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ORIGINAL PAPER

Overweight, insulin resistance and blood pressure (parameters of the metabolic syndrome) in uric acid urolithiasis

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Abstract Overweight, arterial hypertension and disturbances of the carbohydrate metabolism are important parameters of the metabolic syndrome (MS). The most important factor regarding renal pathophysiology is insulin resistance resulting in alterations of urine acidification and low urine pH. Since low urine pH is the main risk factor for uric acid urolithiasis (UAU), UAU may be regarded as a renal manifestation of the MS. So far, there are only few data on the prevalence of parameters of the MS in UAU patients especially with regard to the severity of the disease and recurrence rate, respectively. The objective of this study was to know more about the prevalence of different parameters of the MS and their importance for the natural history of this type of renal stone disease using a total number of 167 consecutive patients with pure UA stones. Stone analysis was performed by polarization microscopy and X-ray diffraction. The following parameters were measured: age, sex, systolic and diastolic arterial blood pressure (RRs and RRd), number of stone episodes, diabetes mellitus (DM); serum: creatinine, calcium, sodium, potassium, uric acid, glucose; urine: pH-profiles, citrate, calcium, uric acid, ammonia, urea, and creatinine. The following results were obtained (means ± standard deviations): age 61 ± 13 years, BMI 30 ± 6 kg/m^2, BP 147/84 ± 22/13 mmHg, number of stone episodes 1.8 ± 1.2, DM 32%; serum: creatinine 1.3 ± 0.6 mg/dl, glucose 136 ± 52 mg/dl, UA 6.3 ± 1.8 mg/dl, calcium 2.4 ± 1.3 mmol/l, sodium 134 ± 18 mmol/l, potassium 4.1 ± 0.4 mmol/l; urine: pH 5.87 ± 0.27, volume 2.4 ± 1.1 l/d, calcium 3.5 ± 2.5 mmol/d, UA 3.9 ± 2.4 mmol/d, citrate 1.3 ± 1.1 mmol/d, ammonia 41 ± 26 mmol/d, urea 390 ± 176 mmol/d. A significant positive correlation could be found for BMI and urea excretion, BMI correlated negatively with RRs and RRd. There was no significant correlation between BMI, urine pH, citrate, ammonia and UA in serum and urine. Undue acidity and hyperuricosuria were found in two-thirds of the UAU patients, increased urea excretion and decreased excretion of ammonia in less than 25%, Hyperuricemia in 37%. There was no significant correlation between the number of stone episodes and any other parameter studied. Overweight, arterial hypertension and DM as parameters of the MS are frequent in many patients with UAU. However, these parameters do explain the pathogenesis in two-thirds of the patients. The severity of the disease and the recurrence are not influenced by the presence of these metabolic parameters. Therefore, MS is no prognostic factor in UAU.

Keywords Metabolic syndrome · Urine pH · Urolithiasis · Nephrolithiasis · Recurrence · Uric acid · Citrate · Ammonia · Diabetes mellitus

Introduction

Overweight, arterial hypertension and disturbances of the carbohydrate metabolism are important parameters of the metabolic syndrome (MS) [17]. In industrialized countries, an increasing percentage of people are affected by MS [1, 4, 7]. Concerning a potential link to urinary stone formation, one of the most important factors in MS is insulin resistance. Insulin increases the production of ammonia in

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the proximal tubules and the Na^+/H^+ ion exchanger [10, 15]. In turn, insulin resistance reduces the production and transport of ammonia resulting in alterations of urine acidification and low urine pH [1]. Insulin resistance may be triggered by hyperuricemia [13]. Since low urine pH is the main risk factor for uric acid urolithiasis (UAU), UAU may be regarded as a renal manifestation of the MS [5, 18]. These observations, however, were derived from very limited numbers of patients. Metabolic investigations with respect to MS in large series of UAU patients are missing so far. Especially with regard to the severity of the disease and recurrence rate no data have been published. Since there is unusually a high percentage of UAU (about 25%) in our region (Upper Franconia) [20], we were interested to know more about the prevalence of different parameters of the MS and their importance for the natural history of this type of renal stone disease.

Patients and methods

A total number of 167 consecutive patients with pure UA (UA and UA dihydrate) stones treated in the Department of Urology and Paediatric Urology at the Klinikum Coburg, Germany were studied. Stone analysis was performed by polarization microscopy and X-ray diffraction.

A detailed history including the number of stone episodes was recorded.

The BMI was calculated after determining body weight and height. Waist circumference was not determined since it could be shown that this parameter did not add more information than the BMI regarding urinary stone pathophysiology [2].

Arterial blood pressure (RR) was measured according to the recommendations of the World Hypertension League sitting after 5 min of rest.

The following parameters were determined in all these patients: Urine pH profiles on three consecutive days at morning (fasting), noon (postprandial) and evening (postprandial). For urine pH measurements, dipsticks were used which allow pH measuring in 0.1 steps (Madaus GmbH, Cologne, Germany). The mean urinary pH was calculated in every patient.

Blood was drawn to measure creatinine (Jaffé reaction, Dade Behring Marburg, Germany), potassium (atomic absorption), calcium (indirect ion sensitive electrode), glucose (postprandially; hexokinase-glucose-6-phosohate dehydrogenase method, Flex™ Siemens Healthcare Diagnostics Newark, DE, USA) and uric acid (modified uricase method, Dade Behring Marburg, Germany). A 24 h-urine specimen was collected to determine the excretion of citrate (citrate lyase method, Boehringer Mannheim, Germany), creatinine (Jaffé reaction, Dade Behring Marburg, Germany), calcium (indirect ion sensitive electrode), uric acid (modified uricase method, Dade Behring Marburg, Germany), ammonia (modified glutamate dehydrogenase method using NADPH, test kit Ammonia Flex™, Dade Int., Newark, DE, USA) and urea (urease-glutamate dehydrogenase, Dade Behring Marburg, Germany) as a marker for protein intake [8].

For statistical analysis means and standard deviations were calculated. In case of equal variance and Gaussian distribution Student's t test, otherwise the Mann–Whitney-test was used.

To assess the influence of different parameters of MS on the severity of UAU, correlations between the stone frequency and these parameters were calculated. For that purpose, the Pearson correlation test was used in case of Gaussian distribution, otherwise the Spearman nonparametric test was used.

Differences were called significant in case of $p < 0.05$. For these analyses, the program Prism 5 (GraphPad Software, San Diego, CA, USA) was used. Calculations were performed on a personal computer.

Results

The clinical characteristics are given in Table 1. Our data show a high number of patients with DM (32%) and a high mean BMI (30 kg/m^2). The mean number of stone episodes was 1.8 per patient.

Blood and urine levels are shown in Tables 2 and 3. Mean urine pH was low as expected. There was an increased excretion of UA and a decreased citraturia.

Patients with and without DM were not different concerning the number of stone episodes (means ± standard deviations 1.73 ± 1.04 versus 1.71 ± 1.26).

We found no significant correlation between BMI, urine pH, UA (blood and urine) and RR. A significant positive correlation could be found for BMI and urea excretion, BMI correlated negatively with RRs and RRd (Table 4).

Table 1 Clinical characteristics (means ± standard deviations) in $n = 167$ UAU patients

	UAU patients (means ± standard deviations)
Age	61 ± 13 years
N° of stone episodes	1.8 ± 1.0
Diabetes mellitus	32%
BMI	30.0 ± 5.6 kg/m^2
RR systolic	147 ± 22 mmHg
RR diastolic	84 ± 13 mmHg

Table 2 Blood parameters (means ± standard deviations) in $n = 167$ UAU patients

	UAU patients (means ± standard deviations)
Creatinine	1.3 ± 0.6 mg/dl
Glucose	136 ± 52 mg/dl
Calcium	2.3 ± 0.2 mmol/l
UA	6.3 ± 1.8 mg/dl
Sodium	134 ± 18 mmol/l
Potassium	4.1 ± 0.4 mmol/l

Table 3 Urine parameters (means ± standard deviations) in $n = 167$ UAU patients

	UAU patients (means ± standard deviations)
Volume	2.4 ± 1.1 l/d
Calcium	3.5 ± 2.5 mmol/d
UA	3.9 ± 2.4 mmol/d
Citrate	1.3 ± 1.1 mmol/d
Urea	390 ± 176 mmol/d
Ammonia	41 ± 26 mmol/d
pH	5.87 ± 0.27

Table 4 Correlations (r) with BMI and levels of significance (p)

	r	p
Blood glucose	0.070	0.61
Blood UA	0.091	0.31
Urine UA	−0.095	0.33
Urine pH	−0.049	0.57
Urine citrate	0.073	0.51
Urine ammonia	0.168	0.09
Urine urea	0.313	0.003*

* Significant correlation

Between RRs/RRd and urine pH, UA (blood and urine) citrate and ammonia, respectively, there was no significant correlation (Table 5).

Blood UA levels did not correlate significantly with uric acid excretion and urinary pH (Table 6).

Between the numbers of stone episodes in UAU patients and the parameters of MS and other clinical characteristics (BMI, age, blood glucose, blood UA, urine levels of pH, UA, citrate, urea and ammonia) we did not observe a significant correlation as well (Table 7).

Not all UAU patients showed the typical risk factors for UAU. Persistently low urine pH and hyperuricosuria was found in about two-thirds, decreased excretion of ammonia and increased urea excretion only in less than a quarter of patients. Hyperuricemia was present in 37% (Table 8).

Table 5 Correlations (r) with RRs and RRd and levels of significance (p)

	RRs		RRd	
	r	p	r	p
BMI	−0.35	0.002*	−0.27	0.02*
Urine pH	0.39	0.75	0.17	0.16
Blood UA	−0.01	0.92	0.24	0.84
Urine UA	−0.08	0.52	−0.02	0.97
Urine citrate	0.17	0.19	0.15	0.23
Urine ammonia	−0.03	0.80	−0.02	0.86
Urine urea	0.10	0.42	0.17	0.17

* Significant correlations

Table 6 Correlations (r) with blood UA and levels of significance (p)

	r	p
Urine UA	−0.11	0.31
Urine pH	0.08	0.40

No significant correlations

Table 7 Correlations (r) with stone frequency and levels of significance (p)

	r	p
BMI	0.11	0.16
Age	0.04	0.62
Blood glucose	−0.21	0.12
Blood UA	−0.08	0.32
Urine UA	0.004	0.96
Urine pH	0.07	0.40
Urine Citrate	−0.13	0.20
Urine Ammonia	0.02	0.84

No significant correlations

Table 8 Percentage of risk factors for UAU in $n = 167$ patients

Risk factor	%
Urine pH ≤5,9	66
Ammonia excretion <20 mmol/d	19
Urea excretion >450 mmol/d	25
UA excretion >3 mmol/d	63
Blood UA >6. 5 mg/dl	37

Discussion

UAU accounts for approximately 10% of urinary stones in most Western countries [14]. In our region Upper

Franconia about 25% of all stones analyzed consist of UA [20]. Risk factors for the formation of UA stones are undue acidity (persistent low urinary pH), hyperuricosuria and low urine volume [9, 14, 19]. Intrinsic metabolic factors and dietary habits contribute to these risk factors.

Concerning undue acidity, insulin resistance plays a key role [1]. Insulin increases the production of ammonia in the proximal tubules and the Na^+/H^+ ion exchanger [10, 15]. In turn, insulin resistance reduces the production and transport of ammonia resulting in alterations of urine acidification and low urine pH [1]. This may explain why obesity and DM are frequently observed in UAU patients [5, 12, 16, 18]. In our large series, the mean BMI was 30.0 ± 5.6 kg/m^2. This is lower than in the small series reported from the USA [1, 16] and higher than those observed in France [5].

DM was observed in 32% of our patients. Daudon et al. [5] observed 28%. The difference may be explained with different BMI and DM findings in the general population in these countries.

Obviously, however, body weight and insulin resistance cannot exclusively explain persistent low urine pH. We did not find a significant correlation between the BMI, blood glucose and urine pH. Furthermore, a decreased excretion of ammonia (<20 mmol/d was found in only 19% of our UAU patients, the mean value (41 mmol/d) being within the normal limits. This is higher than reported in the small series ($n = 13$) reported by Abate [1]. Other factors like arterial hypertension and a diet rich in animal protein could also decrease the urinary pH [11, 14, 21].

Renal Stone patients with hypertension showed a lower urinary pH, a higher excretion of ammonia and hypocitraturia. Losito et al. [11] attributed these observations mainly to a higher BMI in hypertensive subjects and—derived from experimental data—higher salt sensitivity. In our series, we could not observe a significant correlation RRs and d and urinary pH, citrate and ammonia excretion. There was, however, a significant negative correlation between BMI and arterial blood pressure. These differences may be explained—at least in part—by the fact that we studied only patients with pure UAU, whereas Losito et al. [11] reported on renal stone patients, in general, probably being mainly calcium oxalate stone formers.

To assess potential relations to the protein intake, we also investigated the urea excretion in our UAU patients [8]. An increased urea excretion (>450 mmol/d) was observed in 25%. The mean (390 mmol/d) was within the normal limits. There was a significant correlation between BMI and urea excretion. This is in accordance with de Santo et al. [6] who studied urea excretion in children of different age. To our best knowledge, however, our series is the first study investigating urea excretion in UAU patients.

Hyperuricosuria was present in 63% of UAU subjects, the mean (3.9 mmol/d) being higher than the upper limit. The values observed in our study are in accordance with levels reported by others [5, 16, 21]. In idiopathic UAU patients, dietary habits with consumption of food rich in purines may play the most important role [14].

Hyperuricemia could be found in 37% of UAU patients. It is regarded as a trigger for insulin resistance and hypertension [13]. It is frequently found in hypertensive patients and plays a key role in the development and progression of hypertension [23]. Hyperuricemia in hypertensive patients is caused by an impaired renal excretion of uric acid [22]. In UAU patients we found only a slight inverse correlation between serum and urine UA which was far from being significant. Blood UA was not correlated with urine pH.

Concerning the importance of different parameters of the MS for the severity and the recurrence rate of UAU no reports are existing so far. We therefore investigated the influence of various parameters of the MS on the recurrence rate (Table 7). We could not observe any significant correlation between these parameters and the number of stone episodes in UAU patients. The number of stone episodes was not higher in patients with DM than without DM. These parameters of the MS obviously do not influence the course of disease in UAU and cannot be used as a prognostic marker in counselling patients with UAU.

Summing up, we can conclude that UAU is a multifactorial disease. MS with insulin resistance cannot exclusively explain the pathogenesis. UAU patients display single parameters of MS in up to 66%. Hyperuricosuria, however, is present in the same percentage. Concerning the severity of UAU and recurrence rate, parameters of the MS had no influence. Therefore, MS cannot be regarded as a prognostic factor in UAU. Influencing MS by medical measures (e.g. weight reduction, antihypertensive drugs) probably will not result in a lower recurrence rate in UAU patients. Metaphylaxis should rather draw attention to measures improving the solubility of UA. This is in accordance with the observations of Borghi et al. [3] showing that the uric acid supersaturation is the most important factor for UA stone formation with the greatest predictive value.

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