

# The Impact Of Hyperuricemia On Cardiometabolic Risk Factors In Patients With Diabetes Mellitus: A Cross-Sectional Study

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**Purpose:** Hyperuricemia (HUA) is linked to a variety of non-communicable diseases such as atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD) and hypertension, with evidence showing its role in the development of diabetes mellitus (DM). Our study's main aim was to explore the associations of HUA with other traditional risk factors in Romanian patients with DM and to assess the impact of the increase of serum UA on DM complications and HbA1c.

**Patients and methods:** In this cross-sectional, non-interventional study, we enrolled, according to a population-based, consecutive-case principle, 133 patients previously diagnosed with DM. HbA1c, uric acid, lipid profile, urinary albumin/creatinine ratio, glomerular filtration rate, TSH and FT<sub>4</sub> measurements were performed, while the diagnosis of retinopathy and of diabetic neuropathy was established using standardized methods.

**Results:** An increased uric acid level was associated with a significant increase in the risk for development of stroke (OR=1.526; p=0.004). A weak, positive and statistically significant correlation can also be observed between the BMI and the presence of hyperuricemia (r=0.131; p=0.034), and between the triglyceride levels and hyperuricemia (r= 0.173; p=0.004). Glomerular filtration rate was correlated to hyperuricemia in a strong and negative manner, having an important statistical significance (r=-0.818; p=0.003). In our study, UA levels and HbA1c were negatively correlated, without reaching statistical significance.

**Conclusion:** Serum UA is strongly correlated with the BMI, triglyceride level and GFR in Romanian patients with DM and HUA is significantly associated with a higher risk of stroke in these individuals.

**Keywords:** uric acid, diabetes mellitus, metabolic syndrome, chronic diseases

## Introduction

Diabetes mellitus (DM) is affecting almost half a billion people worldwide and its prevalence is rising continuously, being estimated to reach more than 620 million patients by 2045. It is also known that DM is one of the leading causes of cardiovascular disease (CVD), chronic kidney disease (CKD), vision loss and nontraumatic lower-limb amputation.<sup>1</sup> Its presence is strongly associated with an increase in the incidence of both stable and unstable angina, non-fatal myocardial infarction, heart failure and peripheral arterial disease,<sup>2</sup> doubling or even tripling the risk of developing atherosclerotic cardiovascular disease (ASCVD), the leading cause of mortality in the world.<sup>3</sup>

There is a growing body of evidence supporting the fact that high levels of uric acid (UA) are linked to multiple chronic diseases such as hypertension, chronic

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kidney disease, ASCVD, dyslipidemia and non-alcoholic fatty liver disease (NAFLD),<sup>4</sup> while normal concentrations may have a protective effect against dementia (in those without cardiovascular risk factors)<sup>5</sup> and on the bone metabolism.<sup>6</sup>

Emerging evidence underlines the role hyperuricemia (HUA) has in the development of DM, data from the Atherosclerosis Risk in Communities Study showing that UA levels are associated with an increased risk of DM even after adjustment for other risk factors, alongside findings from the Rotterdam Study that state that serum UA is a strong independent risk factor for DM and the Framingham Heart Study that proves that individuals with higher UA levels associate a greater risk for the development of T2DM.<sup>7-9</sup> However, these studies relied on a singular measurement of serum UA levels, whereas it has been proven that persistent HUA is more appropriate in assessing the risk of DM development.<sup>10</sup>

Diabetic dyslipidemia is a cluster of plasma lipid and lipoprotein abnormalities and includes, among others, elevated triglycerides, low HDL cholesterol and an increase in small and dense LDL cholesterol.<sup>11,12</sup> Increased production of triglycerides in the liver also associates with de novo purine synthetization, an accelerator of the production of UA.<sup>13</sup>

Diabetic retinopathy represents the most common cause of vision loss in patients with both T1DM and T2DM patients. In addition to insufficient glycemic control, recent studies found that high monosodium urate levels are correlated with increased inflammation markers and xanthine oxidase expression in the post-mortem analysis of diabetic patient's retinas and vitreous and concludes that even asymptomatic HUA is to be considered a risk factor for the induction and progression of diabetic retinopathy.<sup>14</sup>

It is common for patients with DM to have associated also several other risk factors, such as dyslipidemia, obesity and hypertension and multiple studies have proven the efficacy of addressing all of these conditions simultaneously.<sup>15</sup> DM is also included in the constellation that is represented by the metabolic syndrome (MS).

A singular definition for metabolic syndrome is not available due to slightly different criteria proposed by each of the working groups, thus leading to difficulties in establishing its prevalence.<sup>16</sup> In spite of this aspect, there are elements of the MS cluster unanimously agreed upon, such as: DM and prediabetes, high blood pressure, elevated triglycerides and abdominal obesity. MS also includes a

prothrombotic, hypofibrinolytic state, endothelial dysfunction, chronic subclinical inflammation, NAFLD, hemodynamic changes and HUA.<sup>17</sup>

Diabetic patients usually exhibit higher waist circumferences and higher BMIs, leading to higher leptin production and insulin resistance (IR), both of which are known to decrease the excretion rate of uric acid.<sup>13</sup>

The vast majority of cardiovascular events are caused by atherosclerosis, DM and MS being well known to accelerate this process.<sup>18</sup> HUA is in itself a cause of endothelial dysfunction, therefore increasing the oxidative stress which leads to a decrease in nitric oxide bioavailability and vascular smooth muscle cell proliferation.<sup>19</sup>

A higher risk of premature death was found in patients with gout, as shown from results of large-scale epidemiological studies.<sup>20,21</sup> Men with gout had a 28% higher risk of death compared to men without gout, independent from other risk factors.<sup>22</sup> Associating both the diagnosis of gout and that of HUA increases risk of all-cause mortality mainly derived from an increased CVD mortality.<sup>20</sup>

Given the fact that HUA, CVD and DM oftentimes associate in a patient, special attention must be provided to the treatment of these individuals in order to lower mortality and complication rates, as well as to offer the best quality of life. One study showed that the administration of urate-lowering therapy, namely allopurinol, led to a 23% decrease in mortality, although researchers are unsure if this effect was solely due to the lowering of urate levels or to other beneficial effects of the drug. These results were obtained independent from other factors such as age, sex, BMI, albumin, GFR, comorbidities or health-care utilisation.<sup>23</sup> It is even suggested that an effective control of serum UA may have an important role in the prevention of CVD.<sup>24</sup>

Having these premises, the aim of our study was to explore the associations of HUA with other traditional risk factors in Romanian patients with DM and to assess the impact of the increase of serum UA on DM complications and on HbA1c.

## Patients And Methods

### Study Design And Patients

In this cross-sectional, non-interventional study, we enrolled 133 patients previously diagnosed with DM, admitted in the Diabetes Compartment of the Emergency Hospital Timisoara, Romania. Patients participating in the study were enrolled according to a population-based, consecutive-case principle. All patients provided written

informed consent prior to any study procedure or activity. Since this is a non-interventional, cross-sectional study, according to the local protocols, it had to be approved only by the Ethics Committee of the “Pius Brinzeu” Emergency Hospital Timisoara. The entire study was conducted according to the principles stated in the Declaration of Helsinki. Exclusion criteria had been considered to be the inability to provide informed consent, the inability to provide accurate anamnestic data or any condition which, in the investigators’ opinion, could lead to biases in the study results.

## Clinical, Anthropometric And Laboratory Data

Data regarding the patients’ age, body mass index (BMI), hypertension, coronary artery disease, stroke, peripheral artery disease and peripheral venous insufficiency were collected from the patients’ medical records. HbA1c, UA, lipid profile, urinary albumin/creatinine ratio, glomerular filtration rate, TSH and FT<sub>4</sub> measurements were performed after at least 12 hrs of fasting and the drawn blood and the collected urine were analyzed using standardized methods. UA was measured once during the study. We considered as HUA levels that exceeded the UA reference values of our laboratory which are 2.6–6 mg/dL in women and 3.5–7.2 mg/dL in men. The diagnosis of retinopathy was established after performing a fundoscopic examination by the same trained ophthalmologist, specialized in the diabetic eye complications. The presence of diabetic neuropathy was assessed using the 10-g monofilament test, pinprick and temperature sensation test and vibration perception test using a 128-Hz tuning fork. The diagnosis of stroke was based on history taking, while the diagnosis of peripheral artery disease was established using the ankle-brachial index.

## Statistical Analysis

Data were collected and analyzed using SPSS v.17 (SPSS Inc, Chicago, IL, USA). The results are presented as mean ± standard deviation for numerical variables with Gaussian distribution, median and [interquartile range] for numerical variables with non-parametric distribution, respectively, as percentage from the subgroup’s total and frequencies for nominal variables. To assess the normality of the numerical variable’s distribution, the Shapiro and Wilk method was used – a p-value lower than 0.05 obtained at this test was associated with non-parametric distributions.

The statistical significance of differences between groups was assessed using the unpaired t-student test (numerical variables with Gaussian distribution), Mann–Whitney U-test (numerical variables with non-parametric distribution) respectively, the Chi-Square test for nominal variables.

To evaluate the impact of the UA levels on the risk for development of several pathologies and complications univariable and multivariable logistic regression models were built, containing the UA levels as a predictor. The selection of the other predictors in the multivariable regression models was performed in a backward-stepwise manner.

The sample size of the studied lot was calculated prior enrollment, based on previous similar literature data, to provide a confidence level of 95% and a statistical power of at least 80%.

In this study, a p-value lower than 0.05 was considered the threshold of statistical significance.

## Results

Our study lot included 133 patients of which 53.4% (71) were male. The median age of these patients was 63 [54–69]. The prevalence of patients with hyperuricemia was 26.3% (35 cases), 66.2% (88) had diabetic neuropathy, 27.1% (36) suffered from diabetic retinopathy, 81.2% (108) had hypertension, 60.2% (80) were known to have coronary artery disease, 8.3% (11) presented with a history of stroke, peripheral artery disease was encountered in 9.8% (13) of patients and peripheral venous insufficiency in 21.1% (28). A detailed rendition of the patient’s general characteristics at enrolment can be found in [Table 1](#).

The presence of hyperuricemia was associated with a decreased value of estimated glomerular filtration rate (65 mL/min vs 77.5 mL/min;  $p=0.011$ ; [Figure 1](#)). This association and other parameters stratified according to the presence of hyperuricemia can be found in [Table 2](#).

Of the patients with HUA, our data show that 15 (42.9%) were male and 20 (57.1%) were female, gender being not statistically significant associated to the development of this pathology ( $p=0.146$ ).

Hyperuricemia was present in 5 (14.3%) of those without clinical obesity, in 6 (17.1%) of the overweight patients, and in 24 (68.6%) of those with obesity, without statistical significance ( $p=0.183$ ).

Although our data could not statistically link diabetic neuropathy to hyperuricemia ( $p=0.726$ ), 24 (68.6%) of those with hyperuricemia also presented with DN.

**Table 1** Patients' General Characteristics At Enrolment

Age (years) <sup>a</sup>	63 [54–69]
Male gender <sup>b</sup>	71 (53.4%)
HbA1c (%) <sup>c</sup>	8.9 ± 1.8
BMI (kg/m <sup>2</sup> ) <sup>c</sup>	32.2 ± 6.3
Hyperuricemia (%) <sup>b</sup>	35 (26.3%)
Diabetic neuropathy (%) <sup>b</sup>	88 (66.2%)
Diabetic retinopathy (%) <sup>b</sup>	36 (27.1%)
Hypertension (%) <sup>b</sup>	108 (81.2%)
Coronary artery disease (%)	80 (60.2%)
History of stroke (%) <sup>b</sup>	11 (8.3%)
Peripheral artery disease (%) <sup>b</sup>	13 (9.8%)
Peripheral venous insufficiency (%) <sup>b</sup>	28 (21.1%)
Total cholesterol (mg/dL) <sup>c</sup>	199.2 ± 85.1
LDLc (mg/dL) <sup>c</sup>	113.4 ± 50.8
HDLc (mg/dL) <sup>c</sup>	41.6 ± 13.9
Triglycerides (mg/dL) <sup>a</sup>	149 [102–256]
Dyslipidemia (%) <sup>b</sup>	87 (65.4%)
Uric acid (mg/dL) <sup>c</sup>	5.6 ± 2
Urinary albumin/creatinine ratio (mg/g) <sup>a</sup>	27.7 [13–77]
Glomerular filtration rate (mL/min/1.73m <sup>2</sup> ) <sup>a</sup>	78 [58–91]
TSH (mU/L) <sup>a</sup>	1.85 [1.1–3.04]
FT <sub>4</sub> (ng/L) <sup>c</sup>	14.89 ± 4.6

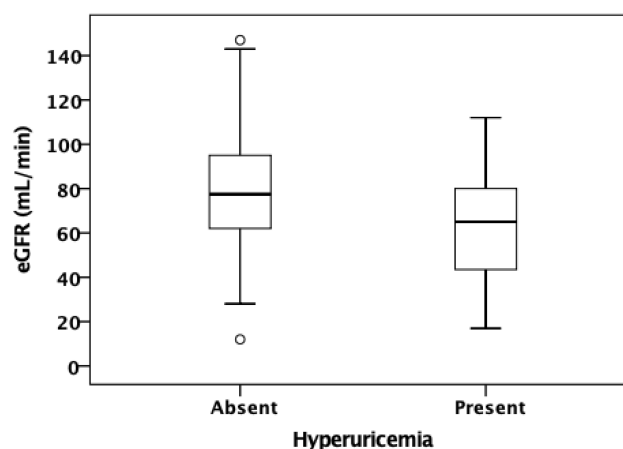
**Notes:** <sup>a</sup>Numerical variables with non-parametric distribution. Results are presented as median and [interquartile range]. <sup>b</sup>Categorical variables. Results are presented as number of cases and (percentage from the total). <sup>c</sup>Numerical variables with Gaussian distribution. Results are presented as mean ± standard deviation.

Of all patients with hyperuricemia, only 9 (25.7%) also had diabetic retinopathy, a statistical significance between the two not being reached ( $p=0.834$ ).

30 (85.7%) of those with hyperuricemia also presented hypertension, without any statistical significance attributed to the link between the two ( $p=0.426$ ).

Coronary artery disease patients represented a total of 23 (65.7%) within the hyperuricemic lot, with a value of  $p=0.433$ , inferring statistical significance.

7 (20%) of patients with hyperuricemia had a history of stroke, this association having a statistically significant quality ( $p=0.003$ ).

**Figure 1** eGFR values in patient with vs without hyperuricemia.

8 (22.9%) of the hyperuricemic patients had chronic venous insufficiency, however without a statistical significance ( $p=0.760$ ).

Steatohepatitis was present in 18 (51.4%) of those with hyperuricemia, although in spite of this important number, a statistical significance regarding the two conditions could not be established ( $p=0.780$ ).

A summary of the data presented above can be found in [Table 3](#).

A weak, positive and statistically significant correlation can be observed between the patient's BMI and the presence

**Table 2** Patients' Characteristics Stratified According To The Presence Of Hyperuricemia

	Without Hyperuricemia	Hyperuricemia Present	p
Age (years) <sup>b</sup>	62 [54–67]	64 [54–70]	0.412
HbA1c (%) <sup>a</sup>	8.9 ± 1.6	8.7 ± 2.3	0.659
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	31.5 ± 5.4	33.5 ± 8.3	0.168
TC (mg/dL) <sup>a</sup>	197 ± 92	205 ± 64	0.634
LDLc (mg/dL) <sup>a</sup>	113.0 ± 53.6	114.7 ± 42.9	0.866
HDLc (mg/dL) <sup>a</sup>	42.7 ± 14.2	38.5 ± 12.5	0.122
TG (mg/dL) <sup>b</sup>	141 [97–248]	176 [125–282]	0.81
GFR (mL/min/1.73m <sup>2</sup> ) <sup>b</sup>	77.5 [62–95]	65 [43–82]	0.011*
ACR (mg/g) <sup>b</sup>	27 [12.9–79.5]	30.3 [13–68]	0.85
TSH (mU/L) <sup>b</sup>	1.85 [1.2–2.9]	1.9 [0.9–3.4]	0.792
FT <sub>4</sub> (ng/L) <sup>a</sup>	14.57 ± 4.37	15.81 ± 5.15	0.298

**Notes:** \*Differences are statistically significant at  $\alpha<0.05$  threshold. <sup>a</sup>Numerical variables with Gaussian distribution. Results are presented as average ± standard deviation. p value was calculated using unpaired t-student test. <sup>b</sup>Numerical variables with non-parametric distribution. Results are presented as median and [interquartile range]. p value was calculated using Mann–Whitney U-test.

**Abbreviations:** BMI, body mass index; TC, total cholesterol; ACR, urinary albumin/creatinine ratio; TSH, Thyroid-stimulating hormone; FT<sub>4</sub>, Thyroxine.

**Table 3** Hyperuricemic Patient's Associated Pathologies

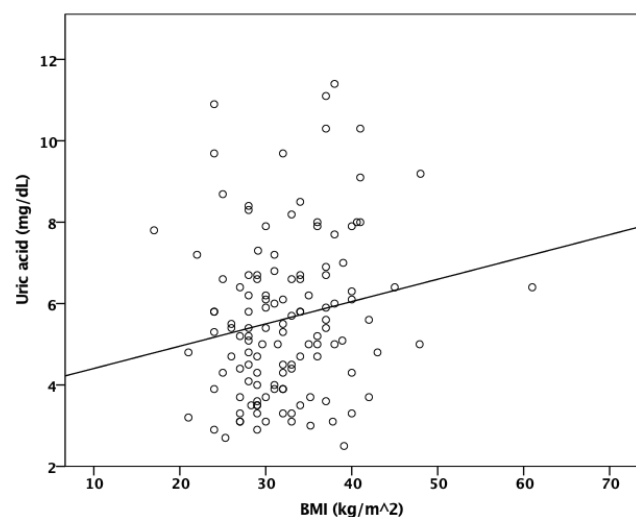
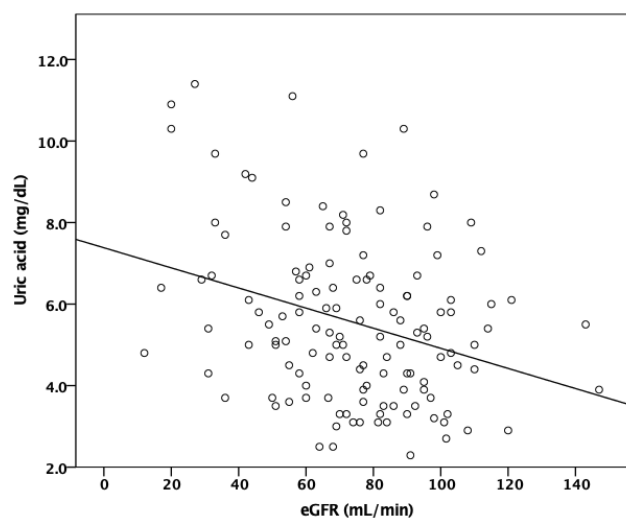
	Hyperuricemia	P value
Diabetic neuropathy (%)	24 (68.6%)	0.726
Diabetic retinopathy (%)	9 (25.7%)	0.834
Hypertension (%)	30 (85.7%)	0.426
Coronary artery disease (%)	23 (65.7%)	0.433
History of stroke (%)	7 (20%)	0.003*
Chronic venous insufficiency (%)	8 (22.9%)	0.760
Steatohepatitis (%)	18 (51.4%)	0.780
Obesity		
Normal BMI (%)	5 (14.3%)	0.183
Overweight (%)	6 (17.1%)	
Obese (%)	24 (68.6)	
Gender		
Male	15 (42.9%)	0.146
Female	20 (57.1%)	

**Notes:** \*Differences are statistically significant at  $\alpha < 0.05$  threshold. Categorical variables. Results are presented as number of cases and (percentage from the total).

of hyperuricemia ( $r=0.131$ ;  $p=0.034$ ; [Figure 2](#)), suggesting that hyperuricemia is more likely to appear with an increase in body weight.

Triglyceride levels and hyperuricemia were also found to be weakly and positively correlated, their correlation being statistically significant ( $r=0.173$ ;  $p=0.004$ ), implying that higher triglyceride levels could be found in patients presenting with hyperuricemia.

Glomerular filtration rate was correlated to hyperuricemia in a strong and negative manner, having an important statistical significance ( $r=-0.818$ ;  $p=0.003$ ; [Figure 3](#)), indicating that hyperuricemia appears in patients with lower glomerular filtration rates.

**Figure 2** Correlation between body mass index and uric acid levels.**Figure 3** Correlation between estimated glomerular filtration rate and uric acid levels.

The detailed correlation analysis between uric acid levels and several parameters is presented in [Table 4](#).

In the univariate logistic regression models built, the UA levels were not associated with a significant impact on the risk for development of diabetic neuropathy (OR= 1.005;  $p=0.956$ ), diabetic retinopathy (OR=0.936;  $p=0.936$ ), hypertension (OR=1.301;  $p=0.053$ ) or coronary artery disease (OR=1.066;  $p=0.489$ ).

An increased uric acid level was associated with a significant increase in the risk for development of stroke (OR=1.526;  $p=0.004$ ). This increase in risk was observed also after correcting several confounding factors, like LDLc, BMI and presence of hypertension ([Table 5](#)).

**Table 4** Correlation Between Patient's Characteristics And Uric Acid Values

	Uric Acid	P value
Age	0.048	0.431
Ketoacidosis	0.064	0.314
BMI	0.131	0.034*
Total Cholesterol	0.052	0.383
LDL <sub>c</sub>	0.036	0.545
HDL <sub>c</sub>	-0.107	0.077
TG	0.173	0.004*
HbA1c	-0.096	0.110
GFR	-0.818	0.003*
ACR	0.088	0.151
TSH	-0.001	0.982
FT <sub>4</sub>	-0.010	0.890

**Notes:** Spearman correlation coefficient. \*Differences are statistically significant at  $\alpha < 0.05$  threshold.



**Table 5** Multivariate Regression Model, Analysing The Risk Of Stroke

Parameter	OR	95% CI	p-value
Uric acid (mg/dL)	1.647	1.163 to 2.332	0.005
BMI (kg/m <sup>2</sup> )	0.936	0.827 to 1.058	0.291
LDLc (mg/dL)	0.990	0.975 to 1.005	0.192

## Discussion

### Findings And Interpretation

This study showed that serum UA is significantly correlated with the BMI, triglyceride level and glomerular filtration rate (GFR) and that HUA is associated with a higher risk of stroke, all of the above in diabetic patients.

Regarding the weight, it is already known that serum UA predicts future weight gain and that HUA induces oxidative stress in the adipose tissue with an impact on insulin resistance and, subsequently, on ASCVD and while it is proven that UA correlates better and positively with waist circumference than with the BMI,<sup>25</sup> the results of our study are similar with the ones already described in literature.

This study's findings about serum UA and triglycerides are supported by others that have confirmed a strong correlation between the dyslipidemia characteristic for metabolic syndrome and UA levels – even better than with the parameters of insulin resistance.<sup>13</sup>

HUA is very prevalent in patients with chronic kidney disease. Moreover, several studies have reported an association between HUA and the reduction of GFR in patients with or without DM, some of them with conflicting results.<sup>26</sup> In our study, serum UA is strongly and negatively correlated with the estimated GFR.

Although multiple studies have shown that HUA is a risk factor for diabetic retinopathy,<sup>14</sup> our data could not statistically link the high levels of UA to this complication. The same applies in our lot of diabetic patients to an association between HUA and hypertension, HUA and coronary artery disease (CAD) and HUA and NAFLD.

However, studies that have investigated an association between serum UA and stroke, in diabetic and non-diabetic patients had conflicting results, some showing a significant and positive correlation, while others concluded the opposite.<sup>27</sup> A meta-analysis including patients with type 2 DM revealed that increased levels of UA may contribute to the development of an ischemic stroke, other prospective studies being recommended.<sup>28</sup> In our

study, a statistical significance regarding the association between HUA and a history of stroke was established.

In regard to the interaction between UA levels and glycaemic values, results vary from suggesting that UA is associated with HbA1c independently of other metabolic factors,<sup>29</sup> to highlighting a non-linear relation between UA and blood glucose levels<sup>30</sup> to some concluding that UA levels are negatively correlated with HbA1c in patients with type 2 DM and positively correlated in individuals with a normal glucose metabolism.<sup>31</sup> The results of our study show that in diabetic patients UA levels and HbA1c are negatively correlated, without reaching statistical significance.

However, our patients were already following an anti-diabetic drug regimen and, in some cases, a hypouricemic therapy. Recent studies have investigated the impact of allopurinol on multiple conditions – results suggesting that it lowers the incidence of ischemic stroke,<sup>32</sup> conflicting results occurring while investigating whether it prevents vascular complications in diabetic patients,<sup>33</sup> findings that could interfere with our data.

Some of the patients included in our study were following an antidiabetic regimen that included a sodium-glucose co-transporter 2 inhibitor, agents that were proven to lower the UA levels<sup>34</sup> and consequently possibly leading to underestimating the prevalence and impact of HUA in diabetic patients.

### Strengths And Weaknesses Of The Study

The strengths of the study are represented by the patients' consecutive enrolment principle which provided a study cohort including individuals with and without hyperuricemia, with a heterogeneous age, BMI, glycaemic control, lipid and complication profile. The sample size is another strong point of our study design, providing enough statistical power and allowing the inference of the results obtained in the sample for the population of interest.

One of the weak points of the study is represented by the possible discrepancy between the characteristics of the evaluated patients and of the general population with DM caused by enrolling individuals admitted in the Diabetes Compartment of the Emergency Hospital for various symptoms, complex treatment changes or for development of acute complications.

Furthermore, the study has a cross-sectional design and thus, knowing that the development of DM complications is a long-term process, it is not possible to establish a time-dependent association between UA levels and stroke, UA levels and diabetic retinopathy or UA levels and the evolution of HbA1c.

## Relevance Of The Findings

HUA is a frequent condition in patients with DM and it is associated with multiple CV risk factors and non-communicable diseases. The results of our study highlight the importance of assessing the UA levels in patients with other cardiometabolic risk factors, with or without DM, for the reason that it appears that UA is correlated with an increased risk of developing CV events – in this case, stroke, and that it is strongly correlated with an increased body weight, hypertriglyceridemia and chronic kidney disease, all of the above commonly found in diabetic patients.

## Future Perspectives

We aim to further develop this study into a prospective one in which we will evaluate the impact of high levels of UA on the development of DM complications. In addition, a possible future approach would be to include patients with a normal glucose metabolism and with prediabetes in order to assess the risk of DM relying on a history of persistent UA levels. Another perspective could be to include data about the hypouricemic agents and to evaluate their impact on different risk factors, on the glycaemic control and on the complications of DM.

## Conclusion

Serum UA is strongly correlated with the BMI, triglyceride level and GFR in patients with DM. Furthermore, HUA is significantly associated with a higher risk of stroke in these individuals. The resulting cluster of risk factors and complications leads to negative consequences on the global management of DM. Therefore, serum UA should be assessed regularly in diabetic patients and if the levels are high, hypouricemic agents should be prescribed accordingly in order to improve the cardiometabolic profile of the patient.

## Disclosure

The authors report no conflicts of interest in this work.

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