

ORIGINAL PAPER

INTERRELATIONSHIPS BETWEEN HYPERURICEMIA, METABOLIC SYNDROME AND CHRONIC KIDNEY DISEASE IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Introduction. Hyperuricemia is a strong predictor of an altered metabolic status. There are complex interrelationships between hyperuricemia, type 2 diabetes mellitus (T2DM), metabolic syndrome (MS) and chronic kidney disease (CKD).

The objective of the study was to investigate the impact of hyperuricemia on the prevalence of MS and glomerular function in patients with T2DM.

Materials and methods. This retrospective study included 300 patients with T2DM, hospitalized for one day in the diabetes clinic, between 01.01.2016-31.12.2018; all the data used for the analysis were obtained from the medical records.

Results. The prevalence of hyperuricemia was 46%. MS was identified in 88.41% patients with

RÉSUMÉ

Interrélation entre l'hyperuricémie, le syndrome métabolique et la maladie rénale chronique chez les patients avec diabète sucré de type 2

Introduction. L'hyperuricémie est un puissant prédicteur d'un état métabolique altéré. Il existe des interrelations complexes entre l'hyperuricémie, le diabète sucré de type 2, le syndrome métabolique et l'insuffisance rénale chronique.

L'objectif de l'étude était d'étudier l'impact de l'hyperuricémie sur la prévalence de la SEP et de la fonction glomérulaire chez les patients atteints de diabète sucré de type 2.

Matériaux et méthodes. Cette étude rétrospective a inclus 300 patients atteints de diabète sucré de type

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hyperuricemia compared to 61.73% in patients with normo-uricemia ($p < 0.01$); also, all the components of MS were better represented among hyperuricemia patients. The prevalence of CKD (defined as glomerular filtration rate $< 60 \text{ mL/min/1.73m}^2$) was 49.28% in patients with hyperuricemia, while in patients with normo-uricemia it was 25.31% ($p < 0.01$). Other metabolic conditions were statistically significantly represented for hyperuricemia patients: obesity (88.4% vs. 61.72%, $p < 0.01$), hepatic steatosis (81.11% vs. 57.41%). The impact of the aggregation of metabolic risk factors in hyperuricemia patients was visible in this study, the prevalence of ischemic heart disease being 83.33% in patients with hyperuricemia and 72.4% in patients with normo-uricemia ($p = 0.02$).

Conclusions. Hyperuricemia is associated with increased MS prevalence and increased prevalence of CKD in T2DM patients.

Keywords: hyperuricemia, metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease.

Abbreviations list

BMI – body mass index
 CKD – chronic kidney disease
 CVD – cardiovascular disease
 GFR – glomerular filtration rate
 HDL – high-density lipoprotein
 LDL – low-density lipoprotein
 MS – metabolic syndrome
 NAFLD – non-alcoholic fatty liver disease
 NO – nitric oxide
 ROS – reactive oxygen species
 TGL – triglycerides
 T2DM – type 2 diabetes mellitus

INTRODUCTION

The contemporary society is confronting with an impressive number of patients who have metabolic syndrome (MS), chronic kidney disease (CKD) or type 2 diabetes mellitus (T2DM); these conditions can coexist, leading to a relevant decline in the quality of life, as well as the lifespan. There is a real concern in conducting research to discover the possible relationships between these disorders and, by means of sanitary management methods, and to implement measures to decrease their prevalence.

MS represents an association of metabolic factors, being an increasingly common syndrome, due to the major impact it has on the health of the population. The characteristics/criteria for the diagnosis of MS were several times defined by the competent authorities in the field until 2009, when a consensus

was reached, and a definition currently used was issued. Thus, international associations (International Diabetes Federation, National Heart, Lung, Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity) gathered and, after analyses and discussions, established a consensual description regarding the medical term of MS, so that it is defined by the presence of at least three of the following anomalies¹: abdominal obesity, waist circumference $> 80 \text{ cm}$ in women and $> 94 \text{ cm}$ in men; hypertriglyceridemia ($\geq 150 \text{ mg/dL}$) or the use of lipid-lowering drugs; low serum lipoprotein levels: low HDL-cholesterol ($< 40 \text{ mg/dL}$ in men and $< 50 \text{ mg/dL}$ in women); high blood pressure: systolic blood pressure $\geq 130 \text{ mmHg}$, diastolic blood pressure $\geq 85 \text{ mmHg}$ or use of antihypertensive

2, hospitalisés pendant une journée à la clinique de diabète, entre le 01.01.2016 et le 31.12.2018; toutes les données utilisées pour l'analyse ont été obtenues à partir des dossiers médicaux.

Résultats. La prévalence de l'hyperuricémie était de 46%. Le syndrome métabolique a été identifiée chez 88,41% des patients présentant une hyperuricémie contre 61,73% chez les patients présentant une normo-uricémie ($p < 0,01$); De plus, toutes les composantes du syndrome métabolique étaient mieux représentées chez les patients avec hyperuricémie. La prévalence de l'insuffisance rénale chronique (définie comme un taux de filtration glomérulaire $< 60 \text{ ml/min/1,73m}^2$) était de 49,28% chez les patients présentant une hyperuricémie, tandis que chez les patients atteints de normo-uricémie, elle était de 25,31% ($p < 0,01$). D'autres pathologies métaboliques étaient statistiquement représentées de manière significative chez les patients hyperuricémiques: obésité (88,4% vs 61,72%, $p < 0,01$), stéatose hépatique (81,11% vs 57,41%). L'impact de l'agrégation des facteurs de risque métaboliques chez les patients hyperuricémiques était visible dans cette étude, la prévalence de la cardiopathie ischémique étant de 83,33% chez les patients avec hyperuricémie et de 72,4% chez les patients atteints de normo-uricémie ($p = 0,02$).

Conclusions. L'hyperuricémie est associée à une augmentation de la prévalence du syndrome métabolique et à une augmentation de la prévalence de l'insuffisance rénale chronique chez les patients atteints de diabète sucré de type 2.

Mots-clés: hyperuricémie, syndrome métabolique, diabète sucré de type 2, maladie rénale chronique.

medication; fasting blood glucose ≥ 100 mg/dL or antidiabetic treatment.

The importance of MS is given especially by its consequences, a patient with this disease having an increased risk of cardiovascular disease (CVD)^{2,3} approximately twice as high compared to those without MS, an increased risk of T2DM⁴ and it is also associated with polycystic ovary syndrome⁵, non-alcoholic fatty liver disease (NAFLD), different forms of cancer, and also sleep apnea syndrome. It strongly influences the quality of life, increases morbidity and mortality of any cause, also having a negative economic impact on the healthcare systems. In western countries, the estimated prevalence of MS is about 20% in the adult population, increasing with age. However, the prevalence of MS also varies according to the population studied, definition used, age, gender, race and ethnicity⁶.

CKD is another widespread disease with a huge economic impact on health systems; it is estimated that around 200 million people suffer from CKD, its prevalence being estimated to 11-13%⁷ and increasing especially in the elderly population (30% of people >65-year-old have stable CKD). It is defined by the presence of abnormalities in renal structure and function, with a duration of more than 3 months, evidenced by the urinary albumin/creatinine ratio above 30 mg/g and/or the decrease of the glomerular filtration rate (GFR) below 60 mL/min/1.73m². Depending on the value of GFR and albuminuria, CKD is divided into five stages. Its importance is given by the fact that all CKD stages are associated with the increase of the risk of cardiovascular morbidity, the decrease of the quality of life and premature deaths, representing the ninth cause of death in the USA⁸. Most often, between CKD and cardiovascular pathology (especially the presence of hypertension) there is a close relationship, so CKD contributes as an accelerator of CVD and the CVD deteriorates faster the GFR, accelerating CKD progression to stage 5, the final stage of CKD. The most common causes of CKD remain high blood pressure, diabetes, atherosclerosis and glomerulonephritis⁸. Patients with CKD stage 1-3 are usually asymptomatic, clinical manifestations begin to appear with reduced GFR, especially in stages 4-5, when hydro-electrolytic disorders (most common hyperkalemia), endocrine disorders (including secondary anemia), metabolic acidosis, caloric protein malnutrition occur, all with a negative impact both on the general condition of the patient and the GFR. Because stage 3 seems to be the most common, it is extremely important to recognize the association with other pathologies (diabetes, CVD, especially hypertension, MS) and to treat them intensively, to try to slow down the reduction of GFR and secondary

to delay the evolution of the patient towards stage 5 of GFR. This not only represents an immense financial burden, but also the quality of life of these patients is greatly affected, and the risk of mortality in patients undergoing renal replacement treatment is much higher⁹.

DM is considered nowadays a global health problem, recent data claiming that in 2017 there were over 450 million diabetic patients; also, it is estimated that in the future the incidence of this disease will rapidly increase¹⁰, due to some relevant factors included in patient's life style: eating habits, level of physical activity, alcohol consumption, tobacco, and/or drugs, etc. The importance of this condition is based on the risk of premature death, representing itself an independent cardiovascular risk factor for CKD and many other complications (micro and macrovascular), that not only strongly influence the quality of life but also the morbidity and mortality (increasing by 2-4 times the cardiovascular mortality)^{8,11}.

Hyperuricemia is induced by alterations in purine metabolism and increased serum uric acid is associated with increased risk of developing T2DM, as shown by recent studies¹². It is arbitrarily defined as serum uric acid values >420 mmol/L in men and >360 mmol/L in women, respectively 6-7 mg/dL. The association of the two factors is frequent and the possible connections between the pathogenic mechanisms by which the presence of hyperuricemia influences and/or induces the appearance of T2DM have been studied. It seems that hyperuricemia is strongly associated with both CKD (which is negatively influenced by the proinflammatory role triggered at the endothelial level) and CVD, being a real connection between them, and the onset of T2DM negatively accentuates the risk of their individual progression, as well as the risk of mortality.

Uric acid itself is a paradox, being both a protective factor, with an antioxidant role, and a well-known pro-inflammatory/pro-oxidant role¹³. The antioxidant action seems to depend a lot on the presence of the hydrophobic environment, when the oxidative stress decreases. It is known that reactive oxygen species (ROS) are associated with local inflammation, nitric oxide (NO) production, insulin resistance, activation of the renin-angiotensin system and fat accumulation, causing changes in adipocytes so that the pro-oxidant role is better studied and strongly associated with cardiovascular, diabetes and renal pathology¹⁴.

THE OBJECTIVE OF THE STUDY

Considering the strong and frequent association between MS, CKD, T2DM, associated or not with hyperuricemia, our study explored the impact

of hyperuricemia on the prevalence of MS, as well as on the glomerular function in a group of T2DM patients.

MATERIALS AND METHODS

In this retrospective study there were included 300 patients with T2DM, hospitalized for one day in the diabetes clinic of the County Clinical Emergency Hospital, Oradea, Romania, between 01.01.2016-31.12.2018. The selection of patients was possible using a systematic sampling method, every tenth hospitalized patient being included in the research; all the data used for the analysis were obtained from the medical records. For each patient there were determined the following variables:

- anthropometric parameters (height, weight, body mass index (BMI));
- type and duration (in years) of T2DM;
- presence of CVD comorbidities (hypertension, myocardial infarction, ischemic heart disease), dyslipidemia, hepatic steatosis, presence of micro/macrovascular complications (diabetic retinopathy, diabetic polyneuropathy, arteriopathy);
- biological tests values: blood glucose, current and previous glycosylated hemoglobin, liver tests, hemoglobin, current and previous creatinine, current and former GFR, uric acid, lipid profile (cholesterol, TGL, HDL, LDL-cholesterol, TGL/HDL-ratio), the presence of proteinuria and/or changes in the urinary sediment;
- treatment for MS components (T2DM, hypertension, dyslipidemia), treatment of hyperuricemia and/or other treatments (antiplatelet/anticoagulant, neurotropic).

The inclusion criteria were as follows: age >18 years, confirmed T2DM and complete data in the medical records. The exclusion criteria were considered: incomplete data needed for the study, subjects under medication that may have influenced the results (glucocorticoids) and/or with major acute infections (not to influence blood glucose levels).

The study was carried out with the agreement of the Hospital Ethics Committee, no. 11379/07.05.2019 and it was conducted respecting the World Medical Association Code of Ethics - 1967, Declaration of Helsinki. Every patient signed an informed consent before being included in the study.

MS has been defined according to International Diabetes Federation¹⁵ as the presence of three of the following conditions: high blood pressure (systolic blood pressure (SBP) \geq 130 mmHg or diastolic blood pressure (DBP) \geq 85 mmHg or treatment for hypertension), hypertriglyceridemia \geq 150 mg/dL or lipid-lowering treatment, increased fasting blood glucose

>100 mg/dL or antidiabetic treatment, reduction of HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women, for those with BMI>30 kg/m² - central obesity can be affirmed, even if abdominal circumference was not measured.

Blood pressure values (according to the European Society of Cardiology/European Society of Hypertension 2018 Guidelines for the management of hypertension¹⁵) were defined as: normal SBP<130 mm Hg, DBP<85 mm Hg; normal-high SBP between 130-139 mm Hg, DBP between 85-89 mmHg; target values for those with hypertension and treatment: below 140/90 mm Hg.

Serum uric acid was considered elevated if it had values above 6 mg/dL in women, respectively 7 mg/dL in men^{16,17}. In the analysis performed there were included patients with hyperuricemia who have values above these thresholds and those who have normal serum uric acid values but have hyperuricemia treatment (regardless of the type of medication).

CKD was defined according to the guidelines by (1) reduction of GFR below 60 mL/min/1.73m², with a minimum duration of 3 months or (2) renal impairment lasting more than 3 months. Renal impairment can be diagnosed in the absence of knowledge of the etiology and consists of structural or functional abnormalities of the kidney reflected by: anomalies of urine examinations (proteinuria, albuminuria, hematuria, and leukocytosis), abnormalities of blood tests (nitrogen retention, dyselectrolytemias, metabolic acidosis), abnormalities of renal imaging investigations, pathological lesions of the kidneys at renal biopsy¹⁸.

Statistical analysis was performed using Biostat software version 5.9.8.5; to compare frequencies, Chi-squared test was used, and to find mean values the ANOVA test was used; p values <0.05 were considered statistically significant.

RESULTS

Following the analysis of the studied group, out of the 300 cases, 138 were identified with hyperuricemia and 162 with normo-uricemia. The prevalence of hyperuricemia was 46%. The average age of the patients was 62 years. The characteristics of the patients with hyperuricemia and normo-uricemia are shown in Table 1. Among patients with hyperuricemia, the prevalence of obesity, hypertension, ischemic heart disease, CKD, MS and its components are statistically significantly higher than in patients with normo-uricemia; all these parameters are presented comparatively in Figures 1 and 2, and Table 2.

In patients with hyperuricemia, the mean values of SBP and DBP were statistically insignificant higher than in patients with normo-uricemia. Triglycerides

Table 1. Comorbidities of patients with hyperuricemia/ normo-uricemia.

Parameter	Unit of measure	Hyperuricemia (n=138)	Normo-uricemia (n=162)	p
Age	Years	62	61.39	NS
Living environment (urban/rural)	%	65.94/34.06	68.51/31.49	NS
Gender (male/female)	%	52.9/47.1	51.85/48.15	NS
T2DM/T1DM	%	99.27/0.73	95.68/4.32	NS
GFR	mL/min/1.73m ²	62.81	73.21	<0.01
BMI	kg/m ²	34.98	30.79	<0.01
Obesity		88.4	61.72	<0.01
Obesity grade 1		46.38	40.74	
Obesity grade 2	%	26.81	16.67	<0.01
Obesity grade 3	%	15.22	4.32	
Normal weight	%	1.45	11.73	
Overweight	%	10.14	26.54	
Diabetes duration	%	9.57	8.84	NS
Diabetic polyneuropathy	Years	71.74	62.35	NS
Diabetic retinopathy	%	33.33	30.86	NS
Chronic kidney disease	%	49.28	25.31	<0.01
Hypertension	%	92.75	83.33	0.01
Ischemic heart disease	%	83.33	72.84	0.02
Heart failure	%	44.93	31.48	0.01
Myocardial infarction	%	6.52	6.17	NS
Stroke	%	9.42	5.56	NS
Peripheral artery disease	%	31.88	22.22	NS
Hepatic steatosis	%	81.11	57.41	<0.01
Chronic obstructive pulmonary disease	%	24.64	22.84	NS
Prostate adenoma		13.77	15.43	NS
Hypothyroidism		28.26	25.31	NS

Table 2. Clinical/ paraclinical characteristics of patients with hyperuricemia/ normo-uricemia.

Parameter	Unit of measure	Hyperuricemia (n=138)	Standard dev.	Normo-uricemia (n=162)	Standard dev.	p
SBP	mm Hg	145.13	18.57	143.56	19.7	0.48
DBP	mm Hg	86.11	11.94	85.37	12.33	0.6
Heart rate	beats/min	80.08	12.31	78.88	11.48	0.38
Ankle-brachial index right foot		0.99	0.14	1.02	0.16	0.14
Ankle-brachial index left foot		0.99	0.14	1.01	0.15	0.18
Glycaemia	mg/dL	175.94	65.57	181.8	81.49	0.49
Cholesterol		191.48	53.21	189.01	55.18	0.69
Triglycerides		227.34	(117.5, 272.5)	174.96	(94, 171.25)	<0.01
LDL-cholesterol		110.97	47.08	117.82	48.9	0.23
HDL-cholesterol		37.34	8.58	46.98	13.59	<0.01
TRIG/HDL-ratio		6.92	8.02	4.46	15.39	0.04
CRP	mg/dL	2.41	4.53	0.72	0.89	<0.01
VSH	mm/h	21.82	17.43	16.63	13.35	<0.01
HbA1c	%	8.04	1.74	8.07	2.01	0.75
Creatinine	mg/dL	1.28	0.73	1.04	0.38	<0.01
GFR	mL/min/1.73m ²	62.96	24.58	73.1	22.09	<0.01
Urea	mg/dL	49.2	25.65	41.67	18.28	<0.01

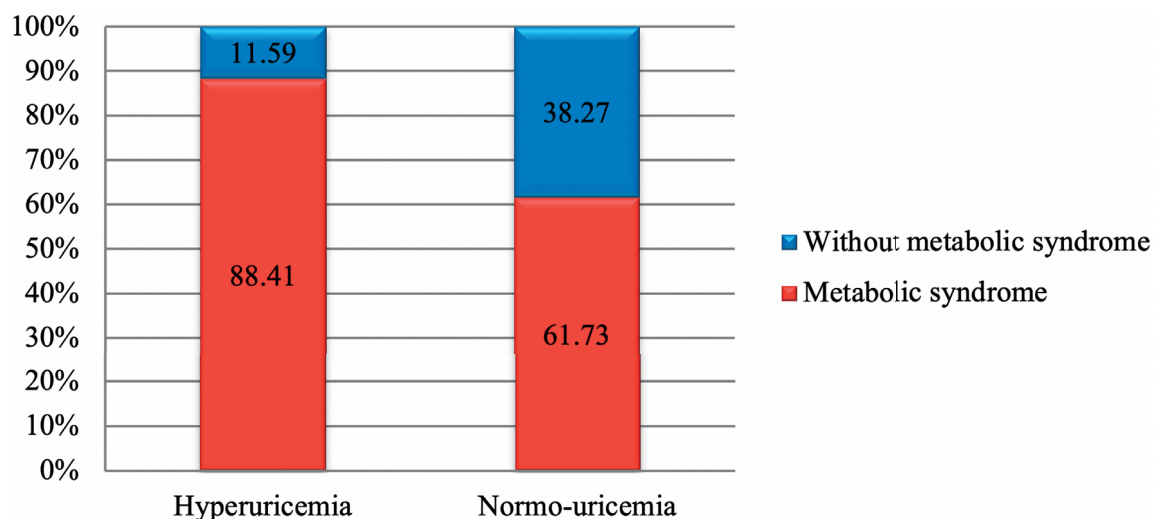


Figure 1. Prevalence of MS in patients with hyperuricemia/ normo-uricemia.

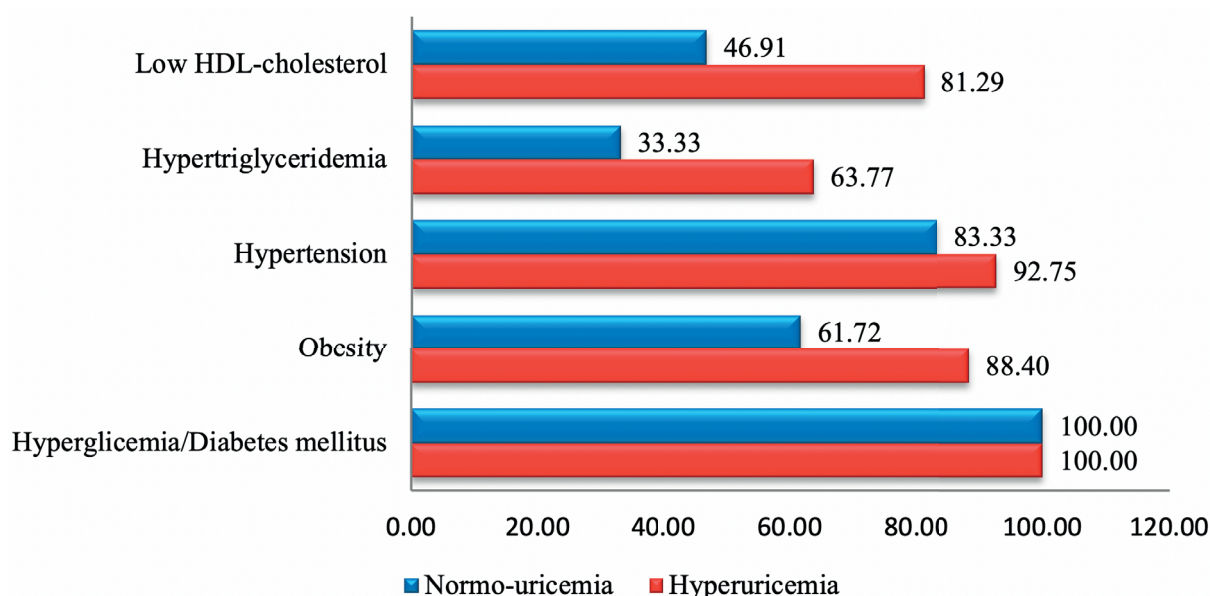


Figure 2. Prevalence of components of MS in T2DM patients with hyperuricemia/ normo-uricemia.

had statistically significant higher values in the hyperuricemia group ($p < 0.01$), the mean HDL-cholesterol value being statistically significant lower in the hyperuricemia group ($p < 0.01$). The TRIG/HDL-cholesterol ratio is statistically significant higher in patients with hyperuricemia compared to those without hyperuricemia ($p = 0.04$). C-reactive protein and erythrocyte sedimentation rate values were statistically significant higher in patients with hyperuricemia ($p < 0.01$). The current renal function evidenced by creatinine, blood urea nitrogen and GFR, was statistically significant lower in patients with hyperuricemia ($p < 0.01$) (Table 2).

Regarding the analysis of groups from the point of view of the renal function, quantified by GFR,

there are statistically significant differences between groups, the prevalence of the altered renal function being statistically significant higher in the hyperuricemia patients (Table 3). The association between hyperuricemia and MS is characterized by the high prevalence of CKD, which demonstrates the negative impact that the two parameters have on the renal function (Figure 3).

DISCUSSION

Hyperuricemia is known as a risk factor for T2DM, as it causes proinflammatory endocrine imbalance in vascular smooth muscle cells and adipose

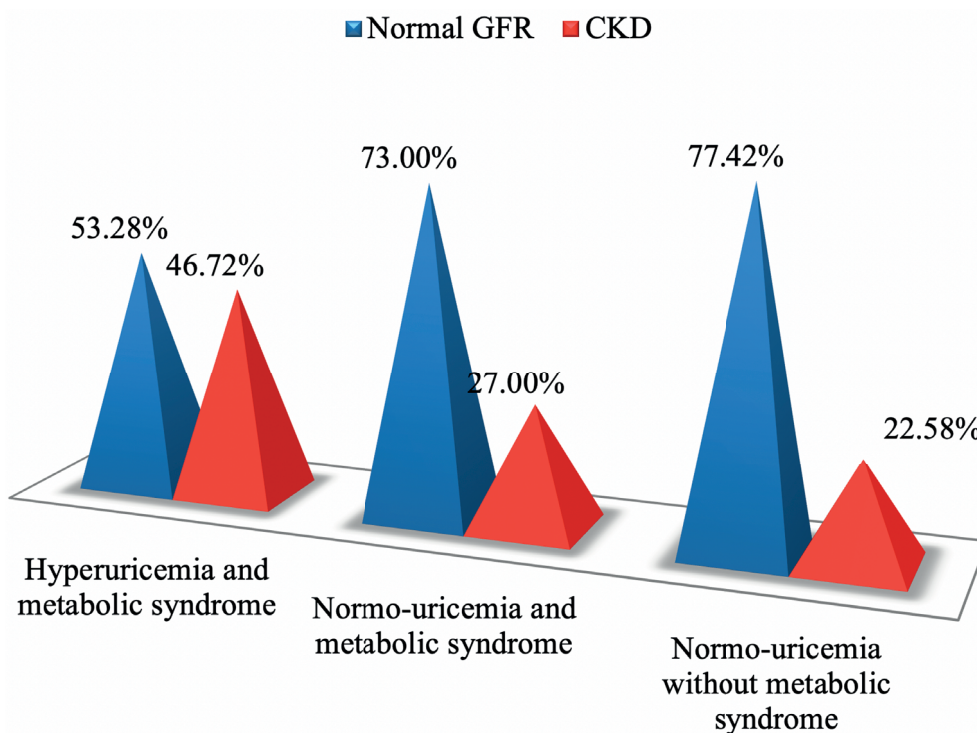


Figure 3. The association between uric acid, MS and CKD.

tissue, which results in morphological changes in cell surface, as well as changes in insulin resistance^{19,20}. Through the mechanisms identified (which lead to an increased risk of T2DM in patients suffering from this imbalance), hyperuricemia produces: increased inflammation (elevated levels of IL-1, IL-6 and TNF- α), increased level/ concentrations of ROS (uric acid has antioxidant actions in plasma and prooxidant action in tissues), endothelial dysfunction, by reducing the bioavailability of NO and inhibiting the insulin pathway²¹.

This study shows that the prevalence of hyperuricemia in a population of 300 patients with T2DM was 46%. This prevalence is much higher than the prevalence of hyperuricemia reported in studies performed on general population; a study performed on the US population demonstrated a prevalence of 21.4%²¹. Data from the literature demonstrated that hyperuricemia in patients with T2DM is associated with an increased risk of macrovascular and microvascular complications. There is a J-shape curve between serum uric acid values and macrovascular complications in patients with T2DM²²; it is also highlighted in the current study, where the patients with hyperuricemia had a statistically significant higher prevalence of ischemic heart disease, hypertension²³ and heart failure. Uric acid is also associated with microvascular complications, among them being the diabetic nephropathy. At the kidney level, hyperuricemia

Table 3. Prevalence of glomerular filtration rate intervals among patients with hyperuricemia/ normo-uricemia ($p < 0.01$)

GFR	Hyperuricemia (n=138)		Normo-uricemia (n=162)	
	No.	%	No.	%
mL/min				
Normal	18	13.04	38	23.46
60-90	52	37.68	83	51.23
30-59	55	39.86	36	22.22
15-29	12	8.70	5	3.09
GFR <15	1	0.72	0	0.00

increases oxidative stress and activates the renin-angiotensin-aldosterone system²¹. Studies demonstrate that serum uric acid is an independent risk factor for reduced glomerular function in patients with T2DM. It was found that even high-normal values of uric acid in patients with T2DM represent a risk factor for progression to CKD stage 3 or higher, in the follow-up period, compared with patients who had lower values of serum uric acid²⁴.

Hyperuricemia was associated with all the other components of MS: hypertension, obesity, dyslipidemia²⁴. Data from the literature show that the presence of serum uric acid ≥ 7 mg/dL was associated with 80% higher risk of developing hypertension²⁵. Hyperuricemia was associated with

atherosclerotic disease, the pathogenic mechanisms being endothelial dysfunction generated by uric acid crystals, increased ROS generation, oxidation of LDL-cholesterol particles, increased proliferation of vascular smooth muscle cells²⁶. In patients with hyperuricemia, an elevated level of serum triglycerides is found due to insulin resistance and free fatty acids that accumulate in the liver, leading to hepatic steatosis²⁷. Hyperuricemia is associated with obesity, increasing monocyte infiltration in the adipose tissue and decreasing the lipid turnover²⁸. In this research, hyperuricemia in patients with T2DM was associated with a statistically significant higher prevalence of all the components of MS. Recent studies suggest that increased serum uric acid is associated not only with increased cardiovascular morbidity risk but also with increased cancer risk, especially breast cancer, because it promotes inflammation and more aggressive tumor cell biology²⁹.

It is advisable for dietitians and those who benefit from public health education to pay more attention to the target values of biological parameters, especially regarding their MS-related illnesses. Associated medical education should be provided when needed. For patients with only hyperuricemia, dietary health education related to MS should be offered as additional help for patients, in order to better control their uric acid value.

CONCLUSIONS

Hyperuricemia is associated with increased MS prevalence and increased prevalence of CKD in T2DM patients. Identifying hyperuricemia in these patients is useful for carefully identifying cardiovascular risk factors and silent CVD in T2DM patients and treating hyperuricemia itself appears to be useful in reducing cardiovascular risk. Obviously, more attention should be paid to the diseases induced or potentiated by hyperuricemia. The incidence of this parameter/pathology can be decreased by changing the eating habits (less foods containing high levels of purine – organs of animal origin, seafood etc, while increasing the consumption of fruits, vegetables, eggs and milk). Health education, promoted in order to reduce the incidence of some pathologies, must be made in such a way as to lead to the awareness of the population regarding the dangers of the appearance/existence of hyperuricemia, but also of its complications.

Author Contributions:

Conceptualization, A.B. and S.B.; methodology, A.B.; software, C.M.V.; validation, T.B. and L.L.; formal

analysis, T.B. and F.U.; investigation, A.B.; resources, R.A.C.A.; data curation, A.B. and C.M.V.; writing–original draft preparation, A.B.; writing–review and editing, S.B, I.R.,C.M.V.; visualization, F.U. and R.A.C.A.; supervision, S.B.; project administration, L.L. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study“

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