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Evaluation of the level of antithrombin in patients with glomerulonephritis and nephrotic syndrome: A cross-sectional study

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Abstract. *The present study aimed to evaluate the level of antithrombin (AT)-III in blood serum in patients with primary glomerulonephritis (GN) and nephrotic syndrome (NS) and to assess its correlation with markers of NS and hypercoagulation.*

Methods. We conducted a cross-sectional observational study involving 76 patients with primary GN and NS admitted to the Ivano-Frankivsk Regional Clinical Hospital (Ukraine) in 2022–2024. The inclusion criteria were: age over 18 years, <1 month since the diagnosis of NS, and glomerular filtration rate (GFR) > 60 ml/min/1.73m^2. During the study, all patients underwent a standard examination, which included general clinical, biochemical, and instrumental research methods. A photometric assay of AT-III in serum using a chromogenic substrate was conducted with a set of reagents from "Granum" (Ukraine).

Results. Normal levels of AT-III were identified in 24 patients (31.6%; 95% CI: 21.4–43.3), while decreased levels were found in 52 patients (68.4%; 95% CI: 56.7–78.6). Correlation analysis revealed a direct moderate correlation between serum albumin levels and AT-III levels ($r = 0.535$, $p < 0.05$), an inverse moderate correlation between daily protein excretion (DPE) and AT-III levels ($r = -0.414$, $p < 0.05$), and an inverse moderate correlation between the albumin/creatinine ratio (ACR) in urine and AT-III levels ($r = -0.467$, $p < 0.05$).

Conclusions. In this cohort of patients with primary GN and NS, 68.4% exhibited decreased AT-III levels, indicating that AT-III deficiency is a common finding. The observed reduction in AT-III levels was significantly correlated with lower serum albumin levels, higher DPE, and higher ACR in urine. No significant association was found between AT-III deficiency and specific histological variants of GN, suggesting that the relationship between AT-III levels and hypercoagulopathy in GN and NS may be independent of the underlying glomerular pathology. The detected AT-III deficiency may warrant consideration for anticoagulant prophylaxis in patients with GN and NS. However, further studies are needed to determine whether AT-III levels can reliably guide anticoagulation therapy and reduce thromboembolic risk in this population.

Keywords: *glomerulonephritis, nephrotic syndrome, hypercoagulopathy, antithrombin III.*

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Оцінка рівня антитромбіну у хворих на гломерулонефрит з нефротичним синдромом: одномоментне обсерваційне дослідження

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Резюме. *Метою даного дослідження було оцінити рівень антитромбіну (АТ)-ІІІ у сироватці крові пацієнтів з первинним гломерулонефритом (ГН) та нефротичним синдромом (НС) та перевірити його кореляцію з маркерами НС та гіперкоагуляцією.*

Методи. Ми провели одномоментне обсерваційне дослідження за участю 76 пацієнтів із первинним ГН та НС, які були госпіталізовані в Івано-Франківську обласну клінічну лікарню (Україна) у 2022-2024 роках. Критерії для включення пацієнтів у дослідження: вік старше 18 років, менше 1 місяця від діагностики НС, швидкість клубочкової фільтрації (ШКФ) > 60 мл/хв/1,73 м^2. Під час дослідження всім пацієнтам проводили стандартне обстеження, яке включало загальноклінічні, біохімічні та інструментальні методи дослідження. Фотометричне визначення антитромбіну ІІІ у сироватці крові з хромогенним субстратом проводили за допомогою набору реактивів «Гранум» (Україна).

Результати. Нормальний рівень АТ-ІІІ діагностовано у 24 (31.6%; 95% CI 21.4-43.3) пацієнтів, знижений – у 52 (68.4%; 95% CI 56.7-78.6) пацієнтів. Після проведення кореляційного аналізу ми виявили прямий середньої сили кореляційний зв'язок між рівнем сироваткового альбуміну та рівнем АТ-ІІІ (r = 0,535, p < 0,05), зворотній середньої сили кореляційний зв'язок між добовою втратою білка (ДВБ) та рівнем АТ-ІІІ (r = -0,414, p < 0,05) та зворотній середньої сили кореляційний зв'язок між співвідношенням альбуміну до креатиніну (САК) у сечі та рівнем АТ-ІІІ (r = -0,467, p < 0,05).

Висновки. У 68,4% пацієнтів з первинним ГН та НС спостерігалось зниження рівня АТ-ІІІ, що вказує на поширеність дефіциту АТ-ІІІ серед цієї категорії пацієнтів. Зниження рівня АТ-ІІІ достовірно корелювало з нижчими рівнями сироваткового альбуміну, вищою ДВБ та підвищеним САК у сечі. Водночас, не було виявлено суттєвого зв'язку між дефіцитом АТ-ІІІ і гістологічними варіантами ГН. Виявлений дефіцит АТ-ІІІ може потребувати уваги під час розгляду питання антикоагулянтної профілактики у пацієнтів з ГН та НС. Однак для уточнення, чи можуть рівні АТ-ІІІ служити надійним індикатором для коригування антикоагулянтної терапії та зниження ризику тромбоемболій у цій популяції, необхідні подальші дослідження.

Ключові слова. *Гломерулонефрит, нефротичний синдром, гіперкоагуляція, антитромбін ІІІ.*

Introduction. Nephrotic syndrome (NS), typically characterised by massive proteinuria (over 3.5 g/day), hypoalbuminaemia, oedema and hyperlipidaemia, is a common presentation of many glomerular diseases [1]. NS is associated with an elevated risk of thromboembolic events (TE) leading to increased morbidity and mortality [2]. The incidence of TE in NS has been estimated to be 3–44% depending on the localization of thrombosis and the extent of the diagnostic screening [3]. The risk of TE is greatest within the first 3 months, although the risk remains elevated for more than 5 years [4].

Membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis (GN), membranous lupus nephritis with antiphospholipid antibody and amyloidosis are glomerular diseases with particularly high rates of venous thromboembolism [5]. Patients with an albumin level <25 g/l are at the highest risk, with a thromboembolic event rate of 8.5 per 1000 patient-years. Each 1.0 g/l reduction in serum albumin resulted in doubling the risk of venous thromboembolism [6].

The hypercoagulability in NS is not fully understood but has been ascribed to at least three different mechanisms. First, elevated thromboxane A2 may increase platelet activation and aggregation [7]. Second, urinary loss of natural anticoagulants such as antithrombin (AT)-III and protein S combined with increased hepatic synthesis of fibrinogen and coagulation factor V and VIII results in a prothrombotic state [3]. Finally, decreased plasmin levels due to urinary loss, in combination with increased plasminogen activator inhibitor-1 levels, result in decreased fibrinolytic activity [8].

Marked urinary AT-III loss resulting in acquired AT-III deficiency has often been proposed as an important mechanism underlying NS hypercoagulopathy [9]. Intuitively, this hypothesis is attractive because familial AT-III deficiency is the most severe heritable thrombophilia described to date [10].

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AT-III is a serine protease inhibitor (serpin) that physiologically inactivates thrombin (factor IIa) and factor Xa and, to a lesser extent, factors IXa, XIa, XIIa, tissue plasminogen activator, urokinase, trypsin, plasmin, and kallikrein. AT-III is an α2-globulin synthesized predominantly in the liver, has a half-life of approximately 2.4 days and a molecular weight of 58 200 Da, and contains 432 amino acids [11]. AT-III has a molecular weight similar to that of albumin and is lost in much the same manner [12]. AT-III physiologically circulates in a form that has a low inhibitory activity. The anticoagulant effect of AT-III is accelerated at least a thousand times in the presence of heparin and other heparin-like glycosaminoglycans, such as heparan sulfate [13].

Appropriate anticoagulation prophylaxis and timely treatment of thromboembolic events are crucial in improving outcomes in patients with NS [3]. The best anticoagulation for TE prevention in patients with NS remains unclear, even if the most used drug is low molecular weight heparin (LMWH) [14]. The therapeutic use of LMWH as an anticoagulant works through the potentiation of endogenous AT-III. Patients with AT-III deficiency may have resistance to therapy with LMWH and may require higher doses for the achievement of therapeutic-activated partial thromboplastin time and protective anticoagulation [15].

However, evidence directly assessing the contribution of AT-III deficiency to NS hypercoagulopathy is lacking. Some studies have attributed venous TE during NS to AT-III deficiency [10]. Others have reported venous TE despite normal AT-III levels [13]. We thus analyzed our data on AT-III deficiency in patients with primary GN and NS to evaluate its influence on NS hypercoagulopathy.

The aim of this study was to evaluate the level of antithrombin (AT)-III in blood serum in patients with primary glomerulonephritis (GN) and nephrotic syndrome (NS) and to check its correlation with markers of NS and hypercoagulation.

Materials and Methods. We conducted a cross-sectional observational study involving 76 patients with primary GN and NS admitted to the Ivano-Frankivsk Regional Clinical Hospital (Ukraine) in 2022-2024. The research was performed in accordance with international standards for the coordinated participation of respondents, the ethical component of research, and biomaterial collection (WMA Declaration of Helsinki – "Ethical Principles for Medical Research Involving Human Subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO)). The research protocol was approved by the local ethics committee of the Ivano-Frankivsk National Medical University. All patients signed a written informed consent to participate in the study. Also, 40 practically healthy individuals were selected comprising a comparison group and were representative of the main group.

Among the patients, there were 62 men (81.6%; 95% CI 71.0-89.5) and 14 women (18.4%; 95% CI 10.5-29.0). The average age of the patients was 45 (40; 49) years. The criteria for including patients in the study were: age over 18 years, <1 month from the diagnosis of NS, glomerular filtration rate (GFR) > 60 ml/min/1.73m^2. Exclusion criteria were: patient's refusal to participate in the study, age <18 years, systemic connective tissue diseases, systemic vasculitis, type 1 and type 2 diabetes, thromboembolic and cardiovascular events in history, chronic heart failure III-IV functional class (according to the NYHA classification), information about acute infectious processes of any etiology, oncological diseases, acute and chronic liver failure, mental disorders.

In all 76 patients the diagnosis of GN was confirmed morphologically as follows 23 patients (30.3%; 95% CI 20.2-41.9) were diagnosed with mesangioproliferative GN, 21 patients (27.6%; 95% CI 18.0-39.1) had membranous GN, 14 patients (18.4%; 95% CI 10.5-29.0) had focal segmental glomerulosclerosis, 11 patients (14.5%; 95% CI 7.5-24.4) had minimal change disease, and 7 patients (9.2%; 95% CI 3.8-18.1) was confirmed membrane proliferative (mesangiocapillary) GN.

Depending on the histological variant of GN, patients received pathogenetic treatment with glucocorticosteroids and cytostatics. All patients have been receiving treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. 48 (63.2%; 95% CI 51.3-73.9) patients have been receiving treatment with sodium-glucose cotransporter-2 inhibitors.

The clinical diagnosis was determined based on standard examination methods according to the Classification of Kidney Diseases and clinical practice guidelines for the management of glomerular diseases [16]. During the study, all patients underwent a standard examination, which included general clinical, biochemical, and instrumental research methods. Biochemical tests were performed in the laboratory of Ivano-Frankivsk Regional Clinical Hospital.

The GFR was determined using a CKD-EPI calculator. Daily protein excretion (DPE) was determined by the colorimetric method (Dialab, Wiener Neudorf, Austria). Photometric Assay of AT-III in serum with a Chromogenic Substrate was conducted with a set of reagents Granum (Ukraine).

STATISTICA 8 software (StatSoft, Serial STA862D175437Q) was used for statistical analysis. The frequency of qualitative indicators was presented as absolute (n) and relative (%) frequencies, along with the 95% confidence interval (CI) in the form of «n (%; 95% CI).» When analyzing quantitative data, the nature of the distribution of the indicator values was determined using the Shapiro-Wilk test. For quantitative data with a normal distribution, the results were presented as the mean value and standard deviation (M±SD). For quantitative data with an abnormal distribution, the median and 25-75 quartiles (Me (Q25-Q75)) were used. Quantitative indicators with a normal distribution in two independent groups were compared using Student's t-

test. Abnormally distributed data were compared using the Mann-Whitney test. A comparison of two independent groups for the qualitative indicator was conducted using Fisher's exact test.

Correlation analysis for quantitative indicators with normal distribution was performed using Pearson's correlation coefficient, while for abnormal distribution, Spearman's rank correlation coefficient was used to examine the relationships between ordinal or interval qualitative indicators and quantitative variables. The statistical significance of the correlation coefficients was established. The critical level of significance (p) for testing statistical hypotheses in this study was set at 0.05.

Results. Key demographic, clinical, and laboratory characteristics of the patients are summarized in Table 1. The patients were divided into two groups according to the level of AT-III, normal levels of AT-III (80-130 %) and low levels of AT-III (<80 %). Normal levels of AT were diagnosed in 24 (31.6%; 95% CI 21.4-43.3) patients, and decreased – in 52 (68.4%; 95% CI 56.7-78.6) patients.

Table 1

Characteristics of patients with GN and NS according to the levels of AT-III

	The group of AT in the normal range (n = 24)	**The group of decreased levels of AT (n = 52)**	***p*-value**
Age, years (Me (Q25-Q75)	41 (35; 47)	43 (38; 50)	p =0.83
Sex, male (%; 95% CI)	79.2 (57.8-92.9)	82.7 (69.7-91.8)	p = 0.75
Sex, female (%; 95% CI)	20.8 (7.1-42.2)	17.3 (8.2-30.3)	p = 0.75
GFR ml/min/1.73 m2 (Me (Q25-Q75)	72 (63; 89)	75 (64; 92)	p = 0.67
Albumin levels, g / l (Me (Q25-Q75)	27.4 (22.3; 29.7)	22.4 (18.1; 24.4)	p <0.05
DPE g / day (Me (Q25-Q75)	4.2 (3.8; 4.6)	5.5 (4.9; 6.3)	p <0.05
ACR mg / g (Me (Q25-Q75)	2376 (2231; 2619)	2885 (2596; 3178)	p <0.05
Mesangioprolifera-tive GN (%; 95% CI)	33.3 (15.6-55.6)	28.9 (17.1-43.1)	p = 0.78
Membranous GN (%; 95% CI)	33.3 (15.6-55.6)	25.0 (14.0-38.9)	p = 0.58
Focal segmental glomerulosclerosis (%; 95% CI)	16.7 (4.7-37.4)	19.2 (9.6-32.5)	p = 1.00
GN with minimal changes (%; 95% CI)	12.5 (2.7-32.4)	15.4 (6.9-28.1)	p = 1.00
Mesangiocapillary GN (%; 95% CI)	4.2 (0.1-21.1)	11.5 (4.4-23.4)	p = 0.42
AT III, % (Me (Q25-Q75)	98 (85; 104)	65 (54; 76)	p <0.001
D-dimer, mg/L, (Me (Q25-Q75)	0.32 (0.16; 0.43)	1.56 (1.02; 2.23)	p <0.05
Platelet Count (*109/L), (Me (Q25-Q75)	238 (187; 289)	257 (212; 310)	p = 0.86
INR, (Me (Q25-Q75)	0.9 (0.8;1.0)	1.0 (0.9; 1.1)	p = 1.00
APTT (s), (Me (Q25-Q75)	43 (38; 48)	46 (41; 50)	p = 0.78
PT (s), (Me (Q25-Q75)	13 (11; 15)	12 (11;14)	p = 1.00
Fibrinogen (g/L), (Me (Q25-Q75)	2.3 (1.8; 3.4)	4.6 (3.8; 5.2)	p <0.05

Abbreviations: *ACR – albumin/creatinine ratio, CI – confidence interval, DPE – daily protein excretion, GFR – glomerular filtration rate; INR – international normalized ratio; APTT – activated partial thromboplastin time; PT – prothrombin time; Me (Q25-Q75) – median and quartiles*

As shown in Table 1, decreased levels of AT-III were associated with decreased serum albumin levels, increased daily protein excretion (DPE), and increased albumin/creatinine ratio (ACR). Also, decreased levels of AT-III were associated with increased levels of D-dimer and fibrinogen in serum. On the other hand, we did not observe a statistically significant difference between the international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin time (PT), and platelet count in two groups of patients ($p > 0.05$).

After conducting correlation analysis, we found a direct average correlation between serum albumin levels and AT-III levels ($r = 0.535$, $p < 0.05$) (Fig. 1), an inverse average correlation between the DPE and AT-III levels ($r = -0.414$, $p < 0.05$, (Fig. 2), an inverse average correlation between the ACR and AT-III levels ($r = -0.467$, $p < 0.05$) (Fig. 3).

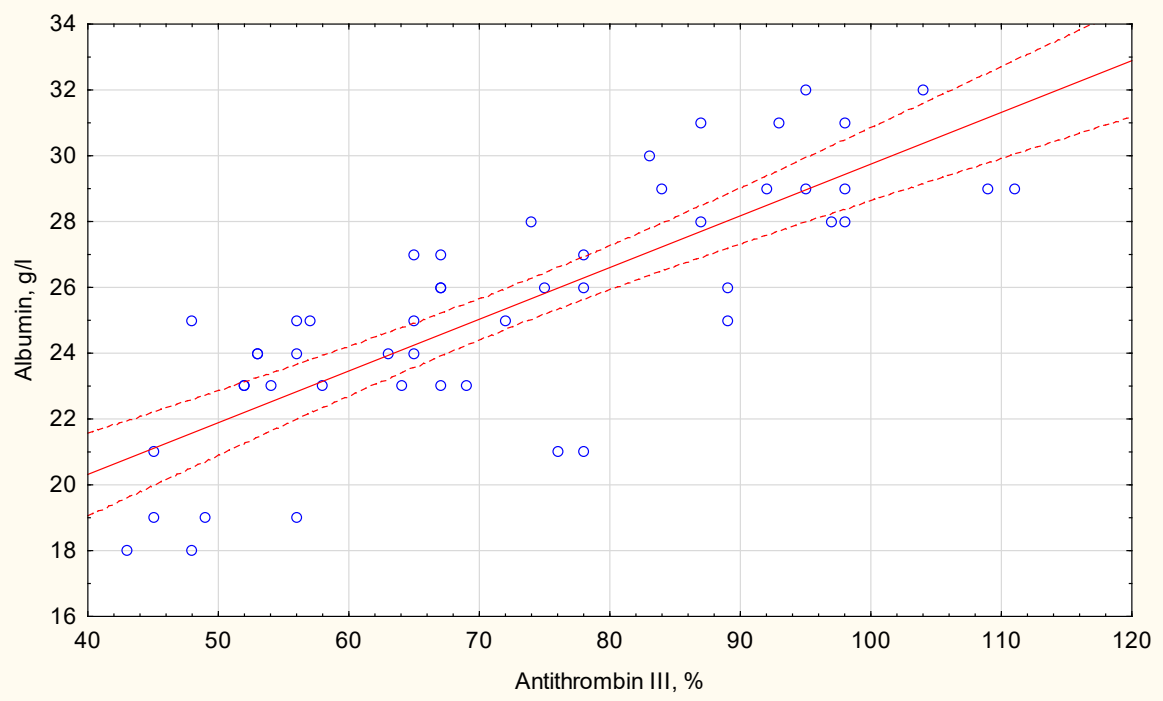

Fig. 1. The correlation between serum albumin and AT-III levels in the study cohort.

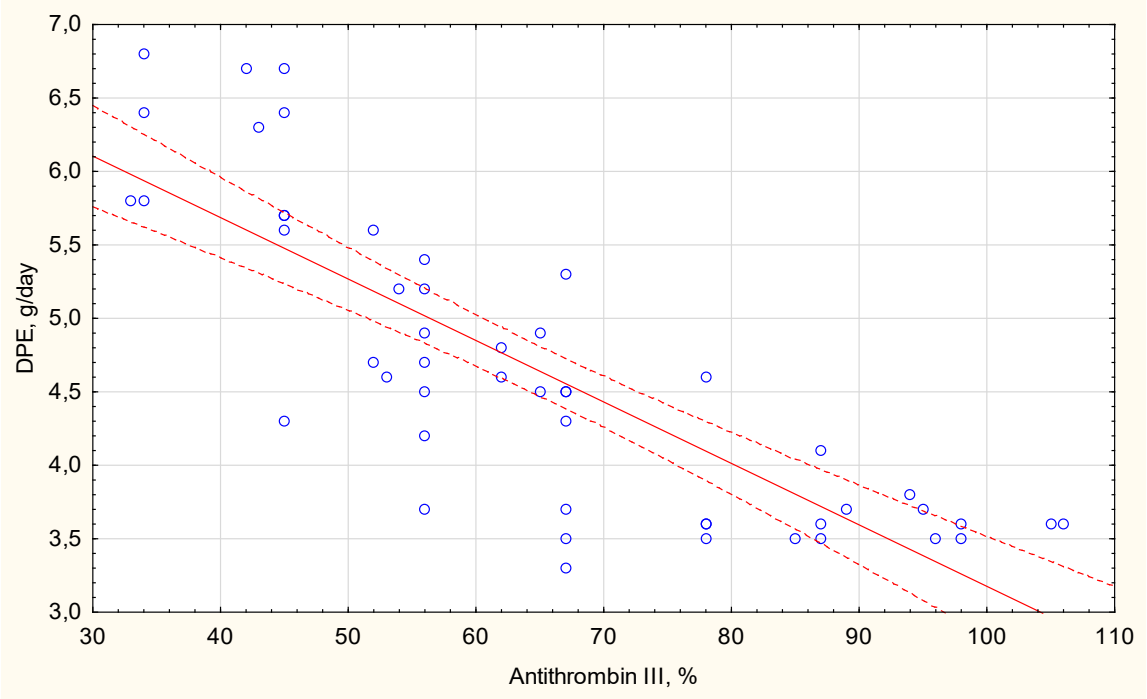

Fig. 2. The correlation between daily protein excretion (DPE) and AT-III levels in the study cohort.

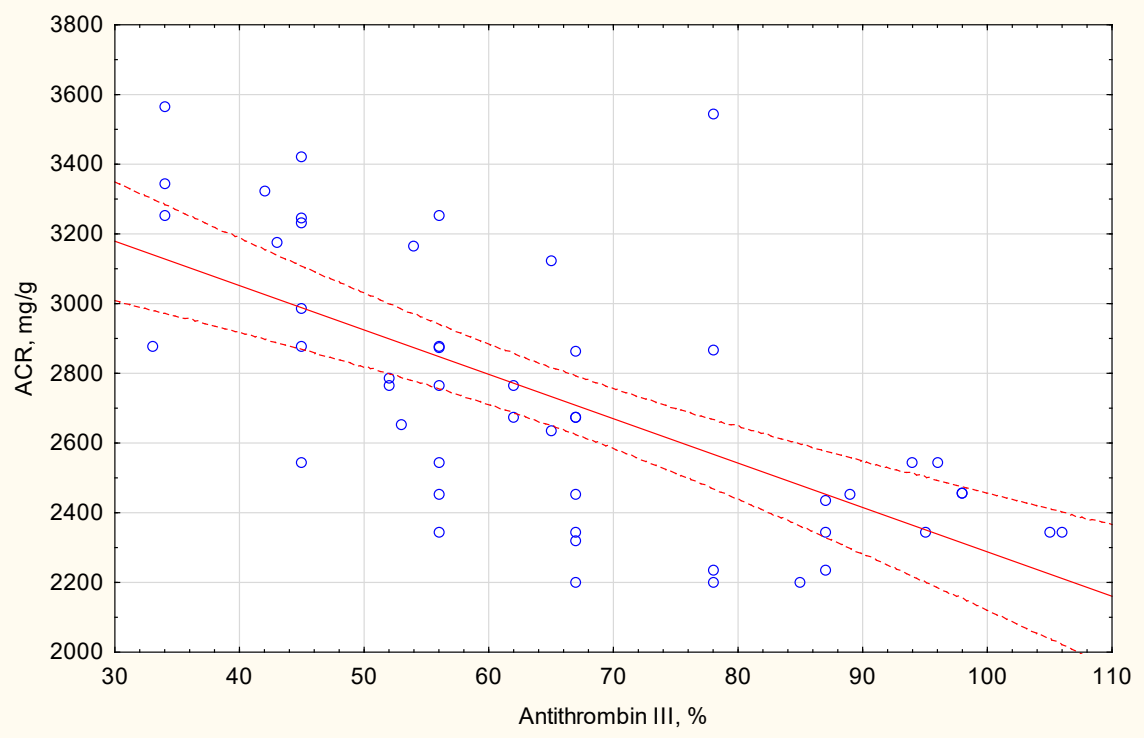

Fig. 3. The correlation between albumin/creatinine ratio (ACR) AT-III levels in the study cohort.

We also found an inverse average correlation between D-dimer and AT-III levels ($r = -0.615$, $p < 0.05$) and an inverse average correlation between fibrinogen and AT-III levels ($r = -0.524$, $p < 0.05$).

There were more men than women in both groups, but the difference was not statistically significant ($p>0.05$). We did not note the relationship between AT-III deficiency and the histological variant of GN ($p>0.05$), which suggests that other factors contribute to the increased risk of TE in membranous GN and focal segmental glomerulosclerosis.

Discussion. The pathophysiology underlying NS hypercoagulopathy is likely multifactorial, but acquired AT-III deficiency secondary to urinary AT-III loss has been postulated to have a prominent mechanistic influence [12]. However, there are conflicting data linking nephrotic syndrome–associated AT-III deficiency to both venous TE and hypercoagulopathy [13]. This study was thus designed to evaluate the relationships between AT-III deficiency and NS disease markers.

Decreased AT-III level at the onset of NS has been confirmed by many studies [17]. Wygledowska et al observed that the activity of protein S and AT-III were significantly decreased at the onset of NS as compared with the control group and increased during the remission state [18]. In this study plasma AT-III levels correlated well with serum albumin, which is compatible with our findings. This relationship is explained by the molecular weight and charge of AT-III that are similar to those of albumin [13]. Elidrissy et al showed that during relapse NS urine AT-III levels were increased, while during remission no AT-III was detected in urine [19].

Kauffmann et al. investigated the relationship between the AT-III value and TE in 48 patients with varying degrees of proteinuria. Nine of these patients had clinical signs of thrombosis and the AT-III value was below 70% in eight cases. There was a significant negative correlation between the AT-III value and urinary protein excretion. AT-III was noted in the urine of 32 of 42 patients in whom it was measured [10].

An increased incidence of TE has been reported with AT-III levels lower than 75% [20]. However, TE complications also occur in patients with normal AT III levels and NS, indicating that although AT-III is a major determinant of plasma antithrombin activity, it is not the only one, because other regulatory proteins of the coagulation cascade play a role [18].

Abdelghani et al found that AT-III deficiency below a clinically accepted threshold was identified in a substantial portion of NS patients. However, AT-III levels were not strongly associated with either proteinuria or hypoalbuminemia severity. These data suggest that while AT-III levels may be a biomarker of NS hypercoagulopathy, AT-III deficiency plays only a limited role in nephrotic NS hypercoagulopathy [13].

However, emerging evidence suggests that AT-III may play an important role in maintaining healthy vascular endothelium via signaling properties that are independent of its coagulation inhibitor function. It is thus possible that AT-III deficiency may drive NS-associated TE risk via vascular mechanisms. Further exploration of this phenomenon will likely require endothelial cell-specific analyses [9].

Several studies have now shown that thrombin generation assays are a useful tool to measure hyperco-

agulopathy and may be helpful in identifying patients at risk for both incident and recurrent venous TE [21]. Meanwhile, other studies have demonstrated a relationship between thrombin generation and AT-III deficiency [20]. A recent study demonstrated that AT-III levels were associated with thromboelastography-determined hypercoagulopathy in adult NS [13].

It is clear that no single factor can explain the hypercoagulability state in patients with GN and NS. The predisposition to thrombosis is probably dependent on the balance between procoagulant and anticoagulant factors. If facilities are available, one should perform a detailed coagulogram including the definition of AT-III level.

Limitations. The sample size in this study is small. Larger sample sizes, long-term clinical trials, and the consideration of a greater number of procoagulant and anticoagulant factors are needed to accurately determine the impact of AT-III on the occurrence of hypercoagulation and thromboembolic (TE) events in patients with GN and NS, in order to draw more valid conclusions.

Conclusions:

1. In the studied cohort of patients with primary GN and NS, 68.4% demonstrated decreased levels of AT-III, indicating that AT-III deficiency is a common finding.
2. The observed decrease in AT-III levels was significantly correlated with lower serum albumin levels, higher daily protein excretion (DPE), and a higher albumin-to-creatinine ratio (ACR) in urine.
3. No significant association was found between AT-III deficiency and specific histological variants of GN, suggesting that the relationship between AT-III levels and hypercoagulopathy in GN and NS may be independent of the underlying glomerular pathology.
4. The detected AT-III deficiency may warrant consideration of anticoagulant prophylaxis in patients with GN and NS. However, further studies are needed to determine whether AT-III levels can reliably guide anticoagulation therapy decisions and reduce thromboembolic risk in this population.

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Information about the contribution of the authors.

I. Mykhaloiko: literature search, study design planning, data analysis, manuscript writing, and submission;

R. Yatsyshyn: concept and management of the work;

I. Dudar: concept and management of the paper.

H. Kuryliv: curation of patients, formation, and work with the database.

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