictors of VTE were studied in 298 NS patients and proteinuria ratio to serum albumin was predictive of VTE. Furthermore, it was demonstrated a correlation between duration of NS and symptomatic VTE, that were remarkably elevated within first 6 months of disease - *the longer the disease duration, the higher the risk* [9].

Nephrotic Syndrome and Renal Vein Thrombosis

The reasons for the high frequency of RVT in associated with NS are not completely understood. The high frequency to develop thrombosis in renal veins than in other vessels may be due in part to the loss of fluid across the glomeruli due to a sustained reduction in blood volume that could lead to decreased venous flow [5]. The resulting hemoconcentration in the postglomerular circulation, especially worsened by diuretic administration and severe dehydration, may promote thrombus formation in renal veins.

Another hypothesis is related to the nature and type of immunological injuries of nephropathies. In membranous glomerulonephritis RVT develop more than in the others nephropathies. In fact, the identification of circulating immune complexes in membranous glomerulopathy patients with RVT, but not in those without thrombosis, may support this theory. Indeed, these complexes may be the triggering factor in the coagulation process [30]. Finally, patients with membranous glomerulonephritis have a 6-fold increase in PAI but not plasminogen activator, suggesting suppressed fibrinolytic activity [19]. Chronic RVT is insidious, usually discovered incidentally or during a workup for the source of a PE [19].

Nephrotic Syndrome and Arterial Thrombosis

Clinical complications of arterial thrombosis are less well known. Less frequent than venous thrombosis, the most common arterial site of thrombosis are femoral arteries, although pulmonary, iliac, mesenteric, axillary, subclavian, brachial, ophthalmic, carotid, brachiocephalic, coronary, cerebral and meningeal arteries may be involved [57, 58]. It has been suggested that arterial thrombosis in NS patients are often associated with steroid and diuretic administration [59].

Several hypotheses have been formulated suggesting that steroids could induce an increase of factor VIII and other serum proteins and account for the hypercoagulable state [60].

Moreover, elevated blood lipid levels lead to their subintimal accumulation at the sites of previous arterial wall injury with narrowing of the vessel lumen. Thus, arterial thrombosis may be triggered by platelet clumping and adhesion promoted by elevated protein bound fatty acids [57].

In NS, diuretics are carefully administered because of their action on edema and an abuse of these drugs is a risk for dehydration and subsequent venous and arterial thrombosis.

ATE was studied in NS patients, confirming a high absolute risk of symptomatic ATE that was elevated within first 6 months; estimated glomerular filtration rate and classic atherosclerosis risk factors were predictive of ATE [9].

MANAGEMENT OF THROMBOSIS

The prophylactic administration of anticoagulant in NS is not well established because large randomized trials are lacking. In the presence of demonstrated thrombosis, the treatment is based on conventional anticoagulation with heparin or warfarin [61].

Heparin and its low molecular weight derivatives are effective as anticoagulant by binding and enhance the effects of antithrombin III (AT III), an enzyme inhibitor of thrombin.

Warfarin inhibits vitamin K-dependent factors of coagulation as factors II, VII, IX and X and some regulatory factors (protein C, protein S and protein Z).

In patients with renal insufficiency, low-molecular weight heparin is at risk of accumulation and should be administered carefully because partially cleared by kidneys [62].

Patients who achieve remission of NS should have anticoagulation discontinued 6 months after remission if there is no other indication. Duration of anticoagulation therapy depends on persistence of nephrotic proteinuria that may lead to recurrent events [63]. Thrombolytic agents should be reserved only when catastrophic event occur, such as bilateral RVT or massive PE [64].

In fact, these drugs require careful administration due to their bleeding risk, especially in patients with NS.

Statins, (3-hydroxy-3-methyl coenzyme A reductase inhibitors) were recently evaluated in NS patients and their use is related to lower risk of venous thrombosis.

The exact underlying mechanism is not clearly known, even if the authors suggest a pleiotropic hypothesis based on lipid lowering, anti-inflammatory effects and coagulation cascade modulation, such as inhibition of platelet-derived protease-activated receptor 1 [65].

In the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), statin administration was associated with a reduction of venous thromboembolism risk compared with placebo [66].

Aspirin (acetylsalicylic acid, an antiplatelet inhibitor of thromboxane production) is a well-established drug, used for prevention of cardiovascular and thromboembolic events [67, 68].

In NS patients, anti-platelet agents are frequently administered for the prevention of thromboembolism, although a significant number of patients are resistant to aspirin therapy [69].

In these cases, thienopyridine derivatives (ticlopidine, clopidogrel) acting as inhibitors of platelet aggregation induced by adenosine diphosphate (ADP, a platelet activator released from damaged endothelial cells, activated platelets and red blood cells) are alternative drugs to be administered, though the lack of clinical trials and the potential adverse effects restrict their use [70].

Factor X inhibitors, such as Dabigatran, approved for stroke prevention and for atrial fibrillation, could be promising drugs for treatment of nephrotic-related thromboembolic events [71, 72].

CONCLUSIONS

The identification of high-risk patients to develop thrombosis is based on parameters such as proteinuria, hypoalbuminemia for venous thrombosis and traditional atherosclerosis risks such as age, sex, hypertension, diabetes, smoking and GFR reduction for arterial thrombosis. Thus, the decision to use prophylactic anticoagulation in NS patients depends on several factors such as type of glomerulonephritis (expecially membranous glomerulonephritis), low plasma albumin level, predisposing factors (bed rest, steroid therapy, obesity, family history of thrombophilia, heart failure) and previous history of thrombosis. Thrombolytic therapy should be limited to those patients with acute bilateral RVT.

Finally, when anticoagulation is administered, we suggest that warfarin should be continued for as long as the patient remains nephrotic, for a minimum duration of 6 months with International Normalized Ratio (INR) values between 2.0 to 3.0.

The decision to treat and the choice of therapy must be individualized based on the conditions and history of the single patient.

CONFLICT OF INTEREST

There are no known conflicts of interest associated with this publication and there has been no financial support for this work.

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