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Nephrotic Syndrome and Coagulation Disease

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Abstract

This review devoted to the nephrotic syndrome (NS) subsequent thrombotic outcomes. The pathogenesis of hyper coagulation disorders that cause venous and arterial vascular system thrombosis are studied. Discussed pro coagulant and anticoagulant mechanisms imbalance due to the anticoagulants natural urinal loss, affected by dis function of the glomerular filter selective permeability, leading to high molecular weight liver-derived proteins (at least of the albumin size) leakage, fibrinolysis depression, excessive liver synthesis of plasma clotting cascade factors and platelet activation. Presented new data on the thrombogenesis at NS concerning the role of endothelial micro particles with high prothrombogenic activity that go from damaged glomerulus endothelial capillary cells into the systemic circulation, which can turn the local renal hyper coagulation (concomitant to the kidney immune inflammation process) into the generalized, working towards the thrombosis development. The most frequent adverse variants of arterial and venous thromboses are studied, specified their basic and general risk factors, as well as individual, varying in different patients. Indications and prophylactic anticoagulant therapy regimen and thrombosis treatment duration in patients with NS are discussed. It also stressed that the decision on time and method of anticoagulant therapy for a NS patients is still a challenge for healthcare providers.

Keywords: Nephrotic syndrome, thromboembolism, venous thrombosis, arterial thrombosis

Mini review article **Corresponding Author*, e-mail: *enasothman60@gmail.com*

1. Introduction

As an important part of physiological hemostasis, coagulation is a complex process involving a series of cascade reactions between coagulation factors, which finally transform fibrinogen into insoluble fibrin, causing blood clotting. Abnormalities in coagulation factors lead to coagulation disorders, resulting in thrombosis or the bleeding [1]. As a blood filter and the most highly perfused organ, the kidney plays an important role in regulating hemodynamics and blood components, which directly affects coagulation processes [2]. In fact, thrombosis is common in patients with nephrotic syndrome (NS) or CKD. While patients with the ESKD are threatened with bleeding [3]. However, improper anticoagulant or the pro coagulant therapies may induce adverse effects, such as the anticoagulation-related nephropathy (ARN), heparin-induced thrombocytopenia (HIT), or bleeding, which trouble clinicians [4]. Over the decades, conducted extensive mechanism studies on the crosstalk between the nephropathy and the coagulopathy, which provide guidance for the clinical treatment to some extent. However, the complex interactions between the kidney and the coagulation system are still not fully understood [5].

2. Mechanism of Thrombosis in NS

It was reported that complicated VTE in NS was mainly caused by the disorders of coagulation and fibrinolytic proteins, while arterial thromboembolism primarily resulted from platelet hyper reactivity. Disorders of the coagulation and fibrinolytic proteins were caused by the breakdown of the perm selectivity barrier of the glomeruli capillary wall in the kidney of patients with NS. Low molecular weight anticoagulant proteins were lost from altered glomeruli, whereas high molecular weight pro coagulant proteins (HMWPPs) were retained in the plasma. These processes led to a decrease in the total concentration of proteins that regulate the coagulation system, which enhanced the compensatory synthesis of both low molecular weight anticoagulant protein and the HMWPP. The net effect was the accumulation of the HMWPP in the blood, resulting in a hypercoagulable state that promoted thrombosis. Clinical data showed that the more severe the NS, higher incidence of thrombosis, which was consistent with above mechanism [6]. Nephrotic syndrome is characterized by coagulation impairment, due to the loss of the main circulating natural anticoagulant proteins of relatively low molecular weight, i.e., the antithrombin and protein S].

Conflicting data are available on plasma levels of protein C, another naturally occurring anticoagulant protein, in patients with nephrotic syndrome. The hypercoagulable state is enhanced by increased plasma levels of fibrinogen and other pro coagulant proteins, such as von Willebrand factor, factor VIII and factor V, that are retained by the kidney because of their high molecular weight. The pro thrombotic imbalance has also been confirmed by the increase of thrombin generation and fibrin deposition. Furthermore, it has been reported that in patients with nephrotic syndrome not only secondary but also primary hemostasis is impaired. Thrombocytosis is common, and an increased platelet reactivity, the presence of circulating platelets exposing the pro coagulant phosphatidylserine and an increased expression of activated glycoprotein IIb-IIIa on the platelet surface have been reported [7]. Platelet hyper reactivity in NS was mainly caused by hypoalbuminemia, hyperfibrinogenemia, and hypercholesterolemia. Hypoalbuminemia resulted from the loss of albumin (69kDa) from the altered glomeruli.

Physiologically, albumin inhibited platelet aggregation by binding to arachidonic acid and preventing its metabolism into thromboxane A2 (TXA2) and endoperoxides. As a consequence, hypoalbuminemia resulted in the excessive production of TXA2 and endoperoxides, leading to platelet hyper reactivity. In addition, hypoalbuminemia also led to the compensatory synthesis of fibrinogen and von Willebrand factors (vWFs) in the liver, resulting in hyperfibrinogenemia that promoted platelet hyper reactivity [8]. Hypercholesterolemia was one of metabolic consequences of NS, which was confirmed as promoter of platelet biogenesis and activation. It reported that in various hematopoietic effector cells, membrane receptor signaling pathways located in lipid enhanced in response to membrane cholesterol accumulation. Therefore, accumulation of cholesterol in plasma membrane enhanced platelet biogenesis in megakaryoblast and pro coagulant signaling transduction in platelets, which promote thrombosis. Indeed, numerous clinical studies detected increased platelet count and platelet hyperactivity in patients with NS, which confirmed important role of platelets in thrombosis in patients with NS [9].

3. Venous Thrombosis and Nephrotic Syndrome

In the clinical course of NS, every vein may be virtually affected by thrombosis, although most frequent sites are vessels of the lower extremities [10]. More rarely, other venous districts may be interested, such as renal vein, inferior vena cava, hepatic vein, and cerebral venous system [11]**.** A study based on a population with membranous glomerulonephritis observed thrombotic events in 7.2% of 898 patients. The only marker of thrombotic risk was serum albumin levels, with threshold level being 28 g/L and risk increasing by approximately twofold for every 10 g/L of albumin decrease below this threshold. Furthermore, the severity and duration of NS related to an increased risk of thrombosis, in particular for concentrations of serum albumin 20 g/L [12]. In 298 nephrotic patients, ratio of proteinuria to serum albumin was best predictor of VTE, demonstrating a correlation b/w symptomatic VTE and duration of NS, which remarkably elevated within first 6 months of disease [8].

4. Renal Vein Thrombosis and Nephrotic Syndrome

NS is associated with a high frequency of RVT and the mechanism of this association is not completely clear. The loss of fluid across glomeruli caused by a sustained reduction in blood volume could lead to decreased venous flow, explaining at least in part the higher frequency to develop thrombosis in renal veins than in other vessels. Thus, the resulting hemoconcentration in the postglomerular circulation may promote thrombus formation in renal veins. Severe dehydration and diuretic administration may increase the thrombotic risk, as contributory causes of this volume-dependent hypothesis [13]. The immune-dependent hypothesis is related to the nature and type of immunological injuries of nephropathies. Membranous glomerulonephritis, in which RVT develops more than in the other nephropathies, is paradigmatic. Circulating immune complexes have been identified in patients with membranous glomerulopathy and RVT, but not in those without thrombosis, as support of this theory. Therefore, these complexes may represent triggering factors of coagulation process [14]. In addition, patients with membranous glomerulonephritis have a six-fold increase in PAI levels but not in plasminogen activator, suggesting a suppression of fibrinolytic activity. Obviously, if volume-dependent and immune-dependent hypotheses are coexisting, the probability of developing the complication is higher, as frequently occurs in membranous glomerulopathy. RVT is insidious, usually discovered incidentally or during a workup for the source of a PE [15]. Unilateral or bilateral RVT has reported in approximately 25 to 30% of nephrotic patients with greatest incidence in membranous glomerulonephritis (37%), membranoproliferative glomerulone-phritis (26%), and minimal-change disease (24%) [16].

5. Arterial Thrombosis and Nephrotic Syndrome

Arterial thrombosis and their clinical complications are less well known because of the lower frequency compared with venous thrombosis. The most common arterial sites of throm-bosis are femoral arteries, and, more rarely, other arteries such as pulmonary, iliac, mesenteric, axillary, subclavian, brachial, carotid, brachiocephalic, ophthalmic, cerebral, meningeal, and coronary arteries. In NS patients, arterial thrombosis is often associated with steroids and diuretics administration. Steroids could increase factor VIII levels and other serum proteins, promoting the hypercoagulable state by different mechanisms [11]. The antiedema action of diuretics could induce water losses and a negative fluid balance. An abuse of these drugs represents an addictive risk for dehydration and the subsequent venous and arterial thrombosis. Moreover, hyperlipidemia could lead to lipid subintimal accumulation at level of previous arterial wall injury. Therefore, platelet clumping and adhesion promoted by elevated protein bound fatty acids may facilitate arterial thrombosis [12]. Higher absolute risk of symptomatic ATE is observed within first 6 months from the onset of NS. The ATE predictors are estimated glomerular filtration rate (GFR) and the other classic atherosclerosis risk factors [17].

6. Pulmonary Embolism and Nephrotic Syndrome

PE represents the most dangerous and potentially lethal complication of VTE, usually arising from the deep venous system of the lower extremities rather than renal veins. PE symptomatology may be variable, ranging from the classic presentation (pleuritic chest pain, shortness of breath, tachycardia, and hypoxia) to an asymptomatic event. In nephrotic patients, PE represents an unusual complication and the estimated prevalence of asymptomatic patients

ranging from 12 to more than 30%, with similar data in pediatric populations as well [16]. Study by Zaidi et al. [18], there was discussion of a number of techniques for identifying PTE in children, including angiography, gold standard for diagnosis; but, due to its intrusive nature, high cost, and radiation exposure, its application in pediatrics is restricted. Computed tomography angiography (CTA) is an additional non-invasive technique that requires little study time; nevertheless, individuals with abnormal kidney function should not use it. Final approach, called ventilation perfusion scans (V/Q) scan, is safe but includes a challenging testing procedure and aerosol inhalation. Consequently, in light of these investigations, it has recommended to utilize a chest X-ray (CXR) rather than ventilation.

7. Prophylactic and Therapeutic Anticoagulant Therapies in NS

Prophylactic and therapeutic anticoagulation is necessary for patients with NS, while thrombolytic therapy is only considered in patients with massive pulmonary embolism and severe bilateral deep vein thrombosis due to the high risk of bleeding. Low-molecular-weight heparin and warfarin are commonly used for prophylactic and therapeutic anticoagulation in patients with NS. But the advantages and disadvantages of these two drugs have not compared. With continuous accumulation of clinical data [19]. Antiplatelet agents employed prevent and treat thromboembolism in patients with NS. The KDIGO guideline indicate that suggested aspirin may be considered for patients with MN. However, patients with NS who are on anticoagulants face a risk of bleeding persists in patients with NS exposed to anticoagulants; thromboembolism risk of bleeding, which requires careful consideration of both thromboembolism and bleeding risks during anticoagulation therapy. As MN is the most common cause of NS, KDIGO provides an algorithm for formulation of prophylactic and therapeutic anticoagulant regimens for patients with MN, which might also be referenced for other pathological types of NS [20].

Faced with the current treatment dilemma, novel anticoagulants or antiplatelet drugs are urgently needed for patients with NS. Interestingly, statins in adults were proven to not only ameliorate kidney injury but also prevent thrombosis in patients with NS. These efficacies might come from the inhibitory effect of stains on hypercholesterolemia, which reversed cholesterol-induced platelet hyperreactivity, as described above. Given the dual therapeutic effects of statins on NS and thrombosis, it may be an ideal choice for antiplatelet in patients with NS. More clinical studies are needed to clarify the benefits and shortcomings of statins in preventing thrombosis [21]. In pediatrics patients with dyslipidemia alternative to statins, such as fibratesand omega -3 fatty acids are often recommended due to concerns about long term safety and potential side effects of statins in children. KDIGO2021 guidelines stress the importance of lifestyle modifications as first line of management this strategy aims to effectively manage lipid levels to minimizing risks of medication [22].

References

[1] M. Gui, B. Zhao, J. Huang, E. Chen, H. Qu, E. Mao. (2023). Pathogenesis and therapy of coagulation disorders in severe acute pancreatitis. Journal of Inflammation Research. 57-67.

[2] R.G. Evans, D.W. Smith, C.J. Lee, J.P. Ngo, B.S. Gardiner. (2020). What makes the kidney susceptible to hypoxia? The Anatomical Record. 303(10): 2544-2552.

[3] P. Garlapati, B. Gajjar, E.O. Then, V. Gayam. (2021). End-stage renal disease and lower gastrointestinal bleeding—A propensity-matched analysis of nationwide inpatient sample. International Journal of Clinical Practice. 75(2): e13633.

[4] A.-M. Hvas, E.J. Favaloro, M. Hellfritzsch. (2021). Heparin-induced thrombocytopenia: pathophysiology, diagnosis and treatment. Expert Review of Hematology. 14(4): 335-346.

[5] E.G. Pavlou, H.T. Georgatzakou, S.P. Fortis, K.A. Tsante, A.G. Tsantes, E.G. Nomikou, A.I. Kapota, D.I. Petras, M.S. Venetikou, E.G. Papageorgiou. (2021). Coagulation abnormalities in renal pathology of chronic kidney disease: the interplay between blood cells and soluble factors. Biomolecules. 11(9): 1309.

[6] Z. Qiu, X. Pang, Q. Xiang, Y. Cui. (2023). The Crosstalk between Nephropathy and Coagulation Disorder: Pathogenesis, Treatment, and Dilemmas. Journal of the American Society of Nephrology. 34(11): 1793-1811.

[7] A. Artoni, S.M. Passamonti, A. Edefonti, F. Gianniello, V. Civelli, I. Martinelli. (2016). Antithrombotic prophylaxis in a patient with nephrotic syndrome and congenital protein S deficiency. Italian Journal of Pediatrics. 42: 1-4.

[8] A. Gigante, B. Barbano, L. Sardo, P. Martina, M. L. Gasperini, R. Labbadia, M. Liberatori, A. Amoroso, R. Cianci. (2014). Hypercoagulability and nephrotic syndrome. Current vascular pharmacology. 12(3): 512-517.

[9] B. Eneman, E. Levtchenko, B. van den Heuvel, C. Van Geet, K. Freson. (2016). Platelet abnormalities in nephrotic syndrome. Pediatric Nephrology. 31: 1267-1279.

[10] N. Htike, K. Superdock, G. Teehan, S. Thiruveedi, W. Surkis. (2012). Evaluating proteinuria and nephrotic syndrome in patients with venous thromboembolism. The American journal of the medical sciences. 343(2): 124-126.

[11] A. Gigante, B. Barbano, G. Barilaro, S. Quarta, M.L. Gasperini, F. Di Mario, A. Romaniello, A. Amoroso, R. Cianci, E. Rosato. (2016). Serum uric acid as a marker of microvascular damage in systemic sclerosis patients. Microvascular Research. 106: 39-43.

[12] S. Lionaki, V.K. Derebail, S.L. Hogan, S. Barbour, T. Lee, M. Hladunewich, A. Greenwald, Y. Hu, C.E. Jennette, J.C. Jennette. (2012). Venous thromboembolism in patients with membranous nephropathy. Clinical Journal of the American Society of Nephrology. 7(1): 43-51.

[13] R. Singhal, K.S. Brimble. (2006). Thromboembolic complications in the nephrotic syndrome: pathophysiology and clinical management. Thrombosis research. 118(3): 397-407.

[14] A. Kakafika, E. Liberopoulos, D. Mikhailidis. (2007). Fibrinogen: a predictor of vascular disease. Current pharmaceutical design. 13(16): 1647-1659.

[15] J. Radhakrishnan. (2012). Venous thromboembolism and membranous nephropathy: so what's new? Clinical Journal of the American Society of Nephrology. 7(1): 3-4.

[16] L.J. Zhang, Z.J. Wang, C.S. Zhou, L. Lu, S. Luo, G.M. Lu. (2012). Evaluation of pulmonary embolism in pediatric patients with nephrotic syndrome with dual energy CT pulmonary angiography. Academic radiology. 19(3): 341-348.

[17] B.K. Mahmoodi, M.K. ten Kate, F. Waanders, N.J. Veeger, J.-L.P. Brouwer, L. Vogt, G. Navis, J. van der Meer. (2008). High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. Circulation. 117(2): 224-230.

[18] A.U. Zaidi, K.K. Hutchins, M. Rajpurkar. (2017). Pulmonary embolism in children. Frontiers in pediatrics. 5: 170.

[19] S. Kelddal, K.M. Nykjær, J.W. Gregersen, H. Birn. (2019). Prophylactic anticoagulation in nephrotic syndrome prevents thromboembolic complications. BMC nephrology. 20: 1-6.

[20] X. Li, X. Xie, Y. Zhao, G. Wang, H. Shao, X. Zhang. (2023). Some points for the KDIGO 2021 guideline for prophylactic anticoagulation in membranous nephropathy: is it clear enough for us to follow? Nephron. 147(3-4): 193-198.

[21] M. Resh, B.K. Mahmoodi, G.J. Navis, N.J. Veeger, W.M. Lijfering. (2011). Statin use in patients with nephrotic syndrome is associated with a lower risk of venous thromboembolism. Thrombosis research. 127(5): 395-399.

[22] C.Y. Cheung, J. Parikh, A. Farrell, M. Lefebvre, C. Summa-Sorgini, M. Battistella. (2021). Direct oral anticoagulant use in chronic kidney disease and dialysis patients with venous thromboembolism: a systematic review of thrombosis and bleeding outcomes. Annals of Pharmacotherapy. 55(6): 711-722.