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Crosstalk between proteinuria, plasma oxalic acid and inflammation in glomerulonephritis patients: an exploratory study

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Abstract. *In the present exploratory cross-sectional cohort study, we evaluated whether plasma and urine oxalate concentrations in patients with primary glomerulonephritis depend not only on the glomerular filtration rate but also on the proteinuria level and influence the inflammatory response.*

Methods. We enrolled 100 participants, including 76 patients with glomerulonephritis having chronic kidney disease stage (CKD) 1–3b (69.7% of them with nephrotic syndrome) and 24 healthy volunteers. We excluded patients with diabetes, cardiovascular disease and those with glomerulonephritis with an estimated GFR (eGFR) < 30 mL/min/1.73 m2. In addition to routine hematological and biochemical tests, plasma oxalate concentration, urinary oxalate excretion, and serum interleukin (IL)-6 and monocyte chemoattractant protein-1 (MCP-1) levels were assessed in all study participants.

Results. We observed that plasma oxalic acid concentration was significantly higher in patients with glomerulonephritis (19.0 [5.9–45.2] μmol/L) than in healthy volunteers (5.5 [3.8–7.3] μmol/L, p < 0.0001). Moreover, nephrotic proteinuria was significantly associated with plasma oxalic acid elevation independent of the patients' age, sex, glomerular filtration rate, and body mass index (odds ratio = 1.42, 95% confidence interval = 1.13–1.77, p = 0.002). In turn, the increased plasma oxalic acid concentration was associated with high levels of serum IL-6 and MCP-1, which may be cardiovascular risk factors in patients with primary glomerulonephritis.

Conclusions. Nephrotic proteinuria was significantly associated with the elevation of plasma oxalic acid concentration and hyperoxaluria in glomerulonephritis patients with CKD stages 1–3b. Plasma oxalate at least partly promotes inflammation, which may be a cardiovascular risk factor in patients with glomerulonephritis in the early stages of CKD. Future studies should recruit at least 156 participants to confirm our preliminary results, validate nephrotic proteinuria as a risk factor for oxalate metabolism violation or determine the role of impaired oxalate homeostasis in clinical outcomes in patients with glomerulonephritis.

Keywords: *glomerulonephritis, proteinuria, oxalate, hyperoxaluria, inflammation, interleukins.*

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Взаємозв'язок між протеїнурією, оксаловою кислотою сироватки та запаленням у пацієнтів з гломерулонефритом: попереднє дослідження

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Резюме. *У цьому обсерваційному поперечному когортному дослідженні ми попередньо оцінили (1) чи залежить концентрація оксалату у плазмі та сечі пацієнтів з гломерулонефритом не тільки від швидкості клубочкової фільтрації, але також від рівня протеїнурії та (2) чи впливає порушення оксалатного метаболізму на стан хронічного запалення.*

Методи. До дослідження залучено 100 учасників, у тому числі 76 пацієнтів з хронічною хворобою нирок (ХХН) 1–3b стадії: гломерулонефрит (69,7% з них мали нефротичним синдром) та 24 здорових добровольця. Цукровий діабет та швидкість клубочкової фільтрації (ШКФ) < 30 мл/хв/1.73 м2 були критеріями виключення з дослідження. Окрім звичайних гематологічних та біохімічних тестів, у всіх учасників дослідження оцінювали концентрацію оксалової кислоти крові, екскрецію оксалату з сечею, а також рівень інтерлейкіну (ІЛ) -6 та моноцитарного хемоаттрактантного протеїну-1 (МХП-1) у сироватці крові.

Результати. Визначено, що концентрація щавлевої кислоти у плазмі крові була значно вищою у пацієнтів з гломерулонефритом (19,0 [5,9–45,2] мкмоль/л), ніж у здорових добровольців (5,5 [3,8–7,3] мкмоль/л, p <0,0001). Більш того, нефротична протеїнурія була значною мірою асоційована з підвищенням рівня щавлевої кислоти крові незалежно від віку, статі, ШКФ та індексу маси тіла (відношення шансів = 1,42; 95% довірчий інтервал = 1,13–1,77, p = 0,002). У свою чергу, підвищена концентрація щавлевої кислоти крові асоціювалась з високим рівнем ІЛ-6 та МСР-1, що може бути одним з факторів серцево-судинного ризику у пацієнтів з первинним гломерулонефритом.

Висновки. Протеїнурія нефротичного рівня асоційована з підвищенням концентрації оксалової кислоти крові та гіпероксалурією у хворих на ХХН 1–3b. Щавлева кислота крові, принаймні частково, сприяє розвитку хронічного запалення, що може бути фактором ризику серцево-судинних захворювань у пацієнтів з гломерулонефритом на ранніх стадіях ХХН. Майбутні дослідження мають включати щонайменше 156 учасників для підтвердження наших попередніх результатів, підтвердження нефротичного рівня протеїнурії як фактора ризику порушення оксалатного метаболізму або визначення ролі порушення гомеостазу оксалатів у клінічних наслідках пацієнтів з гломерулонефритом.

Ключові слова: *гломерулонефрит, протеїнурія, оксалат, гіпероксалурія, запалення, інтерлейкіни.*

Introduction. In the past decade, accumulating evidence has suggested the role of oxalate in oxidative stress [1], inflammation [1, 2], atherosclerotic dyslipidemia/cardiovascular diseases (CVD) [3, 4], chronic kidney disease (CKD) progression [5, 6], and renal allograft failure [7]. Elevated plasma oxalic acid (POx) concentration has been considered as a surrogate marker of systemic oxalosis and kidney function decline in primary hyperoxaluria and advanced CKD patients [8]. Moreover, 2 recently published studies have demonstrated that POx could predict end-stage kidney disease in primary hyperoxaluria patients with CKD stages 2–3b [9, 10]. However, POx concentration has never been studied in non-primary hyperoxaluria patients with earlier stages of CKD, particularly in glomerulonephritis (GN) patients.

Severe proteinuria (>500 mg/24-h) is a proven indicator of glomerular damage and the major risk factor for rapid CKD progression and cardiovascular morbidity and mortality [11-13]. In addition, proteinuria is the most common clinical finding in patients with secondary oxalate nephropathy (up to 69%) [14]. Currently, it has been demonstrated that similar to glomerular diseases [15, 16], podocyte and tubular injuries are involved in the oxalate-induced proteinuria pathway [17]. In this context, we hypothesized that plasma and urine oxalate concentrations in patients with GN may depend not only on the glomerular filtration rate (GFR) but also on the proteinuria level and influence the inflammatory response. Therefore, this exploratory study assessed whether (i) POx concentration and urinary oxalate (UOx) excretion in patients with GN differ depending on the proteinuria level and (ii) elevated POx influences chronic inflammation in patients with GN.

Methods. This exploratory cross-sectional cohort study was a part of an ongoing Institute project: "Effect of oxalate and urate metabolism on the evolution of kidney disease" (ClinicalTrials.gov Identifier: NCT04399915) conducted at the Institute of Nephrology of the National Academy of Medical Science of Ukraine between January 2020 and January 2021. The

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study protocol was approved by the Ethics Committee of the Institute. Written informed consent was obtained from all participants before enrolment.

Sample Size. The sample size was estimated using MedCalc Statistical Software (Ostend, Belgium) based on the study by Marangella et al. [**18**]. A minimum sample size of 21 participants per group was required to achieve a power of 0.95, detecting differences in plasma and urine oxalate concentrations at a significance level of 0.05 between the groups using the Student's t-test or the nonparametric Mann–Whitney test. Similarly, a minimum sample size of 23 participants was required to achieve a power of 0.80 and an alpha of 0.05 in the correlation analysis. Considering the recommended sample size of at least 50 participants for a pilot study [**19**], at least 50 patients with PGN and nephrotic syndrome (NS) were considered necessary.

Participants. We eventually enrolled 100 participants, including 76 patients with GN with CKD stages 1–3b (average age: 41 ± 1.83 years) and 24 healthy volunteers on a free-choice diet who served as a control group to evaluate POx concentration. We excluded patients with diabetes, CVD and those with PGN with an estimated GFR (eGFR) < 30 mL/min/1.73 m^2.

Laboratory measurements. In addition to routine hematological and biochemical tests, POx concentration, UOx excretion, and serum interleukin (IL)-6 and monocyte chemoattractant protein-1 (MCP-1) levels were assessed in all study participants. POx was measured spectrophotometrically by using a commercially available kit (MAK315, Sigma, Barcelona, Spain). Daily UOx excretion was determined using an oxalate oxidase/peroxidase reagent (BioSystems, Barcelona, Spain). IL-6 and MCP-1 concentrations were detected using STAT FAX-303 PLUS and commercially available ELISA test kits (Diaclon, Besancon, France; DRG, Marburg, Germany), according to the manufacturer's protocols. Urinary protein excretion (UPE) was measured using a 24-h urine collection; eGFR was calculated using the CKD-EPI formula. Body mass index (BMI) was calculated as weight in kg/(height in m^2). All clinical and laboratory data were measured at the time of renal biopsy (before the start of immunosuppressive therapy) or the first patient's admission to the clinic with a newly clinically confirmed diagnosis of GN.

Statistical analysis. The statistical analysis and graphs were performed using MedCalc. Data are represented as mean (M) and standard deviations (SD) or median (Me) and interquartile range (Q25-Q75), depending on whether they were normally or nonnormally distributed, respectively, and analyzed using the Student's t-test and the nonparametric Mann–Whitney test, respectively. Categorical variables are expressed as proportions and were compared using the chi-square ($\chi 2$) test. The Spearman correlation test, partial rank correlation coefficient, and logistic regression analysis were used to explore associations between the examined markers. Given the multicollinearity of POx with patients' age, sex, eGFR, and BMI, these variables were included in the logistic regression analysis as possible confounders. Because of the exploratory nature of the study, no other confounders were included in the logistic regression model. Finally, the effect size in the post hoc test was computed using G*Power software (version 3.1.9.4) to determine the probability of a type I error and calculate the required sample size for future large-scale research [**20**].

Cases with missing data on any variable used in the analyses were excluded.

Results. Among the 76 patients with GN, 53 (69.7%) had NS and biopsy-proven PGN and 23 (30.3%) had a clinical diagnosis of GN. The detailed patient characteristics are presented in Table 1.

Table 1

Demographic and clinical characteristics of the healthy volunteers and the GN patients according to the NS status

Parameters	Healthy volunteers (n = 24)	A total of GN patients (n = 76)	Patients with nephrotic proteinuria (n = 53)	Patients with mild proteinuria (n = 23)	p-value between PGN groups
Male gender, n (%)	11 (45.8%)	37 (48.7%)	30 (56.6%)	7 (30.4%)	0.002
Age, years	38 ± 13.83	41 ± 11.83	38.1 ± 14.6	44.3 ± 13.2	0.601
CKD vintage at the study entry, months	-	8.0 (4.0-25)	5.5 (2.5-7.0)	11.0 (5.0-28.0)	0.073
eGFR, mL/min/1.73m2	82.0 (73.0-87.8)*	64.1 (34.7-84.3)	68.5 (36.5-86.5)	54.2 (34.1-76.3)	0.131
BMI, kg/m2	24.1 (20.5-27.2)	23.8 (21-25.3)	22.9 (20.7-29.3)	24.2 (20.5-26.0)	0.303
Renal biopsy findings after enrollment					
IgA nephropathy, n (%)	-	-	5 (9.4%)	-	
Minimal change disease, n (%)	-	-	14 (26.4%)	-	
Focal segmental glomerular sclerosis 'NOS', n (%)	-	-	6 (11.3%)	-	
Focal segmental glomerular sclerosis 'tip', n (%)	-	-	17 (32%)	-	
Membranous GN, n (%)	-	-	7 (13.2%)	-	
Immunoglobulin and complement-mediated glomerular diseases, n (%)	-	-	4 (7.5%)	-	
Clinical parameters					
Diuresis, mL/24-h	2375 ± 460*	1375 ± 764	1142 ± 730	1490 ± 608	0.048
UPE, g/d	0.08 (0.05-0.11)	4.99 (3.08-9.1)	5.9 (4.3-9.4)	1.9 (0.8-2.6)	<0.001
Cr, µmol/L	68.3 (57.2-97.5)*	113.1 (88.7-207.2)	104.1 (88.1-202.1)	118 (88.6-231.7)	0.597
Ur, mmol/L	4.95 (3.7-6.3)*	5.6 (3.4-12.3)	5.6 (3.6-10.1)	7.9 (2.5-18.6)	0.741
Serum albumin, g/L	43.4 (41.1-45.1)*	31.8 (26.2-39.1)	30.7 (25.7-36.8)	37.1 (35.2-41.4)	0.003
Total blood protein, g/L	69.6 ± 4.7*	53.2 ± 12.5	51.3 ± 12.9	58.6 ± 10.8	0.041
Systolic blood pressure, mm Hg	115 (100-125)*	123 (117-140)	127.5 (120-148)	120 (113-132)	0.153
Diastolic blood pressure, mm Hg	79.0 (66.2-82.0)*	84.0 (75-92)	85 (76.5-92)	80 (75-90)	0.212

Continuation of Table 1

Parameters	Healthy volunteers (n = 24)	A total of GN patients (n = 76)	Patients with nephrotic proteinuria (n = 53)	Patients with mild proteinuria (n = 23)	p-value between PGN groups
Hb, g/L	129.3 ± 11.5	130.1 ± 26.8	131.8 ± 29.3	126.9 ± 21.5	0.482
Glucose, mmol/L	5.3 (4.9-5.5)	5.03 (4.6-5.5)	4.9 (4.6-5.3)	5.1 (4.8-5.6)	0.723
Calcium, mmol/L	2.4 (2.3-2.5)	2.23 (2.1-2.35)	2.21 (2.11-2.34)	2.38 (2.12-2.37)	0.441
Phosphorus, mmol/L	1.1 ± 0.1*	1.35 ± 0.33	1.37 ± 0.42	1.31 ± 0.49	0.583
Potassium, mmol/L	4.38 (4.1-4.9)	4.5 (4.08-4.8)	4.4 (4.1-4.7)	4.6 (4.2-5.1)	0.084
Uric acid, mmol/L	266 (162.8-375.6)*	362.5 (269.8-464.1)	364.6 (261.4-441.5)	396.3 (271.8-551.7)	0.192
TC, mmol/L	4.9 ± 0.96*	7.7 (5.7-10.4)	8.7 (6.1-11.6)	5.8 (5.2-6.6)	0.031
Triglyceride, mmol/L	1.1 (0.8-1.6)*	1.99 (1.27-2.56)	2.1 (1.6-2.8)	1.7 (1.08-2.4)	0.107
Oxalate balance parameters					
POx, μmol/L	5.5 (3.8-7.3)*	19.0 (5.9-45.2)	37.0 (16.4-63.1)	20.5 (13.9-34.1)	<0.001
UOx, mg/24-h	55.2 (43.4-58.6)	48.1 (39.2-68.4)	43.9 (34.7-56.9)	48.1 (39.1-64.4)	0.285
Pro-inflammatory markers					
CRP, mg/L	4.9 (3.7-9.9)*	9.3 (5.9-21.5)	10.8 (7.4-20.2)	8.8 (5.2-24.1)	0.922
IL-6, pg/mL	0	0.21 (0.11-0.47)	0.23 (0.15-0.48)	0.16 (0.09-0.39)	0.202
MCP-1, pg/mL	68.9 (62.1-80.2)	76.7 (51.5-105.2)	76.7 (56.5-105.5)	74.6 (45.9-149.2)	0.914
Medications, n (%)					
ACE inhibitors / RAAS blockers	-	72 (94.7%)	51 (96.2%)	21 (91.3%)	0.383
Beta blockers	-	18 (23.7%)	14 (26.4%)	4 (17.4%)	0.399
Diuretics	-	47 (61.8%)	38 (71.7%)	9 (39.1%)	0.007
Erythropoietins	-	16 (21.0%)	10 (18.9%)	6 (26.1%)	0.482
Phosphate binders	-	8 (28.0 %)	3 (5.7%)	5 (21.7%)	0.038
Lipid-lowering therapy	-	6 (7.9%)	2 (3.8%)	4 (17.4 %)	0.045

The values are expressed as mean ± standard deviation (M ± SD) or as the median and interquartile range [Me (Q25-Q75)]. The values are compared between the groups using the Chi-square tests, the Student's t-test and the Mann–Whitney U test as appropriate.

* $p<0.05$ vs a total of PGN patients' group.

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CKD, chronic kidney disease; Cr, serum creatinine; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; RAAS, renin-angiotensin-aldosterone system; TC, total cholesterol; UPE, urine protein excretion; Ur, serum urea.

POx concentration was significantly higher in patients with GN (19.0 [5.9–45.2] μmol/L) than in healthy volunteers (5.5 [3.8–7.3] μmol/L, p < 0.0001). Although the eGFR did not differ between the patients with NS and mild proteinuria, patients with nephrotic proteinuria had significantly high POx concentrations than those with mild proteinuria (Fig. 1a). POx concentration was significantly negatively associated with eGFR (r = -0.27, p = 0.005) and had a direct correlation with UPE level (r = 0.29, p = 0.011) (Fig. 1b).

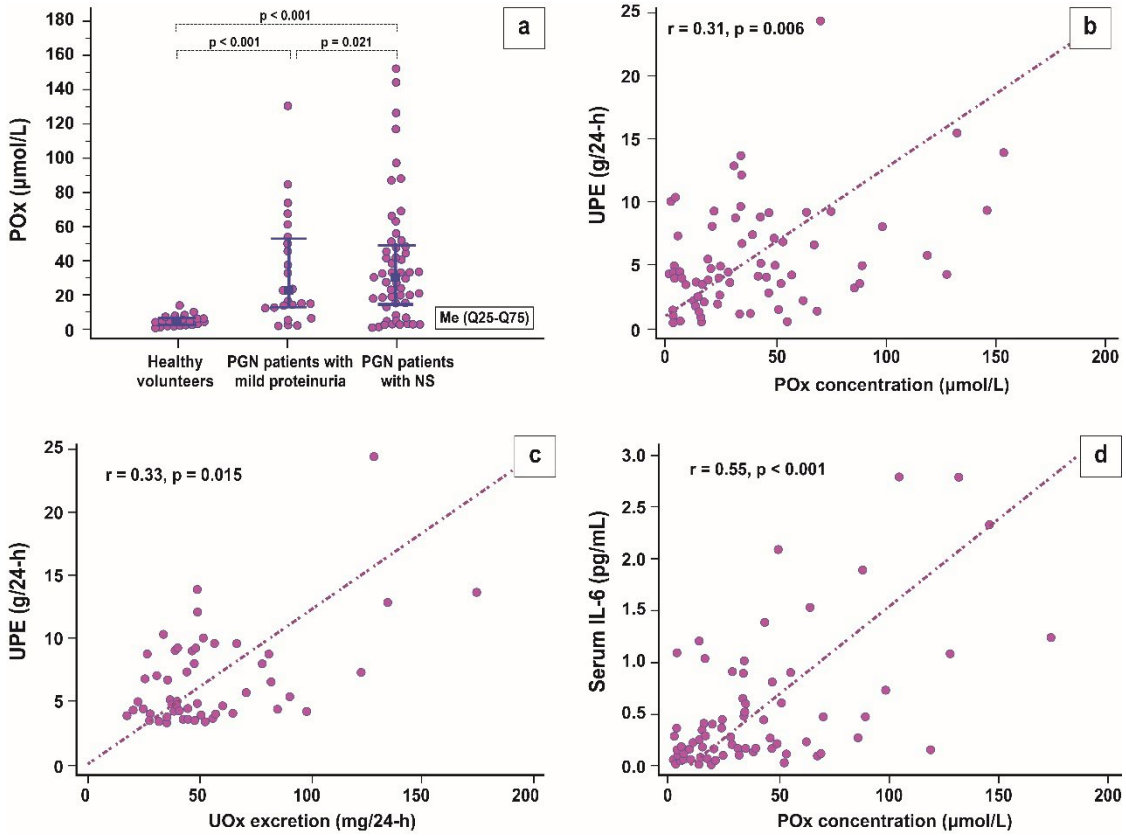

Fig. 1. Oxalate homeostasis in patients with GN: (a) POx concentration in healthy volunteers and patients with GN stratified by the presence of NS; (b) Association between UPE and POx concentrations in patients with GN; (c) Association between urinary protein and oxalate excretions in patients with GN with NS; (d) Association between serum IL-6 and POx concentrations in patients with GN.

Abbreviations: IL-6, interleukin 6; NS, nephrotic syndrome; PGN, primary glomerulonephritis; POx, plasma oxalic acid; UOx, urinary oxalate; UPE, urinary protein excretion.

Partial correlation analysis reveals a moderate association between UPE and POx concentration (r = 0.34, p = 0.01) independent of the patients' age, sex, BMI, and eGFR levels. The logistic regression result suggested a significant association between nephrotic-ranged UPE and the risk of hyperoxalaemia (Odds ratio = 1.42, 95% confidence interval = 1.13–1.77, adjusted p = 0.002). However, the post hoc power analysis demonstrated a low power (1-β error probability) of 0.48 for detecting nephrotic-range proteinuria as a risk factor for hyperoxalaemia in patients with PGN, implying a false-positive result. A minimum sample of 156 patients was required to observe a statistically significant association in the logistic regression analysis with an alpha of 0.05 (two-tailed) and a power of 0.95.

No significant differences were found in UOx excretions between the nephrotic and mild proteinuria groups (see Table 1). However, the higher the level of UPE was, the higher the level of UOx observed in patients with PGN and NS (Fig. 1c).

Serum IL-6 and MCP-1 levels were nonsignificantly higher in patients with PGN and NS than in those with mild proteinuria (see Table 1). Both IL-6 and MCP-1 serum concentrations were positively associated with proteinuria level (r = 0.26, p = 0.044 and r = 0.31, p = 0.014, respectively) and negatively with eGFR (r = -0.27, p = 0.023 and r = -0.24, p = 0.046, respectively). Moreover, serum IL-6 and MCP-1 were significantly correlated with POx (r = 0.44, p < 0.001 and r = 0.48, p < 0.001, respectively). However, in the partial correlation analysis adjusted for age, sex, UPE, BMI, and eGFR levels, only the association between POx concentration and IL-6 was confirmed (Fig. 1d) (r = 0.55, p < 0.001).

The effect size analysis for the association between POx and serum IL-6 concentrations in patients with PGN revealed a risk of 15.7% for committing a type I error and power of 84.3% with an alpha of 0.05 and a sample size of 76 observations.

Discussion. This preliminary study was the first to highlight the association between nephrotic proteinuria and POx elevation, which, in turn, was reflected in increased serum IL-6 concentration independent of the patients' age, sex, UPE, and eGFR levels. Unfortunately, no clinical study has analysed the relationship between POx and proteinuria and/or cytokine levels in patients with GN. Therefore, our results cannot be compared directly with previous reports. However, our findings agree with those of Waikar et al., who demonstrated that hyperoxaluria was associated with administration of diuretics, increased UPE, hypoalbuminemia, and GFR regression in patients with CKD [6]. However, unlike their study, we observed a direct association between UOx and UPE only in patients with GN having NS but not in patients with PGN in general. In our opinion, it is logical because the patients with nephrotic-range proteinuria had a significantly high POx concentration compared to the mild-proteinuria patients, while glomerular filtration of oxalate directly depends on POx concentration. Moreover, our findings corroborate other recent studies that demonstrated a statistically significant inverse correlation between POx and eGFR in primary hyperoxaluria populations with CKD stages 1–3b [9, 10]. The authors also found that POx concentration begins to rise before a significant loss in kidney function occurs.

It is not difficult to explain the possible pathway of the effect of NS on the POx concentration. In our opinion, not only GFR decline but the combination of different factors such as dietary restriction, the use of diuretics, corticosteroids or antibiotics, and the violation of intestinal oxalate absorption due to oedema or medicine taking might be the main cause of oxalate balance impairment in patients with PGN with NS.

Conversely, oxalate itself can induce both glomerular and tubular injury and contribute to proteinuria [17]. On the experimental model of crystalline-induced acute kidney injury, it has been demonstrated that a single injection of sodium oxalate solution led to a loss of podocyte viability in addition to strong tubulointerstitial injury resulted in albuminuria [17]. Although our data cannot fully support above mentioned findings, the observed correlation suggested that POx concentration may, at least along with proteinuria, serve as a marker of renal disease progression, and should be an area for further research.

Atherosclerosis has been described as the pivotal mechanism of serum IL-6 and MCP-1 elevation in CKD, which may explain the lack of changes in serum IL-6 and MCP-1 concentrations in early CKD stages [21-23]. In turn, the expression of these pro-inflammatory markers is induced by oxalate in HK-2 cells, resulting in hyperoxaluria [24, 25]. Moreover, POx may trigger inflammation and atherosclerosis in patients with kidney stones or end-stage kidney disease [3, 26-28]. Consistent with the published data [21, 22], we observed no differences in serum IL-6 and MCP-1 concentrations between healthy volunteers and the GN group since the average eGFR in our patients consisted of 64.1 (34.7–84.3) mL/min/1.73 m^2. However, the elevation of both pro-inflammatory mediators was significantly associated with increased POx levels. Notably, the interaction between POx and serum MCP-1 lost its significance after adjustment for age, sex, UPE, and eGFR.

Our study has some limitations. It was a small sample size study performed in a single centre, which may not be representative of other populations. The cross-sectional and correlational study design precluded the determination of causal interpretations and predictive conclusions. Finally, the participants' dietary preferences or restrictions and medication intake that could affect intestinal oxalate absorption were not considered. Nevertheless, this study is the first to provide new insights into the relationship between nephrotic proteinuria, oxalate homeostasis, and chronic inflammation in patients with GN.

In conclusion, nephrotic proteinuria was significantly associated with the elevation of POx concentration and hyperoxaluria in GN patients with CKD stages 1–3b. POx at least partly promotes inflammation, which may be a CVD risk factor in patients with GN in the early stages of CKD. Future studies should recruit at least 156 participants to confirm our preliminary results, validate NS as a risk factor for oxalate metabolism violation or determine the role of impaired oxalate homeostasis in clinical outcomes in patients with GN.

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Authors' contributions.

Natalia Stepanova: conceived the presented concept, designed the study, analyzed and interpreted the patient data, and was a major contributor in writing the manuscript;

Lyudmyla Snisar and Larysa Lebid: the patients' management and data collection;

Olga Kompaniets: database formation;

Victoria Driianska: performed the laboratory measurements.

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