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ORIGINAL CONTRIBUTION

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The effect of a vegetarian and different omnivorous diets on urinary risk factors for uric acid stone formation

Summary *Background* About 10–15 % of all urinary stones are composed of uric acid. A high urinary uric acid excretion, a low urine volume and an acidic urinary pH value are suggested to be the most important risk factors for uric acid stone formation. *Aim of the study* The effect of a vegetarian diet and different omnivorous diets on the risk of uric acid crystallization was investigated. *Methods* Ten healthy male subjects ingested a self-selected meat-containing diet (SD) for two weeks, and three different standardized diets for a period of 5 days each. The Western-type diet (WD) was representative of the usual dietary habits, whereas the balanced omnivorous diet (OD) and the ovo-lacto-vegetarian diet (VD) were calculated according to the requirements. *Results* The risk of uric acid crystallization was highest on the ingestion of diets SD and WD, due to the high urinary uric acid excretion and the acidic urinary pH. The relative supersaturation with uric acid declined significantly by 85 % on the intake of diet OD, consequent to the decrease in uric acid excretion and concentration and the increase in urinary pH value. The ingestion of the vegetarian diet VD led to a further significant reduction in the risk of uric acid crystallization by 93 % compared to diet WD. *Conclusions* The results indicate that the intake of a balanced vegetarian diet with a moderate animal protein and purine content, an adequate fluid intake and a high alkali-load with fruits and vegetables results in the lowest risk of uric acid crystallization compared to the omnivorous diets.

Key words diet – purine – uric acid – urolithiasis

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Introduction

About 10–15 % of all urinary stones are composed of uric acid [1]. Thus, uric acid stones rank second in incidence after calcium oxalate stones. A high urinary uric acid excretion, an acidic urinary pH value and a low urine volume are suggested to be the most important risk factors for the formation of uric acid stones [2].

Diet is the major environmental determinant in the formation of uric acid stones. An elevated protein consumption results in an endogenous acid load and a subsequent increase in renal net acid excretion [3]. A low urinary pH contributes to a rise in the concentration of the poorly soluble undissociated uric acid, whereas the solubility of urinary uric acid increases strongly with increasing pH value [4]. Urinary alkalinization is therefore the most important measure in the treatment and metaphylaxis of uric acid stone formation.

An adequate fluid intake and consequently a sufficient urine volume lowers urinary uric acid concentration. Moreover, the type of beverage may influence urinary composition. Alcohol has been suggested to contribute to an enhanced uric acid production and a delayed excretion. Beer also contains purines that are catabolized to uric acid [5].

Urinary uric acid has been reported to be mainly influenced by modification of dietary purine level. A high dietary purine intake is associated with an enhanced endogenous production and urinary excretion of uric acid [6]. The exchange of foods of animal origin for isoenergetic amounts of vegetable foods may provide the same

quantity of total purines. Since numerous vegetable foods such as cereals and cereal products (bread, pasta), some kinds of fruits and vegetables, seed, nuts, mushrooms, yeast and yeast extracts, dry fruits, chocolate, and legumes (beans, peas, lentils) including soy products contain considerable amounts of purines that may enhance urinary uric acid excretion [7], the effect of a vegetarian diet on the risk of uric acid crystallization is unclear.

Although some information is available concerning the effect of selected foods on urinary uric acid excretion in man [8], the efficacy of the combination of dietary measures assumed to reduce urinary risk factors for uric acid stone formation and consequently the risk of uric acid crystallization has not been validated to date. The formulation of a diet for the prevention of uric acid stone recurrence is based on controlled studies evaluating metabolic induced changes of urinary risk profile in healthy subjects without disturbances in purine metabolism or acid-base status. The present study was designed to assess the benefit or risk of an ovo-lacto vegetarian diet (VD) and different omnivorous diets, i. e. a self-selected (SD), Western-type (WD) and a balanced omnivorous diet (OD) under standardized conditions.

Subjects and methods

Subjects

Ten healthy male volunteers aged 21 to 32 years (mean age: 28 years) participated in the study. The average weight and height of the subjects amounted to (M ± SD) 78.9 ± 11.7 kg and 178.7 ± 4.5 cm. The individuals had no history of gout, renal calculus or other renal disorders. Each subject had normal findings from Combur-9-test strips (Boehringer, Mannheim, Germany) screening urine for pH, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, leucocytes, and blood and did not use any medication or dietary supplements.

Study design and diets

The subjects were studied initially while on their customary home diet for 14 days. The volunteers were instructed to avoid the consumption of purine-rich foods like organ meats and seafood during the free diet. In the following three phases, the subjects were maintained on three different standardized diets for a period of five days each. Recent nutritional studies have shown that most adaptation to a standardized diet, that is the daily constant intake of prescribed foods and fluids, occurs within the first 3 days so that urinary values reach constant levels [3, 9]. The following standard diets were administered to the volunteers: a typical affluent meat-containing Western-type diet (WD), a balanced omnivorous diet (OD), and an ovo-lacto vegetarian diet (VD). Diet WD is representative of the usual dietary habits [10]. Characteristic for a Western diet is a high energy, alcohol and protein content and a fluid intake with beverages of 1.5 l/d. Diets OD and VD were calculated according to the dietary recommendations for the subjects [11]. Diets OD and VD were isoenergetic with equal amounts of the main nutrients and a constant fluid intake of 2.5 l/d. The fluid intake of 2.5 l/d with beverages was adjusted to the dietary recommendations for stone patients to allow investigation of the effect on the risk of uric acid crystallization [12]. Neither diet contained purine-rich foods. In contrast to diet WD, diets OD and VD provided moderate and similar amounts of total purines to enable comparison of changes in the risk of uric acid crystallization induced by both healthy diets. The components of the three standard diets are estimated by use of the computer program PRODI 4 and are specified in Table 1. Purine intake with foods was calculated from tables of Wolfram & Colling, which provided comprehensive data on purine content of most foodstuffs [7]. Daily potential renal acid load (PRAL) of the diets was estimated according to data derived from Remer & Manz [13].

All foods and meals prepared for the diets were exactly weighed, and the apportioned meals were completely ingested. Subjects collected 24-hour urine samples weekly on diet SD. During ingestion of the standard diets, daily 24-hour urines were collected from each subject and analyzed for urinary parameters to ensure the

Table 1 Nutrient contents of the Western-type (WD), balanced omnivorous (OD) and ovo-lacto vegetarian (VD) diets

	Diet WD (n = 10)	Diet OD (n = 10)	Diet VD (n = 10)
Energy (MJ/d)	15.01	10.63	10.88
Total protein (g/d)	95	65	65
• animal protein	56	37	28
• vegetable protein	39	28	37
Total protein (g x kg^{-1} x d^{-1})	1.2	0.8	0.8
Fat (g/d)	132	82	84
Carbohydrates (g/d)	380	370	386
Potassium (mg/d)	3560	3314	6584
Fibers (g/d)	24	28	52
Alcohol (g/d)	49	0	0
Total purines (mg/d)[a]	820	659	643
PRAL (mEq)[b]	82	32	−10
Fluid			
• total fluid (ml/d)	2340	3560	4030
• fluid intake with beverages (ml/d)	1500	2500	2500

[a] Data were estimated from reference 7
[b] Data were estimated from reference 13

adaptation to each diet. Freshly voided urines were preserved with thymol and kept refrigerated at 4 °C. Urine samples were immediately stored below –20 °C after collection.

Analytical procedures

Urine volume, pH-value (potentiometry) and the concentrations of creatinine (Jaffé reaction; CV 2 %), chloride (coulomb metric titration; CV 2 %), sodium (flame photometry; CV 1.3 %), sulfate (nephelometry, CV < 5 %), phosphate (phosphate molybdate reaction; CV < 5 %), ammonium (ion selective electrode; CV 1.5 %) and uric acid (enzymatically, uricase; CV < 5 %) were measured by standard methods.

The risk of uric acid crystallization computed as relative supersaturation of each 24-hour urine sample was estimated by means of the computer program EQUIL2 [14]. The program EQUIL2 is the international state-of-the-art procedure for estimation of the risk of crystallization according to thermodynamic considerations based on measurements of urinary pH and molar concentrations of a number of urinary constituents. Supersaturation with uric acid is mainly a function of urinary uric acid concentration and urinary pH. Crystalluria occurs as a consequence of supersaturation in both normal and stone forming subjects. For crystallization a sufficient level of urinary supersaturation is required. Stone formation is the end result of a pathological crystallization process.

Statistical analysis

Data are presented as means ± SD. A repeated-measures analysis of variance approach (one-way ANOVA) was applied to evaluate the effect of different diets on urinary variables. Comparisons between paired observations at different diets (SD vs. WD, WD vs. OD, OD vs. VD, WD vs. VD) were evaluated by linear contrasts. The last day of each diet was considered as control day, since then conditions of steady state were reached. Calculations were performed with the SPSS Statistical Software, SPSS Inc., Chicago, IL, Version 8.0. P-values lower than 0.05 were considered significant.

Results

The data are presented in Table 2. Urinary uric acid excretion was highest during ingestion of both, the customary home diet SD and the purine-rich Western-type diet WD. During the intake of the balanced omnivorous diet OD uric acid excretion decreased significantly by 1 mmol/d (25 %) compared to diet WD. On the vegetarian diet VD a significant decline in urinary uric acid excretion was achieved by 0.4 mmol/d (12 %) compared to diet OD and by 1.3 mmol/d (34 %) compared to diet WD.

The urinary pH value was consistently at the lower physiological limit of 5.8 on the self-selected diet SD and the standardized diet WD, which correspond to the usual dietary habits. The shift to diet OD resulted in a significant increase in urinary pH value up to 6.5 on the last day of the phase. The urinary pH finally reached the upper physiological pH limit of 6.8 on the last day of the vegetarian diet VD. The estimation of the potential renal acid load (PRAL) of the diets indicated that an average 24-h urinary pH of about 6.1 should be yielded on the consumption of diet WD, 6.6 on diet OD and 6.9 on diet VD.

Urinary ammonium, sulfate and phosphate excretion were inversely related to the course of urinary pH. On the intake of the free diet SD and the standardized diet WD, urinary ammonium, sulfate and phosphate excretion were highest, decreased significantly on diet OD

Table 2 Urine composition and the relative supersaturation with respect to uric acid (RS uric acid) of ten healthy male subjects consuming a self-selected (SD), Western-type (WD), balanced omnivorous (OD) and an ovo-lacto vegetarian diet (VD) (M, SD)

	Diet SD (n = 10)	Diet WD (n = 10)	Diet OD (n = 10)	Diet VD (n = 10)	P (ANOVA)
Urine volume (l/24 h)	1.29 ± 0.49	1.48 ± 0.38	2.30 ± 0.39[a]	2.45 ± 0.76[b]	< 0.001
pH	6.01 ± 0.47	5.95 ± 0.34	6.51 ± 0.22[a]	6.80 ± 0.21[b, c]	< 0.001
Sodium (mmol/d)	159 ± 75	176 ± 40	146 ± 13[a]	102 ± 48[b, c]	0.045
Chloride (mmol/d)	164 ± 66	169 ± 39	139 ± 17[a]	106 ± 43[b, c]	0.024
Ammonium (mmol/d)	30.8 ± 12.2	38.7 ± 5.1	25.6 ± 6.4[a]	18.7 ± 5.9[b, c]	< 0.001
Phosphate (mmol/d)	32.6 ± 8.1	35.4 ± 5.5	29.4 ± 3.5[a]	25.2 ± 6.3[b]	0.043
Sulfate (mmol/d)	18.5 ± 9.2	22.5 ± 3.1	18.1 ± 1.9[a]	16.1 ± 3.7[b]	0.004
Creatinine (mmol/d)	16.09 ± 4.37	16.88 ± 1.97	15.32 ± 1.31	13.78 ± 3.16	0.183
Uric acid (mmol/d)	3.59 ± 0.94	3.91 ± 0.67	2.93 ± 0.32[a]	2.58 ± 0.52[b, c]	< 0.001
RS Uric acid	2.90 ± 2.70	2.71 ± 2.82	0.41 ± 0.41[a]	0.18 ± 0.15[b, c]	0.009

[a] $P < 0.05$ for the paired observations: diet WD vs. OD
[b] $P < 0.05$ for the paired observations: diet WD vs. VD
[c] $P < 0.05$ for the paired observations: diet OD vs. VD

and were lowest on the ingestion of the vegetarian diet VD compared to all other diets.

The risk of uric acid crystallization was highest on both, the self-selected diet SD and the standardized diet WD, which is representative of the typical affluent eating and drinking habits. On the intake of the balanced omnivorous diet OD, relative supersaturation with uric acid was significantly reduced by 85 % as consequence of the decrease in uric acid excretion and concentration and the increase in urinary pH value. The intake of the vegetarian diet VD led to a further significant decline in the risk of uric acid crystallization by 93 % compared to the Western-type diet WD (Fig. 1).

Discussion

The data presented confirm that the diet composition significantly influences urinary risk factors for uric acid crystallization. Although the intake of purine-rich foods like organ meats, fish, seafood and legumes was excluded, urinary uric acid excretion reached the upper physiological limit of 4 mmol/d on the free diet SD as well as on the standardized diet WD [12], representing typical affluent Western-style dietary habits. The ingestion of the balanced omnivorous diet OD resulted in a significant decrease in urinary uric acid excretion, whereas the lowest urinary uric acid excretion was achieved on the vegetarian diet VD.

Uric acid is the end-product of purine metabolism in humans and is derived from endogenous production as well as from dietary sources. The contribution of endogenous uric acid production to urinary uric acid levels has been demonstrated to be considerably lower than assumed. In 11 healthy individuals on a purine-free, isoenergetic liquid formula diet 24-hour urinary excretion of uric acid reached a minimal value of 330 mg/d (1.96 mmol/d) corresponding to the level of endogenous uric acid production [15]. Between dietary purine intake and urinary uric acid excretion a positive linear correlation has been established [6, 16]. The four purine bases adenine, guanine, hypoxanthine and xanthine are the main dietary sources of uric acid in food. Data from human studies suggested that different purine bases and compounds yielded distinctly marked differences in serum and urinary uric acid levels [17]. Mononucleotides (AMP, GMP) showed a high recovery rate of 80 %, whereas purine nitrogen administered as RNA accounted for about 50 %, and purines in DNA for only about 25 % for urinary uric acid excretion [6, 15, 16]. About 40 % of the purine nitrogen in foods can be expected to be recovered as urinary uric acid, because of the relatively high content of RNA in most foodstuffs and a 30 % intestinal elimination of uric acid [15, 18].

The calculation of the partial contribution of dietary purines to urinary uric acid excretion revealed marked differences in the absorption rate of purines from various diets. Assuming an endogenous uric acid production and excretion of 330 mg/d [15], about 40 % of urinary uric acid on the meat-containing Western-type diet WD would be attributed to the dietary purine compounds, which corresponds to the estimate by Zöllner [15]. On the balanced omnivorous diet OD 25 % and on the vegetarian diet 16 % of urinary uric acid, respectively, are suggested to be derived from exogenous purine intake, although both diets provided similar amounts of purines, protein and energy. The results indicate that dietary purine compounds contribute to urinary uric acid excretion according to the rate of enzymatic hydrolysis of nucleic acids of the foods in the intestine and to the availability of various nucleosides, nucleotides and purine bases for absorption.

Among the nutritional factors that may have influenced purine metabolism and renal uric acid excretion

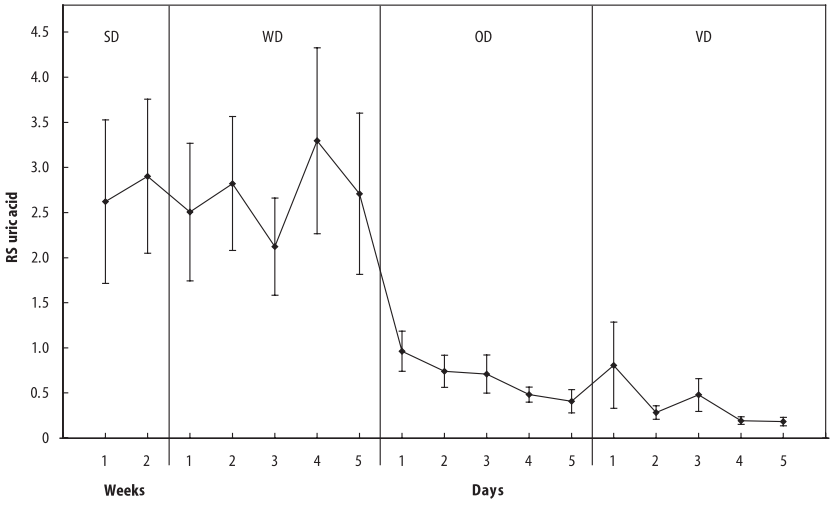

Fig. 1 Relative supersaturation for uric acid (RS uric acid) on a self-selected (SD), Western-type (WD), balanced omnivorous (OD) and an ovo-lacto vegetarian diet (VD) (M, SE)

during ingestion of diet WD, dietary protein and alcohol may play the most important role. Whereas dietary protein is reported to exert uricosuric effects [19, 20], ethanol is suggested to increase uric acid production and to inhibit renal tubular uric acid excretion due to an increased elimination of lactate, a degradation product of ethanol metabolism [21]. Whether a simultaneous increase in both factors, dietary protein and ethanol, exerted antagonistic effects on renal uric acid clearance and urinary excretion cannot be determined from the present study.

Urinary pH value, an important determinant in uric acid stone formation, is the result of the maintenance of a constant plasma pH and therefore strongly influenced by the acid-base status of the organism [2]. Urinary hydrogen ion concentration is dependent on the composition of the diet and represents an index of the renal net acid excretion [3]. A high dietary protein intake accounts for a transient metabolic acidosis and results in a low urinary pH [22, 23]. An inverse relationship between dietary protein intake and urinary pH has been established [24]. The acidic urinary pH on the typical Western-style diet WD is mainly attributable to the high protein content and the only moderate amounts of plant foods. The ingestion of the balanced omnivorous diet OD composed according to the dietary requirements of the subjects resulted in a significant increase in urinary pH mainly due to the reduction of dietary protein. The alkali-load with foods of vegetable origin during the ingestion of the vegetarian diet VD accounted for the further significant increase in urinary pH due to bicarbonate generated from the metabolism of organic acids salts of potassium. The pH values obtained on the intake of the standardized diets WD, OD and VD are close to the calculated acid-forming or base-forming potential, respectively, of the diets obtained with the model for estimation of the potential renal acid load (PRAL) [13]. Obviously, the effective acid load supplied with each diet was higher than the PRAL, since urinary pH values were slightly overestimated. The ratio of the dietary protein and potassium content has been demonstrated to be the major determinant and a significant predictor of variations in the renal net acid excretion among diets in healthy subjects [23]. The present data demonstrate that a urinary pH adjustment to 6.8, according to the recommendations for the treatment of uric acid lithiasis, can be achieved by purely dietary measures.

On the intake of the vegetarian diet (VD), urinary ammonium, sulfate and phosphate excretion were, as expected, lower compared to the omnivorous diets SD, WD and OD. The excretion of ammonium, sulfate and phosphate in urine were inversely related to urinary pH values on the different diets. The tubular glutaminase releases free ammonia from glutamine. In the tubular lumen of the kidney diffused ammonia combines with hydrogen ion to form the physiologically neutral ammonium ion which replaces the sodium ion and preserves the plasma bicarbonate. In patients with uric acid stones, the acidic urinary pH has been attributed to impaired urinary ammonium excretion. The normal systemic acid-base parameters were found to be preserved due to compensation of the lower urinary ammonium excretion by higher titratable acidity [25].

Phosphate can effectively buffer hydrogen ions. Excreted hydrogen ions are bound to secondary phosphate ions, preventing depletion of plasma bicarbonate. Thus disodium hydrogen phosphate is converted to sodium dihydrogen phosphate and sodium bicarbonate. The amount of acid fixed in the urine in these forms is referred to as the titratable acids, i. e. the amount of acid required to neutralize the urine [26].

The level of sulfate excretion in urine is mainly determined by the endogenous degradation of sulfur-containing amino acids (cystine, cysteine and methionine) to sulfuric acid that dissociates to protons and sulfate. A strong and direct correlation of urinary sulfate excretion both with total protein content and with animal protein content is frequently reported [23, 27]. Therefore, the present investigation confirms previous findings of Breslau et al. that the animal protein-rich diet was associated with the highest urinary excretion of undissociated uric acid, sulfate, phosphate, ammonium and net acid excretion, with a corresponding decrease in urinary pH [27].

During the ingestion of the customary home diet (SD) and the typical affluent Western-type diet (WD), respectively, the 24-hour urinary volume was consistently below the therapeutical minimum for uric acid stone patients of 2 l/d. [12]. Due to a higher fluid intake with the balanced omnivorous diet (OD), according to the recommendations for uric acid stone patients, the urinary volume augmented significantly by 0.8 l/d to 2.3 l/d. The additional water intake with fruits and vegetables on the ovo-lacto vegetarian diet (VD) resulted in a further increase in urinary volume by 200 ml/d. A sufficient fluid intake is one of the most important general advices for the prevention of uric acid stone disease.

The risk of uric acid crystallization was highest on both the self-selected diet SD and the customary Western-type diet WD, due to the acidic pH, the low urinary volume and the high urinary uric acid excretion. No difference in the risk of uric acid crystal formation, computed as relative supersaturation, was established between diets SD and WD. The shift to the balanced omnivorous diet OD caused a significant decrease in relative supersaturation for uric acid by 85 % compared to diet WD, due to the significant decline in uric acid excretion and concentration and the increase in the urinary pH value. An additional reduction in the risk of uric acid crystallization by 55 % compared to the balanced mixed diet OD and by 93 % compared to the Western-type diet WD was achieved with the consumption of

the vegetarian diet VD. The main factors of influence were the reduced urinary uric acid excretion and concentration and the alkaline urinary pH on diet VD. Fig. 1 shows that the risk of uric acid crystallization is immediately achieved on each diet and already on the first day of the administration of each diet.

In conclusion, the comparison of urinary parameters of the healthy subjects on their self-selected meat-containing diet (SD) and on the controlled affluent Western-style diet (WD) demonstrated that the usual dietary habits appear to be quite typical of the Western male population, resulting in the highest risk of uric acid crystallization. The results indicate that urinary uric acid levels can be lowered to a great extent by purely dietary measures. On the average meat-containing diet, a maximum of about 40 % of urinary uric acid was derived from dietary purine compounds. The different responses to administration of the balanced isoenergetic omnivorous and vegetarian diets with similar purine content demonstrate that different dietary purine compounds exert different effects on purine metabolism. Therefore, the values for total purines in conventional food tables are of limited value for dietary recommendations. Although a strong reduction in the supersaturation with uric acid can already be obtained with a balanced omnivorous diet, the intake of the balanced ovo-lacto-vegetarian diet with a moderate animal protein and purine content and a high fluid intake accounts for the lowest risk of uric acid stone formation.

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