RISK FACTORS OF HYPERURICEMIA IN TYPE II DIABETES MELLITUS PATIENTS

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ABSTRACT

Background: Pakistan has an increased incidence of type II diabetes mellitus, a serious national health problem. Hyperuricemia, which is marked by increased Serum Uric Acid (SUA) levels, often goes along with diabetes mellitus type II and raises the threat of Kidney disease, BMI, dietary intake, and other comorbid diseases all contribute significantly to hyperuricemia. The research on hyperuricemia among Pakistani diabetic type II patients is very little. **Objectives:** To identify the associated risk factors of hyperuricemia in type II diabetes mellitus. **Method:** An Analytical Cross-Sectional Study was conducted at Government Kot Khwaja Saeed Teaching Hospital Lahore, involving 362 participants recruited through convenient sampling over 9 months. Patients aged 30–60 with type II diabetes mellitus for at least one year were included, while those with type I or gestational diabetes, known patient of hyperuricemia, relevant medication use, or unwillingness to participate were excluded. **Results:** Key results show that 69.6% of patients had no hyperuricaemia levels, while 30.4% had hyperuricemia. The mean uric acid level ranged from 2.90 to 9.30 mg/dL, with an average of 5.60 ± 0.75 mg/dL. Female gender is the strongest indicator of hyperuricemia, while BMI, diabetes duration, glycemic control, and comorbidities showed no correlations. Hyperuricemia was highly prevalent among housewives, indicating potential lifestyle factors. These findings stress the need for focused treatments, especially for women, to reduce hyperuricemia risks in TDM II female patients. **Conclusion:** This study reveals that female gender, height, housewives, low saturated fat foods and eating of the lean meats (poultry, fish, eggs etc.,) are the strongest predictor of hyperuricemia, with higher prevalence and odds. Factors like duration of diabetes mellitus in years, glycemic control, BMI and comorbidities showed no significant associations. Housewives exhibited a higher prevalence, suggesting lifestyle-related influences. These findings emphasize the need for targeted measures among females to reduce hyperuricemia risks and complications.

INTRODUCTION

Diabetes mellitus is considered as a chronic metabolic condition and caused by the presence of high glucose levels in the blood has remained a significant health challenge in the world. The major causes of the increased prevalence of diabetes are lifestyle changes, urbanization, population aging [1]. In 2021, type 2 diabetes mellitus (T2DM) affected almost 536.6 million individuals worldwide and the same issue is expected to grow to 783.2 million by 2045 [2].

Out of the many complications related to T2DM, a synergistic relationship between metabolic abnormalities, and the high concentrations of uric acid referred to as hyperuricemia, have been identified as major determinants of disease progression [3]. Non-traditional DM marker is uric acid which is a product of purine metabolism. Recently, there has been growing evidence of the existence of a relationship between serum uric acid and DM, however, it still remains unclear [4].

Since T2DM is a metabolic disease, it usually makes it hard in patients to metabolize uric acid and results to HUA, but its presentation is less evident, especially in diabetic patients [5]. Whether it is a DM risk marker or independent risk factor remains unknown, since hyperuricemia is commonly linked to well-known DM risk factors, obesity, high fructose content in diet, and alcohol drinking [6].

Hyperuricemia was previously reported in diabetic patients to have a poor prognosis associated with high mortality and likelihood to face diabetes complications which include nephropathy, retinopathy and neuropathy [7]. As per the recent studies, the prevalence rates of hyperuricemia have been recorded to be different, among T2DM patients in various regions. In a cross-sectional study performed in North-western Tanzania, it was recorded that 44.4 percent of diabetic patients were hyperuricemic; the values were greater among female and patients with obesity, chronic kidney disease, or more prolonged duration of diabetes [8]. In a like manner, a local retrospective study has revealed that 8.8 percent of patients had hyperuricemia. It was also strongly related with an increased duration of diabetes and nephropathy. The majority of patients had poor glycemic control (74.2%) [9]. In other local studies, it has been noted that the levels of SUA and the complications of microalbuminuria and poor indicators of diabetes control such as HbA1c, fasting glucose, and albumin-to-creatinine ratio (ACR) are strongly linked [10,11]. Despite a growing body of evidence, inconsistencies exist in the strength and direction of associations with factors such as age, gender, diabetes duration, body mass index (BMI), HbA1c, and renal parameters like microalbuminuria. For instance, while some studies report a stronger correlation of SUA with female gender and older age

Although there is an increasing body of evidence, inconsistencies exists in magnitude and direction of associations with factors like age, gender, diabetes duration, body mass index (BMI), HbA1c, microalbuminuria and other renal parameters. As an example, although some authors indicate that SUA is increased during older age and female gender [12], other studies claim that male sex and obesity are more predictable [13]. Thus, a thorough assessment on the issue of hyperuricemia and its risk factors that vary among individuals with T2DM especially in underrepresented local populations is necessary and this research is intended to determine the risk factors of hyperuricemia in the population with T2DM.

MATERIALS AND METHODS

Study Design: Analytical Cross- sectional.

Study Setting: Government Kot Khwaja Saeed Teaching Hospital, Lahore.

Study Duration: 09 months after the acceptance of Study Proposal.

Sample Technique: Non-probability convenient sampling.

Sample Size: The study sample was calculated by using proportion of adult population with hyperuricemia which is 38% in parent article [14]. The sample size for the current study (n) calculated 362 individuals by using open epi calculator.

Sample selection Criteria:

Inclusion Criteria:

- Patient with type II, Diabetes Mellitus.
- Either gender, age ranged from 30 to 60 years older with type II diabetes mellitus were included.
- Duration of DM-II at least of 01 years.

Exclusion Criteria:

- Diabetic Patients with Type 1, Gestational diabetes mellitus and who were taking medications / drugs which can affect the uric acid metabolism were excluded from the study.
- Known cases of hyperuricemia were excluded from the study.
- Subjects who are not willing to take part in the current research were excluded.

Data Collection procedure

Permission was obtained from the ethical board of the University of Lahore and hospital authorities at the Diabetic Clinic, Government Kot Khwaja Saeed Teaching Hospital Lahore (GKKSTHL). Patients were enrolled based on inclusion and exclusion criteria. Each patient was approached directly by the principal investigator (PI), and oral/written consent was obtained. Information was recorded on a predesigned questionnaire divided into three parts: (1) Socio-demographic factors, (2) Other relevant information, (3) Dietary scale. Weight (kg) and height (meters) were recorded to calculate BMI (kg/m^2) using the standard formula. According to Asian classification: Underweight <18.5, Normal 18.5–22.9, Overweight 23–24.9, Obese I 25–29.9, Obese II ≥30. Lab tests included Blood Glucose, HbA1c, Uric Acid, and USG KUB when needed. Dietary intake was evaluated using the Healthy Unhealthy Eating Behavior Scale (HUEBS) by Gurtine C. (2020) [15], consisting of 22 items (11 healthy, 11 unhealthy), rated on a 7-point Likert scale (Cronbach's Alpha = 0.87, cut-off score = 77).

In the current study, Diabetes Mellitus was defined as having Glycosylated Hemoglobin (HbA1c) ≥ 6.5%, a Blood Sugar Level of Fasting (BSF) ≥ 110 mg/dL, and a random blood sugar level between 160-200 mg/dL [14]. Hyperuricemia was described as an increased level of Serum Uric Acid (SUA), often > 5.7 mg/dL in females and > 7.0 mg/dL in males, with cut-off values of SUA being 2.5-5.7 for females and 3.4-7.0 for males. Uric acid levels and USG KUB were conducted to rule out Hyperuricemia in the adult population. Body Mass Index (BMI) was used to show the accumulation of adipose tissue in the body.

Dietary intake of different food items was measured by assessing the food intake over the last 24 hours, which defined a person's routine dietary intake, with full nutrition requiring a specified number of calories. The dietary intake in the current study was measured using the Healthy & Unhealthy Eating Behavior Scale (HUEBS), where the minimum score was 22, the maximum score was 154, and the cut-off value was 77 [15]. IBM SPSS 25 was used for data entry and analysis. Descriptive analysis assessed frequencies, while means ± SD were reported for continuous variables. Chi-square tested associations between categorical variables. Logistic regression identified predictors of hyperuricemia, presenting odds ratios. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Among the males, 9 out of 153 (8.2%) had hyperuricemia. Among the females, 101 out of 209 (91.8%) had hyperuricemia. The p-value for males is 0.438, which is greater than 0.05, indicating that there is no statistically significant association between hyperuricemia and being male. The p-value for females is 0.001, which is less than 0.05, suggesting that there is a statistically significant association between hyperuricemia and being female. The higher prevalence of hyperuricemia in females compared to males is statistically significant ($p = 0.001$). However, for males, the association is not significant ($p = 0.438$), meaning hyperuricemia occurrence among males may be due to chance rather than a true difference. The chi-square test results suggest that gender plays a significant role in hyperuricemia prevalence, with females being more likely to have hyperuricemia compared to males. However, hyperuricemia among males does not show a strong statistical association.

The duration of Type II diabetes mellitus (T2DM) did not significantly differ between groups ($p = 0.816$), with a mean of 6.23 ± 3.99 years in the non-hyperuricemic group and 6.06 ± 3.23 years in the hyperuricemic group. Median durations were 5.0 years and 6.0 years respectively. As expected, uric acid levels were significantly higher in individuals with hyperuricemia (6.20 ± 0.51 mg/dl) compared to those without (5.25 ± 0.69 mg/dl), ($p < 0.001$), with respective medians of 6.0 mg/dL and 5.40 mg/dL. HbA1c levels were similar between groups ($p = 0.185$), with means of 10.10 ± 1.19 and 10.22 ± 1.33, and medians of 10.20 and 10.30 for non-hyperuricemic and hyperuricemic individuals, respectively.

The total HUEBS score was slightly lower in individuals with hyperuricemia (58.75 ± 9.19) compared to those without (60.06 ± 8.37) ($p = 0.054$), but the difference was not statistically significant. Among the healthy dietary practices, the intake of low-saturated fat foods and lean meats (poultry, fish, eggs) revealed statistically significant associations with hyperuricemia, with p-values of 0.018 and 0.026 respectively. This indicates that individuals who rarely or never consume such foods are more likely to present with hyperuricemia, suggesting a potential protective role of these dietary choices.

Conversely, other healthy behaviors such as frequent consumption of fruits, vegetables, whole grains, unsaturated fat foods, natural sweeteners, and boiled or grilled foods did not show statistically significant differences between hyperuricemic and non-hyperuricemic individuals ($p > 0.05$). Similarly, high water consumption, although prevalent among both groups, did not demonstrate a significant impact. In terms of unhealthy dietary behaviors, none of the listed items including the consumption of refined grains, artificial sweeteners, snack foods, sugar-sweetened beverages, deep-fried foods, pre-packaged meals, processed meats, added salt, fast food, baked goods, or alcohol exhibited statistically significant associations with hyperuricemia (all $p > 0.05$). This suggests that while these items may contribute to general poor dietary quality, their direct link to hyperuricemia in this cohort was not supported by the data.

Overall, the findings emphasize the importance of incorporating "lean proteins and low-saturated fat foods" in the diet as potentially modifiable factors in managing or preventing hyperuricemia. However, further longitudinal or interventional studies may be required to establish causal relationships and clarify the role of other dietary components. Using univariate logistic regression, it was found that female gender was the strongest predictor of hyperuricemia, with females being 8.64 times more likely to have hyperuricemia than males ($p < 0.001$, OR = 8.637, 95% CI: 3.24–43.28). Other variables, including age, BMI, education, diabetes duration, and glycemic control, were not significant predictors. After adjusting for all confounders, the final logistic regression model for predicting hyperuricemia identified gender as a significant predictor. The regression coefficient (B = 2.706) for females indicates a strong positive association with hyperuricemia. The adjusted odds ratio (OR = 14.963, 95% CI: 7.240 – 30.926, $p < 0.001$) suggests that females have approximately 15 times higher odds of developing hyperuricemia compared to males, and this association is highly significant. The constant (B = -5.478, $p < 0.001$) indicates the baseline odds of hyperuricemia in the absence of predictor variables. These findings suggest that gender plays a crucial role in hyperuricemia risk, with females being significantly more likely to develop the condition.

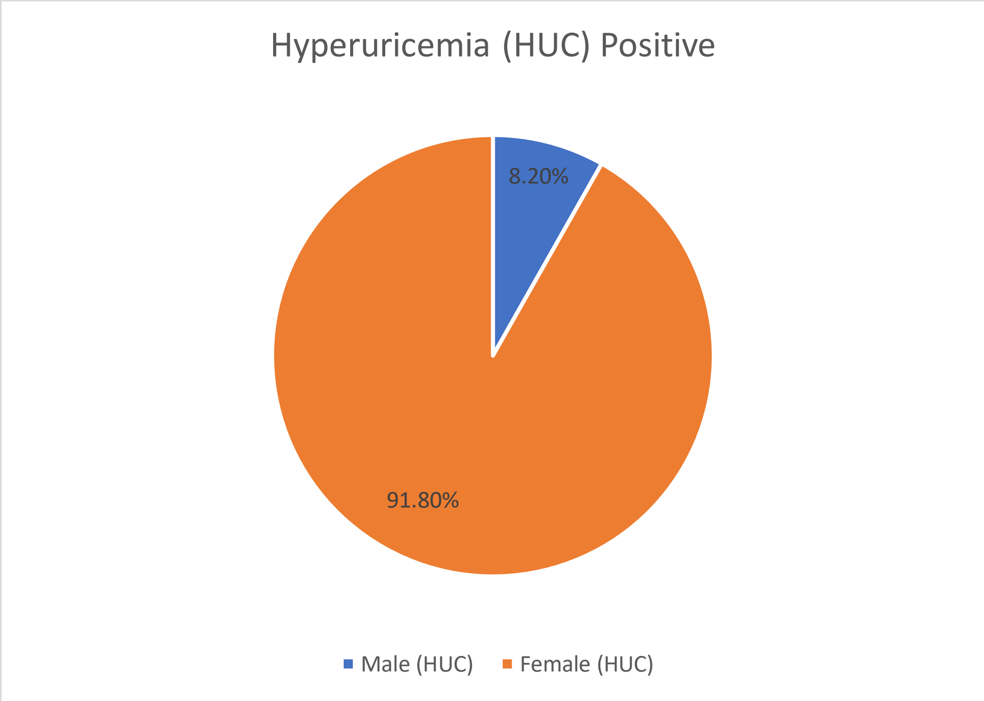

Figure 1: Comparison of Hyperuricemia Positive prevalence between males and females Shows 91.8% of hyperuricemic patients are female and 8.2% are males.

Table 1: Comparison of gender, clinical profiles and dietary habits with respect to hyperuricemia

Variables	Category/Stats	Hyperuricemia: Yes (n=110)	Hyperuricemia: No (n=252)	p-value
Gender	Male	9 (8.2%)	144 (57.1%)	0.438
	Female	101 (91.8%)	108 (42.9%)	0.001
Duration of Type II DM (years)	Mean ± SD	6.06 ± 3.23	6.23 ± 3.99	0.816
	Min–Max	1–15	1–24	
Glycemic Control	Uncontrolled	95 (86.4%)	211 (83.7%)	0.524
	Controlled	15 (13.6%)	41 (16.3%)	
HbA1c	Mean ± SD	10.22 ± 1.33	10.10 ± 1.19	0.185
	Min–Max	6.8–13.5	6.8–13.7	
Associated Diseases	None	67 (60.9%)	129 (51.2%)	0.153
	Hypertension	10 (9.1%)	25 (9.9%)	
	IHD	27 (24.5%)	66 (26.2%)	

	Others	0 (0%)	9 (3.6%)	
	Multiple	6 (5.5%)	23 (9.1%)	
Total HUEBS Score	Mean ± SD	58.75 ± 9.19	60.06 ± 8.37	0.054
	Min–Max	43–80	40–83	

**Highly Significant, *Significant

Table 2: Results of Logistic Regression for prediction of hyperuricemia

Univariate logistic Regression for prediction of hyperuricemia						
	B	**S.E.**	**P-value**	**Unadjusted Odds ratio**	**95% C.I. for EXP(B)**	
					Lower	**Upper**
Gender	2.962	0.411	<0.001	19.335	8.637	43.283
Age (years)	0.011	0.021	0.616	1.011	0.970	1.053
BMI	-0.025	0.025	0.323	0.975	0.928	1.025
Education (years)	-0.030	0.031	0.338	0.971	0.914	1.031
Occupation	0.138	0.183	0.449	1.148	0.803	1.643
Monthly income (k)	0.000	0.011	0.979	1.000	0.978	1.022
Marital status	-0.280	0.203	0.169	0.756	0.508	1.126
Family size	0.015	0.029	0.601	1.015	0.959	1.074
Type of housing	0.056	0.284	0.845	1.057	0.606	1.845
Other diseases	-0.211	0.114	0.064	0.810	0.648	1.012
Family type	0.029	0.316	0.926	1.030	0.554	1.913
Duration of type II DM (years)	-0.021	0.040	0.610	0.980	0.905	1.060
Family history of DM (Diabetes Mellitus)	0.675	0.427	0.114	1.964	0.850	4.535
Glycemic Control	-0.088	0.383	0.819	0.916	0.432	1.942
Constant	12.604	4019 3.292	1.000			

Table 4: Final Logistic regression model for prediction of hyperuricemia

Final Logistic regression model for prediction of hyperuricemia						
	B	**S.E.**	**p-value**	**Adjusted OR**	**95% C.I. for EXP(B)**	
					Lower	**Upper**
Gender | Female	2.706	0.370	<0.001**	14.963	7.240	30.926
Constant	-5.478	0.701	<0.001**	0.004		

DISCUSSION

This study aimed to identify risk factors to hyperuricemia in a sample of patients with type II diabetes mellitus and paying special attention to the dietary and demographic factors. Though the other factors such as the duration of diabetes, glycemic control and poor diets did not demonstrate significant statistical correlation, it is revealed that the female gender was the strong predictor of hyperuricemia.

We found that prevalence of hyperuricemia was considerably higher among females (91.8%) compared to males (8.2%) whereas the difference between their prevalence was significant statistically (p = 0.001). Logistic regression analysis revealed that the likelihood of women developing hyperuricemia was nearly 15 times higher in comparison with men (OR = 14.96, 95% CI: 7.24-30.92). This is proven by some of the international researches. A cross-sectional study conducted in Tanzania found out that out of 360 respondents consulted, the proportion of females was 59.7 percent. Mean serum uric acid level in female was 385 +/- 119 mu mol / L. The research established a close relationship between hyperuricemia and the female gender (P =.001), thereby indicating that female women afflicted with T2DM were at higher risks of being afflicted by hyperuricemia relative to their male counterparts [8].

Another study found, consistently, that women over 45 had hyperuricemia and that of centrally obese people [16]. In another cross- sectional study involving 655 of patients with diabetes type 2 in Jordan, gender was also significant with reference to hyperuricemia; the female had higher chances of having hyperuricemia (OR: 2.37; 95% CI: 1.63 3.45) as compared to males. This is to highlight that women with diabetes are more burdened with hyperuricemia [12].

Many studies, on the contrary, found increased levels of uric acid in men and premenopausal woman, in whom estrogen is believed to stimulate uric acid excretion. Even in a cross-sectional study of 1577 diabetic patients in Chengdu, the frequency of hyperuricemia, in fact, was remarkably higher among the men (29.35 percent) than in the women (13.03 percent) [13]. Local or regional dietary patterns, body composition, postmenopausal status, or genetic predisposition, however, could help to explain the higher sensitivity among women in our cohort.

Remarkably, the time since the development of diabetes and HbA1c were not linked to hyperuricemia ($p = 0.816$ and $p = 0.185$, respectively), implying that failure to manage glycaemic index, on its own, may not predict hyperuricemia among these individuals. Nonetheless, the research studies showed a close correlation of the serum uric acid and HbA1c levels. A cross-sectional study conducted in Cameroon reported that hyperuricemia was not significantly correlated with uncontrolled diabetes ($p=0.095$); nevertheless, a significant positive association was also found between serum uric acid and HbA1c ($r=0.318$, $p=0.002$) [16]. Also, this was undertaken in a large cross-sectional study of 30,772 participants looking at the linkage of HbA1c, hemoglobin glycation index (HGI) with serum uric acid (SUA) associated both by gender and diabetes status. It was found that HGI and HbA1c were positively related to the level of SUA in the women without diabetes. On the contrary, HbA1c had an inverse connection with SUA in people with diabetes among both genders. In non-diabetic men, SUA was in the shape of a bell curve in relation to HbA1c- levels, increasing to 5.7 percent and decreasing after this level. This information indicates the existence of complicated, sex-specific associations between glycemic markers and uric acid, thus implying that glycemic regulation can interact with the risk of hyperuricemia in diabetic and non-diabetic people in various ways [17]. The classification criteria we applied was proven correct in our study where the serum uric acid level was much higher (mean = 6.20 U +/-0.51 mg/dL) in the hyperuricemic group when compared to the non-hyperuricemic group (mean = 5.25 U +/-0.69 mg/dL). Furthermore, HUEBS score, assessing the compliance with the healthy lifestyle and diet, did not vary significantly across the groups ($p = 0.054$), but had shown the trend toward higher levels in non-hyperuricemic patients. On the contrary, a recent study revealed that healthier lifestyle score (HLS) was strongly linked to the lower serum uric acid (SUA) levels and the decreased risk of hyperuricemia (OR: 0.82; 95% CI: 0.77-0.86). Further, SUA mediated (13.06%) the association between a healthy lifestyle and a decrease in the risk of type 2 diabetes, which confirmed the involvement of SUA as a possible metabolic mediator [18].

Only two of the dietary habits; intake of lean proteins (poultry, fish, eggs) and low-saturated fat food; demonstrated a statistically significant protective effect toward hyperuricemia with $p = 0.026$ and $p = 0.018$ respectively. This implies that the daily consumption of healthy sources of proteins and fat-regulated food could reduce the chances of high serum uric acid. This is in favor with past literature which raised the importance of diet especially purine content and fat consumption in uric acid metabolism. These findings are in line with previous studies that indicated that greater adherence to the DASH diet was strongly linked with low numbers of serum uric acid ($\beta = -0.11$; 95 percent CI = -0.12, -0.10; $p < 0.001$) and decreases odds of hyperuricemia (OR = 0.85; 95 percent CI = 0.83, 0.87; $p < 0.001$) in Chinese population [19]**.** Equally, an increased compliance to the DASH diet was linked to the rapid reduction of SU levels ($P < 0.01$), whereas a one-point elevation in the DASH score was correlated to 4.3 percent reduced risk of spiking up on uric acid levels (IRR: 0.957; 95% CI: 0.938-0.977). These data lead to the recommendation of the contribution of the DASH diet as a preventive and intervention strategy to hyperuricemia [20].

Unexpectedly, there were no great links to conventionally unhealthy food constituents, such as sugar-sweetened drink, fast food, refined cereal, and processed meat. Beneficial effects supposedly contributed by high water intake, which is used to facilitate excretion of uric acid, did not have a significant correlation either, probably because of standard consumption rates exhibited by the participants. On the other hand, a Mexican longitudinal study examined 1,300 participants who included adults in a research of 14 years and determined that greater sugar-sweetened beverages (SSBs) intake was significantly related to higher levels of hyperuricemia. The study also established that the participants consuming 7 or more servings of SSB were almost two times more likely to experience hyperuricemia than the participants consuming fewer than 1 serving of SSB per week. This association was still present after confounding factors were accounted and the soft drinks sweetened with diet did not have a similar association [21]. In another research, some of the most imminent risk factors found to lie behind hyperuricemia involved the frequent intake of fatty food, smoked, and fried foods, sugar liquids, alcohol, and decreased intake of milk and Soya products, and less sleep duration [22].

Overall, this research brings forward the fact that female gender is an important independent risk factor of hyperuricemia among the diabetic individuals as well as the implication of the protective effect of lean proteins and low-saturated fat diets. But other lifestyle and clinical factors that are usually presumed to have a bearing on uric acid levels failed to find statistical significance association in the present cohort. The results point to the relevance of gender-related screening and nutritional education approaches to the treatment of diabetics. This research was limited by the fact that it was a cross-sectional research and thus it was not possible to come up with a causal relationship. A certain biasness was possible due to the rather small sample size and the use of self-acquired data on the diet. In addition to this, the menopausal profile, serum insulin, or renal markers were not assessed, which might affect uric acid levels.

CONCLUSION

The study concluded that there is a high likelihood of women with type II diabetes to develop hyperuricemia compared to men. Most clinical and lifestyle variables were not significantly associated but eating lean protein and food with low fat appeared to be helpful. These findings indicate the necessity of gender-sensitive treatment and easy-to-grasp dietary recommendations as the methods of monitoring uric acid levels.

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