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Association of serum uric acid with albuminuria in type 2 diabetic patients with comorbid obesity and/or essential arterial hypertension

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Abstract. *Decompensation of diabetes mellitus type 2 (T2DM), duration of the disease, level of proteinuria, obesity and essential arterial hypertension (AH) play the main role in the development and progress of diabetic nephropathy.*

The present study aimed to analyze the level of serum uric acid in type 2 diabetic patients with comorbid overweight/obesity and AH and to find its possible correlations with lipid panel data and urinary albumin excretion.

Methods. 579 medical records of type 2 diabetic patients treated at the Endocrinological department of the municipal non-profit enterprise "Ternopil University Hospital" of Ternopil Regional Council (Ternopil) in 2018–2019 years were analyzed.

Results. The analysis of renal panel data of type 2 diabetic patients with comorbid overweight/obesity and AH found out that only serum levels of urea and uric acid were statistically different in the patients with only T2DM and comorbid course of T2DM. Herewith the maximal changes were established for serum uric acid level, which in type 2 diabetic patients with comorbid obesity exceeded by 175.9 % data of only T2DM patients. Moreover, it was established a significant direct relationship between serum uric acid level and BMI and dyslipidemia in both groups of type 2 diabetic patients - with comorbid obesity and with comorbid obesity and AH. At the same time, a significant direct association between serum uric acid level and albuminuria was established only in type 2 diabetic patients with comorbid obesity and AH.

Conclusions. Our retrospective study indicates that serum uric acid level is markedly elevated and positively associated with albuminuria in type 2 diabetic patients with comorbid obesity and AH and can be used as a biomarker allowing further risk stratification for development and/or progress of diabetic nephropathy in this cohort of the patients.

Key words: *diabetes mellitus type 2, comorbidities, uric acid, albuminuria.*

Conflict of interest statement. The authors declare no competing interest.

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Зв'язок сечової кислоти сироватки крові з дисліпідемією та альбумінурією у хворих на цукровий діабет 2 типу з коморбідним ожирінням та/або есенціальною артеріальною гіпертензією

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Резюме. Декомпенсація цукрового діабету (ЦД) 2 типу, тривалість захворювання, рівень протеїнурії, ожиріння та есенціальна артеріальна гіпертензія (АГ) відіграють основну роль у розвитку та прогресуванні діабетичної нефропатії.

Метою роботи було проаналізувати вміст сечової кислоти в сироватці крові пацієнтів з ЦД 2 типу з коморбідною надмірною вагою/ожирінням та АГ і встановити можливі кореляції з показниками ліпідного профілю та екскрецією альбуміну з сечею.

Методи. Проаналізовано 579 медичних карт хворих на ЦД 2 типу, які перебували на лікуванні в ендокринологічному відділенні комунального некомерційного підприємства «Тернопільська університетська лікарня» Тернопільської обласної ради (м. Тернопіль) у 2018-2019 роках.

Результати. Аналіз ниркового профілю у біохімічному аналізі крові хворих на ЦД 2 типу з коморбідною надмірною масою тіла/ожирінням та АГ виявив, що лише рівні сечовини та сечової кислоти статистично відрізнялися у пацієнтів із ЦД 2 типу без коморбідної патології та ЦД 2 типу з коморбідністю. При цьому максимальні зміни були встановлені для рівня сечової кислоти в сироватці крові, який у хворих на ЦД 2 типу з коморбідним ожирінням на 175,9 % перевищував дані хворих на ЦД 2 типу без коморбідної патології. Крім того, встановлено статистично вірогідний прямий кореляційний зв'язок між рівнем сечової кислоти в сироватці крові та індексом маси тіла та дисліпідемією як у хворих на ЦД 2 типу з коморбідним ожирінням, так і у хворих на ЦД 2 типу з коморбідним ожирінням та АГ. У той же час вірогідна пряма залежність між рівнем сечової кислоти в сироватці крові та альбумінурією була встановлена лише у хворих на ЦД 2 типу з коморбідним ожирінням та АГ.

Висновки. Наше ретроспективне дослідження вказує на те, що вміст сечової кислоти в сироватці крові пацієнтів з ЦД 2 типу з коморбідним ожирінням та АГ виражено підвищується і прямо корелює з альбумінурією і може використовуватися як біомаркер для стратифікації ризику розвитку та/або прогресування діабетичної нефропатії у цих пацієнтів.

Ключові слова: цукровий діабет 2 типу, коморбідність, сечова кислота, альбумінурія.

Introduction. Diabetes mellitus (DM) is a serious problem of health care and non-infectious epidemics of the XXI century [1-2]. According to International Diabetes Federation, the number of diabetic patients around the world was 463 000 000 in 2019, and 91 % of the patients suffered from diabetes mellitus type 2 (T2DM) [3]. There are more than 1.2 million officially registered patients with DM in Ukraine, and the annual growth in the spreading of DM in Ukraine is about 4.4 % [4]. DM is characterized by early disability and high mortality, mainly due to micro- and macrovascular complications. Besides, DM is determined recently as one of the main burdening factors of the COVID-19 course and mortality [5].

Comorbidity is the presence of several diseases, connected by the joint pathogenetic mechanism, in the same patient is very common in the present clinical

practice [6]. The presence of comorbidities drastically affects DM patient outcomes, treatment and management options, and associated healthcare expenses [7]. While the hallmark of T2DM is insulin resistance (IR), it is associated with other metabolic disorders such as dyslipidemia and obesity [8]. At the same time, the prevalence of essential arterial hypertension (AH) in diabetic patients is higher 2-3 times than in the general population; whilst 70% of patients with T2DM have elevated blood pressure, which significantly increases the risk of cardiovascular complications, that worsen prognosis and quality of the lives of the patients being one of the main causes of mortality [9-11]. It was found that elevation of systolic blood pressure for every 10 mmHg in patients with T2DM increases the risk of development of cardiovascular complications by 20% [12].

Kidneys are the target organs that are affected most often at T2DM. Decompensation of DM, duration of the disease, level of proteinuria, obesity, and AH play the main role in the development and progress of diabetic nephropathy [4, 13]. Besides, it is known that more than 80% of cases with terminal stage of chronic kidney disease (CKD) are caused by DM, AH, or their

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combination [14]. Timely evaluation of biomarkers of kidneys impairment at a comorbid course of T2DM may improve the stratification of the risk for development or progress of diabetic nephropathy in this cohort of the patients.

Uric acid is the end product of purine metabolism, mainly excreted by the kidneys [15]. There are data that serum uric acid is biologically active and can stimulate oxidative stress, endothelial dysfunction, inflammation, and vasoconstriction [16]. In addition, hyperuricemia is an established risk predictor for CKD independently of the presence of gout [17]. Furthermore, high levels of serum uric acid, even within the normal range, have been shown to predict the development of albuminuria [18] and both the occurrence and progression of CKD [19]. However, whether it is simply a biomarker of impaired kidney function or has a true pathogenic role in

kidney function remains inconclusive [20]. In addition, what factors may be involved in renal uric acid excretion in case of comorbid course of T2DM are not yet fully understood.

Our research aimed to analyze the level of serum uric acid in type 2 diabetic patients with comorbid overweight/obesity and AH and to find its possible correlations with lipid panel data and urinary albumin excretion.

Materials and methods. We analyzed 579 medical records of type 2 diabetic patients treated at Endocrinological department of the municipal non-profit enterprise “Ternopil University Hospital” of Ternopil Regional Council (Ternopil) in 2018-2019 years. All patients were divided into 6 study groups depending on the presence of overweight/obesity and AH. The distribution of the groups is shown in Table 1.

Table 1

Groups of type 2 diabetic patients, including in the study

N	Group	n	%
1	T2DM + normal weight	39	6.74
2	T2DM + overweight	33	5.70
3	T2DM + obesity	22	3.80
4	T2DM + normal weight + AH	59	10.19
5	T2DM + overweight +AH	131	22.63
6	T2DM + obesity +AH	295	50.95

Inclusion criteria. Clinical, laboratory, and instrumental features of T2DM, AH and overweight/obesity.

Exclusion criteria. Signs of the clinically significant disturbances: neurological, psychiatric, nephrological, hepatological, immunological, gastroenterological, urological; injuries of the skeletal system, muscle, skin, organs of sensitivity; endocrine system disorders (except T2DM); the presence of diabetic nephropathy in anamnesis; the presence of gout in anamnesis; non-controlled hematological diseases; acute pancreatitis, nonstable or life-threatening cardiac disease (including patients with AH stage 3, chronic heart failure higher than functional class II (NYHA III-IV)); patients with malignant neoplasms without complete remissions within 5 years, drug and/or alcohol dependence.

Age aspect did not have a significant difference within the study groups of the patients. Analysis of the sexual dimorphism of the patients included in the research revealed that males were prevalent in the 1st, 2nd, 3rd and 4th groups while females prevailed in the 5th and 6th groups. Herewith, among the patients with T2DM with comorbid AH it was revealed the higher percentage of males with normal body weight and females with obesity.

Verification of T2DM was performed according to recommendations of the American diabetic association (2019) [21]. The level of HbA1c was determined using an automatic biochemical analyzer COBAS 6000 (Roche Diagnostics, Germany) and glucose level was

determined using automatic biochemical analyzer BAS INTEGRA® 400 (Roche Diagnostics, Germany) with commercially available kits.

Body mass index (BMI) was calculated using the formula: body weight (kg)/height (m²). Data were interpreted according to the WHO guidelines: normal weight in the range of 20.0-24.9 kg/m²; overweight (pre-obesity), 25.0-29.9 kg/m²; class 1 obesity, 30.0-34.9 kg/m²; class 2 obesity, 35.0-39.9 kg/m² and class 3 obesity, > 40 kg/m².

Essential arterial hypertension (AH) was defined as office systolic blood pressure values \geq 140 mmHg and/or diastolic blood pressure values \geq 90 mmHg at least for three measurements during one month, according to national and European Societies of Hypertension and Cardiology (ESH/ESC, 2018) recommendations requirement [22]. Left ventricular hypertrophy was confirmed by electrocardiography and/or echocardiography.

Renal panel data (urea, creatinine and uric acid) in blood biochemical profiles were determined using automatic biochemical analyzer BAS INTEGRA® 400 (Roche Diagnostics, Germany) with commercially available kits.

Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) levels were determined with commercially available kits on a Cobas 6000 analyzer (Roche Diagnostics, Germany). Friedewald's formula was used to calculate low-density

lipoprotein cholesterol (LDL-C) levels (if serum TG <4.5 mmol/L) [23]: LDL-C (mmol/L) = TC- HDL-C - (0.45 × TG).

Urinary albumin excretion was measured with the immuno-turbidimetric method in 24-h urine samples.

Statistical analysis. Statistical analysis was performed using Statistica 7.0 (StatSoft Inc., Tulsa, OK, USA) software. The Kolmogorov-Smirnov test was used to compare probability distributions (parametric or non-parametric). Quantitative values, due to their non-parametric distribution, are presented as the median, lower, and upper quartiles – Me (Lq; Uq). Comparative analysis of study groups was performed using the non-parametric Kruskal-Wallis test. Having obtained

its probable values ($p < 0.05$), further pairwise comparison of groups was performed using the Mann–Whitney U-test, taking into account Bonferroni correction when assessing statistical significance. For frequency values, the percentage ratio and its 95% confidence interval (CI) were calculated, and their comparative analysis was performed using Pearson's chi-square test and Fisher's bilateral test. The relationship between the studied indices was established based on the results of the correlation analysis using Spearman's rank correlation coefficient.

Results. BMI was significantly different in the patients of 2nd, 3rd 5th and 6th groups compared with the patients of 1st and 4th groups (Table 2).

Table 2

BMI of type 2 diabetic patients, including in the study

N	Group	n	BMI
1	T2DM + normal weight	39	21.93±2.16
2	T2DM + overweight	33	27.09±1.69*
3	T2DM + obesity	22	34.95±5.99*
4	T2DM + normal weight + AH	59	22.96±1.39
5	T2DM + overweight +AH	131	27.81±1.31*
6	T2DM + obesity +AH	295	35.27±5.24*

Note. * – statistically significant results (compared to study group 1).

The analysis of renal panel data in blood biochemical profile of type 2 diabetic patients with comorbid overweight/obesity and AH found out that only serum

levels of urea and uric acid were statistically different in the patients from the different study groups according to Kruskal-Wallis analysis of variance by ranks (Table 3).

Table 3

Renal panel data in blood biochemical profile of type 2 diabetic patients with comorbid overweight/obesity and hypertension

Index	T2DM + normal weight	T2DM + over-weight	T2DM + obesity	T2DM + normal weight + AH	T2DM + over-weight + AH	T2DM + obesity + AH	Kruskal-Wallis criterion
Urea, mmol/L	4.5 (3.4; 6.3)	5.2 (4.7; 6.9)	4.9 (3.6; 6.0)	5.1 (4.2; 6.2)	5.5 (4.4; 6.9)	5.6 (4.5; 7.0)	H=16.07; p<0.05*; p1-6<0.05*
Creatinine, μmol/L	66 (56; 75)	68 (58; 81)	77 (55; 87)	71 (55; 85)	70 (61; 85)	72 (61; 85)	H=7.82; p>0.05
Uric acid, mmol/L	158 (141; 175)	258 (206; 343)	436 (343; 515)	240 (179; 410)	273 (220; 349)	305 (247; 401)	H=11.41; p<0,05*; p1-3<0.05* p1-6<0.05*

Note. * – statistically significant results.

Thus, urea level was the highest in type 2 diabetic patients with comorbid obesity and AH; it was statistically different for 24.4 % compared to this value in type 2 diabetic patients with normal body weight. It should be noted, that in type 2 diabetic patients with comorbid overweight and AH, urea level was not statistically different from such index in type 2 diabetic patients with normal weight.

As for the level of uric acid, this value revealed the maximal changes in type 2 diabetic patients with comorbid obesity and it exceeded 175.9 % the results in type 2 diabetic patients with normal weight. Meanwhile, the level of uric acid in type 2 diabetic patients with comorbid obesity and hypertension was higher compared to such index in type 2 diabetic patients with normal body weight only for 93.0 %.

A direct association between serum uric acid level and BMI in type 2 diabetic patients with comorbid obe-

sity and T2DM patients with comorbid obesity and AH was established (Table 4).

Table 4

Correlative linkages between serum level of uric acid and BMI in type 2 diabetic patients depending on the degree of excessive body weight and presence of arterial hypertension

Index	Groups	BMI
Uric acid, mmol/L	T2DM + normal weight	0.16
	T2DM + overweight	0.35
	T2DM + obesity	0.55*
	T2DM + normal weight + AH	0.11
	T2DM + overweight + AH	0.15
	T2DM + obesity + AH	0.31*

Note. * – the significance of Spearman's correlation coefficient $p < 0.05$.

Analyzing lipid panel data, we found that only serum levels of TC and TG were statistically different in

the patients from the different study groups according to Kruskal-Wallis analysis of variance by ranks (Table 5).

Table 5

Lipid panel data in blood biochemical profile of type 2 diabetic patients with comorbid overweight/obesity and hypertension

Groups	TC, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	TG, mmol/L
T2DM + normal weight	4.48 (3.80; 5.31)	0.94 (0.74; 1.13)	2.98 (2.22; 3.37)	1.16 (0.86; 2.29)
T2DM + over-weight	4.97 (4.32; 6.16)	0.92 (0.82; 1.16)	3.19 (2.65; 4.17)	1.78 (1.10; 2.90)
T2DM + obesity	4.97 (4.36; 5.81)	0.85 (0.71; 1.10)	2.92 (2.37; 3.30)	2.66 (1.78; 5.16)
T2DM + normal weight + AH	4.64 (4.23; 5.45)	0.95 (0.77; 1.24)	2.93 (2.51; 3.77)	1.51 (0.95; 2.54)
T2DM + over-weight + AH	5.30 (4.48; 6.15)	1.03 (0.79; 1.24)	3.40 (2.69; 4.10)	1.92 (1.19; 3.32)
T2DM + obesity + AH	5.14 (4.46; 5.94)	0.95 (0.81; 1.18)	3.14 (2.46; 3.92)	2.24 (1.48; 3.22)
Kruskal-Wallis criterion	H=17.07; p=0.004*	H=5.57; p=0.351	H=9.50; p=0.091	H=38.62; p<0.001*

Note. * – statistically significant results

Thus, it was revealed the statistically higher values of serum TC level in patients with T2DM, overweight and obesity (by 18.3 %) and in patients with T2DM, obesity and AH (by 14.7 %) vs. data of type 2 diabetic patients with normal body weight. As for the level of TG, significantly higher values were found in patients with T2DM and obesity (by 129.3 %), in patients with T2DM, overweight and AH (by 17.8 %) and in patients with T2DM, obese and AH (by 93.1 %) vs. data of type 2 diabetic patients with normal body weight. It should be noted, that TG level in T2DM patients with

comorbid obesity was statistically higher for 76.2 % vs. data of T2DM patients with normal body weight and comorbid AH.

In type 2 diabetic patients with comorbid obesity regardless of the presence/absence of comorbid AH statistically significant direct correlations between serum uric acid level and TC and TG levels (Table 6) were established. It should be noted, that in type 2 diabetic patients with excessive body weight such interdependence was not observed.

Table 6

Correlative linkages between serum level of uric acid and TC and TG levels in type 2 diabetic patients depending on the degree of excessive body weight and presence of arterial hypertension

Index	Groups	TC, mmol/L	TG, mmol/L
Uric acid, mmol/L	T2DM + normal weight	0.26	0.18
	T2DM + overweight	0.12	0.25
	T2DM + obesity	0.49*	0.67*
	T2DM + normal weight + AH	0.09	0.12
	T2DM + overweight + AH	0.11	0.14
	T2DM + obesity + AH	0.21*	0.39*

Note. * – the significance of Spearman’s correlation coefficient $p < 0.05$.

The next step was to analyze urinary albumin excretion in type 2 diabetic patients with comorbid overweight/obesity and AH, because albumin excretion rate ≥ 30 mg/24 hours, is used as a marker of renal damage

and is used to define CKD along with low estimated glomerular filtration rate (GFR) [24]. We found normoalbuminuria in all type 2 diabetic patients including in the study (Table 7).

Table 7

Excretion of albumin with urine in type 2 diabetic patients, including in the study

N	Group	Albuminuria, mg/24 hours	Kruskal-Wallis criterion
1	T2DM + normal weight	0.11 (0.08; 0.12)	H=24.01; $p < 0.05$ p1-3<0.05* p1-6<0.05*
2	T2DM + overweight	0.14 (0.12; 0.19)	
3	T2DM + obesity	0.28 (0.18; 0.35)	
4	T2DM + normal weight + AH	0.21 (0.12; 0.25)	
5	T2DM + overweight + AH	0.17 (0.11; 0.29)	
6	T2DM + obesity + AH	0.29 (0.19; 0.33)	

Note. * – statistically significant results

However, the analysis of Kruskal-Wallis rank variations revealed significant differences in albumin excretion rate of type 2 diabetic patients with normal body weight vs. patients with comorbid obesity (by 2.8 times) and patients

with comorbid obesity and AH (by 2.9 times). Moreover, a direct association between serum uric acid level and albuminuria was established only in type 2 diabetic patients with comorbid obesity and AH (Table 8).

Table 8

Correlative linkages between serum level of uric acid and albuminuria in type 2 diabetic patients depending on the degree of excessive body weight and presence of AH

Index	Groups	Albuminuria, mg/24 hours
Uric acid, mmol/L	T2DM + normal weight	0.03
	T2DM + overweight	0.15
	T2DM + obesity	0.24
	T2DM + normal weight + AH	0.11
	T2DM + overweight + AH	0.08
	T2DM + obesity + AH	0.41*

Note. * – the significance of Spearman’s correlation coefficient $p < 0.05$.

Discussion. A high prevalence combined with severe outcomes of CKD determines the interest of the researchers in biomarkers and molecular mechanisms of the kidneys' impairment during T2DM [25]. After analysis of the renal panel data in blood biochemical profile of type 2 diabetic patients with comorbid obesity/overweight and AH, we revealed that only serum levels of uric acid and urea were significantly different in the patients from the investigated study groups according to Kruskal-Wallis analysis of variance using ranks ($p < 0.05$). Herewith, the most prominent changes were observed with the uric acid level, such as in type 2 diabetic patients with comorbid obesity, where serum level of uric acid exceeded the results of type 2 diabetic patients with normal body weight by 175.9 %.

The role of hyperuricemia, which is typically defined as serum uric acid levels above 6.0 mg/dL (360 $\mu\text{mol/L}$) in women, above 7.0 mg/dL (415 $\mu\text{mol/L}$) in men, and above 5.5 mg/dL (330 $\mu\text{mol/L}$) in children and adolescents [26], has been a subject of debate in case of DM pathogenesis. Some researchers reported it to be a resultant effect of DM, while others considered it to be a risk factor for T2DM development [27]. Hyperuricaemia has also been found to be associated with IR and components of the metabolic syndrome [28].

Moreover, hyperuricemia is a well-known independent predictor of CKD development and progression [9]. Thus, the research of Okinawa General Health Maintenance Association, which included 6400 persons with baseline normal renal function, has shown that uricemia at the level of more than 8 mg/dl is associated with increased risk of renal impairment by 2.9 times in males and by 10.0 times in females within two years of observation [29]. It was demonstrated by observational seven-year-long Vienna Health Screening Project, which included 23 475 persons without kidney diseases at the beginning of the project, that increased level of uric acid in serum was associated with a higher risk of CKD independently of age, gender, waist circumference, level of lipids, glucose, glomerular filtration rate, blood pressure and usage of antihypertensive drugs [30].

There are several mechanisms by which high levels of uric acid increases the risk for CKD development and progression [31, 32]: direct toxicity to the kidney; exacerbation of other risk factors for kidney disease, such as hypertension; or by being a marker of the severity of other risk factors, including those attributable to or associated with DM and the metabolic syndrome. In a study in rats, hyperuricemia increased systemic blood pressure, proteinuria, renal dysfunction, progressive renal scarring and induced vascular disease via a cyclooxygenase-2-dependent pathway [33].

Some other experimental studies suggest that hyperuricemia induces renal injury through renal vasoconstriction mediated by endothelial dysfunction, activation of the renin-angiotensin system, afferent arteriopathy, and epithelial to mesenchymal transition in renal tubular cells. Additionally, hyperuricemia increases renin activity, leading to the upregulation of

angiotensin II and the proliferation of vascular smooth muscle cells [34]. This results in vascular wall thickening, which leads to lumen obliteration and hypoperfusion of the kidney, with tubulointerstitial inflammation and fibrosis, as well as AH [35]. L.G. Sánchez-Lozada et al. in hyperuricemic rats fed with a low-salt diet demonstrated glomerular hypertension, which appeared to be due to insufficient vasoconstriction of the afferent arteriole [36].

Recent evidence also confirms an important role of uric acid-induced inflammation, both by the more known crystal-dependent mechanisms, but also by the direct effect of soluble urate, through oxidative stress, proinflammatory signaling, autophagy and intracellular immunometabolic sensors [37].

At the same time despite the vast evidence of an association between hyperuricemia and CKD, there are still conflicting results in clinical studies, with several unanswered questions regarding the role of uric acid as a casual, compensatory or coincidental phenomenon in these patients [32].

On the other hand, some researchers did not confirm the association between uric acid and the incidence of CKD and its progression. In particular, Sturm G. et al. in a study with 227 patients followed for 7 years, with CKD of non-diabetic etiology, determined that there was no relationship between serum uric acid levels and kidney disease progression when the analysis was adjusted for baseline kidney function parameters [38]. In another study with 838 patients with CKD stages 3-4 followed for 10 years, the results showed a positive association of hyperuricemia with all-cause and cardiovascular mortality, but not with kidney failure [39].

Even more, questions arise about the association between hyperuricemia and CKD in the comorbid course of diabetes, in particular in obese patients with dyslipidemia and AH. Albuminuria has been classically considered the first diabetic kidney disease clinical indicator, a biomarker for its progression, and a cause of impairment of GFR [40]. In the present study, we found normoalbuminuria in type 2 diabetic patients of all studied groups. However, significant differences have been identified in the albumin excretion rate of type 2 diabetic patients with comorbid obesity and patients with comorbid obesity and AH vs. type 2 diabetic patients with normal body weight without hypertension. Moreover, a direct association between serum uric acid level and albuminuria was established only in one study group – in type 2 diabetic patients with comorbid obesity and AH.

Recent studies suggest that elevated urinary albumin excretion, even within the normal range, predicts a faster decline in GFR in diabetic patients [41] and is associated with a greater risk of cardiovascular disease [42]. That is why the presence of albuminuria should be interpreted as an important risk marker that should be evaluated when stratifying the risk of progressive CKD in an individual patient.

Our study supports that hyperuricemia is positively associated with albuminuria in type 2 diabetic patients with comorbid obesity and AH, which probably indicates a connection between high serum uric acid and diabetic kidney disease development and/or progress in case of comorbid course of T2DM.

The precise mechanisms by which obesity independently, or in concert with AH contributes to the development and/or progression of CKD are not completely understood. Obesity and hyperglycemia both promote a low-grade inflammatory state and are associated with the infiltration of macrophages into the kidney. The infiltrated macrophages, in turn, become a source of a whole host of proinflammatory mediators such as tumor necrosis factor- α , interleukin-6, C-reactive protein, monocyte chemoattractant protein-1 and macrophage migration inhibitory factor. In addition, visceral fat releases adipokines such as adiponectin and leptin into the circulation which also play a role in the pathophysiology of renal injury. Elevated systolic blood pressure further exacerbates the disease progression to proteinuria, nodular glomerulosclerosis and tubulointerstitial injury and a decline in glomerular filtration rate [43].

Furthermore, dyslipidemia has been shown to play crucial roles in the development and progression of diabetic kidney disease [44]. Under the diabetic milieu, hormone-sensitive lipase is activated, which results in the release of free fatty acids (FFAs) from the adipose tissue. The flux of FFAs promotes hepatic TG production, leading to excessive apoB and VLDL synthesis. In addition, lipoprotein lipase activity is suppressed under the condition of IR. These changes increase the serum levels of TG and remnant particles. It has been demonstrated that IR is aggravated along with the progression of diabetic nephropathy, even in the early stage of microalbuminuria [45].

In the present study, we found a direct association between serum uric acid level and BMI in type 2 diabetic patients with comorbid obesity and T2DM patients with comorbid obesity and AH. Moreover, in type 2 diabetic patients with comorbid obesity, regardless of the presence or absence of comorbid AH, statistically significant direct correlations between serum uric acid level and TC and TG levels were established.

H. Wang et al. showed that serum uric acid level was positively correlated with age, blood pressure, BMI, red blood cell count, hemoglobin, white blood cell count, platelet count, serum cholesterol, TG, HDL-cholesterol, LDL-cholesterol, ALT, AST, bilirubin, albumin, and creatinine in healthy subjects. Serum uric acid level was significantly elevated in a linear dependency as BMI increased, and serum uric acid level in obese participants was significantly higher than in underweight participants. The prevalence of hyperuricemia remained approximately 2.98 times greater among overweight individuals, and 5.96 times greater among obese participants compared to underweight individuals [46].

Obesity may be linked to serum uric acid levels through the involvement of two factors: overproduction and poor renal excretion [47]. A study conducted among the subjects with visceral fat obesity showed that increased levels of uric acid were strongly influenced by its overproduction with a decrease in urinary urate excretion and clearance [48]. Moreover, visceral fat accumulation causes an elevated influx of plasma-free fatty acids into the liver and hepatic portal vein, which in turn stimulates the synthesis of TG followed by an associated increase in uric acid production through the activation of the corresponding synthesis pathway [49]. Besides, data are showing that obesity promotes IR, which in turn decreases renal urate excretion, causing hyperuricemia [50].

M. Akram et al. evaluated the connection between obesity and the incidence of high uric acid levels in obese individuals. In a population-based cohort, obesity and subsequent weight gain were found to be strongly associated with hyperuricemia [51]. Serum uric acid was also shown to be positively correlated with several indices, such as BMI, waist circumference, and dyslipidemia [52]. The cross-sectional study among Bangladeshi adults, conducted by Ali N. et al., showed that the estimated prevalence of hyperuricemia was 9.3% overall, with 8.4% in male and 10.2% in female participants [47]. As for the BMI grouping categories, the prevalence of hyperuricemia was found to be 1.9% in normal individuals, 1.6% – in overweight, and 5.8% – in the obesity group. The average level of serum uric acid was 275 ± 61 $\mu\text{mol/L}$ (max 416 $\mu\text{mol/L}$) and 460 ± 86 $\mu\text{mol/L}$ (max 826 $\mu\text{mol/L}$) in the non-hyperuricemic and hyperuricemic group, respectively.

A. O. Ogbera and A. O. Azenabor have determined the prevalence of hyperuricemia and evaluated its associations with metabolic syndrome, in people with T2DM [27]. 601 patients with T2DM in the 34 to 91 years-old group were recruited for the study. The prevalence rates of hyperuricemia and metabolic syndrome were 25% and 60%, respectively. The frequency of hyperuricemia occurrence was comparable in both genders (59% vs 41%, $p=0.3$). Although the prevalence of the metabolic syndrome in participants with hyperuricemia and normouricemia was comparable (61 vs 56%, $p=0.1$), a higher proportion of hyperuricemic subjects had three or more components of the metabolic syndrome compared to normouricemic subjects. Possible predictors of hyperuricemia may include obesity, smoking habit, and elevated serum TG.

Although we did not find more profound changes in serum uric acid level in type 2 diabetic patients with comorbid obesity and AH vs. type 2 diabetic patients with comorbid obesity only, the relationship between uric acid and blood pressure is certainly important and multiple studies have demonstrated an independent correlation between hyperuricemia and hypertension [53].

On the one hand, uric acid has demonstrated a major role in the pathogenesis of AH [54, 55]. Pos-

sible mechanisms may involve renin-angiotensin-aldosterone system upregulation, kidney afferent arteriopathy, oxidative stress, endothelial dysfunction, and systemic inflammation [53, 56]. Additionally, genetic population-based association studies have shown a significant correlation of xanthine oxidoreductase genetic polymorphisms with hypertension. However, those polymorphisms, which involve major urate transporters genes, have not been demonstrated to relate with hypertension [56].

Some studies have confirmed the prognostic value of uric acid in hypertension prediction, demonstrating that higher blood uric acid levels were significantly associated with an increased relative risk for hypertension [57]. In particular, Y. Taniguchi et al. studied the association of serum uric acid level with the risk of hypertension and T2DM development [58]. A total of 6,356 Japanese men, aged 35 to 60 years with systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg, and no history of diabetes or hypertension at baseline, were included in the project. During the 61,716 person-years follow-up observation, the researchers confirmed 639 cases of hypertension and 454 cases of T2DM. Serum uric acid level was associated with an increased risk for hypertension, but not for T2DM.

P. C. Grayson et al. published a systematic review and meta-analysis to determine the hyperuricemia association with incident hypertension, particularly in well-defined demographic subgroups [59]. A total of eighteen prospective cohort studies with combined data from 55,607 participants were analyzed. Hyperuricemia was associated with an increased risk for incident hypertension (adjusted risk ratio [RR] 1.41, 95% confidence interval [95% CI] 1.23-1.58). Per each 1 mg/dl increase in uric acid level, the pooled RR for incident hypertension after adjustment for potential confounding increased by 1.13 (95% CI 1.06-1.20). The observed effects were significantly larger in younger study populations and more likely larger among women.

E. Krishnan et al. studied the risk of hypertension development in normotensive men with baseline hyperuricemia (serum uric acid >7.0 mg/dL), without diabetes/glucose intolerance or metabolic syndrome, over 6 years [60]. Researchers used Cox regression models for adjustment for the influence of serum creatinine, body mass index, age, blood pressure, serum cholesterol and triglycerides, proteinuria, alcohol and tobacco use, risk factor interventions, and use of diuretics. In these models, normotensive men with baseline hyperuricemia had an additional 80% risk increase for incident hypertension compared to those who did not have this condition. Each unit increase in blood uric acid was associated with a 9% increase of the risk for incident hypertension.

Moreover, there is evidence that high concentration of uric acid in blood serum is an independent predictor of mortality among the population of patients with very high risk of cardiovascular diseases [54, 55]. The study conducted by Ndrepepa et al. [61] included

5124 patients with acute coronary syndromes (1629 with ST-segment elevation myocardial infarction, 1332 with non-ST-segment elevation myocardial infarction and 2163 with non-stable coronary disease) that were divided into the groups according to the uric acid level in blood serum. Specifically, the 1st group had serum uric acid level between 77 and 315 $\mu\text{mol/L}$; the 2nd – level ranged from 315 to 375 $\mu\text{mol/L}$; the 3rd group – from 375 to 446 $\mu\text{mol/L}$; the 4th group – level ranged from 446 to 1094 $\mu\text{mol/L}$. Within one year, 80 deaths were registered in the 1st group, 77 – in the 2nd, 72 – in the 3rd, and 122 – in the 4th group. Mortality risk, not adjusted, was 3.05 (95% CI 2.54–3.67; $p < 0,001$) for the 4th group compared to the 1st one. It should be noted that the correlation between the concentration of uric acid and mortality remained significant (increase by 12 % of mortality risk per year for each 1 mg/dl (59 $\mu\text{mol/L}$) of uric acid concentration increase).

On the contrary, hypertension is a risk factor for hyperuricemia [54]. As a consequence of increased blood pressure, microcirculation becomes impaired, resulting in systemic ischemia of the tissues, which affects all cells with a massive decomposition of adenosine triphosphate into adenine and xanthine and increased production of xanthine oxidase. Increased concentration of both substrate (xanthine) and enzyme (xanthine oxidase) contributes to the excessive synthesis of uric acid [62].

Study limitations. The study involved a small sample size; because of this, significant relationships between study factors were difficult to prove. The patients included in T2DM + obesity and T2DM + obesity + AH groups were not randomly selected, potentially causing selection bias. While we cannot support the assumption that study participants represent the whole population of type 2 diabetic patients with comorbid obesity and AH in Ternopil region, the obtained results give grounds for further studies with larger sample sizes, reflecting a more inclusive population.

Conclusions. The analysis of renal panel data in blood biochemical profiles of type 2 diabetic patients with comorbid overweight/obesity and AH showed that only serum levels of urea and uric acid were statistically significantly different in the patients with only T2DM and comorbid course of T2DM. Herewith, the maximal changes were observed for serum uric acid level in type 2 diabetic patients with comorbid obesity, where an increase by 175.9 % was noted compared to the data of T2DM patients with normal weight. In addition, a significant direct relationship was established between serum uric acid level and BMI and dyslipidemia in both type 2 diabetic patients' groups – with comorbid obesity and with comorbid obesity and AH. At the same time, a direct association between serum uric acid level and albuminuria was established only in type 2 diabetic patients with comorbid obesity and AH. Therefore, our retrospective study indicates that serum uric acid level is markedly elevated and positively associated with albuminuria in type 2 diabetic patients with comorbid

obesity and AH and can be used as the biomarker allowing further risk stratification for development and/or progress of diabetic nephropathy in this cohort of the patients.

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Authors contribution.

M. Marushchak: provided the conception and design of the study, acquisition of data, analysis and inter-

pretation of data, drafting the article, revised it critically for important intellectual content, and final approval of the version to be submitted;

I. Krynytska: supplied the acquisition of data, drafting of the manuscript; supplied the design of study, analysis and interpretation;

A. Lepyavko: provided the critically manuscript revision and gave final approval of the version to be submitted.

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