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Original Article

Evaluation of uric acid levels and other biochemical parameters among Gout patients with Ketogenic diet in Erbil province

Kwestan R Muhammad[1,2*]

[1] *Clinical Biochemistry Department, College of Health Sciences, Hawler Medical University, Erbil, Iraq*
[2] *Nursing Department, Gasha Technical Institute, Erbil, Iraq*

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Abstract

Gout is a systemic disorder that occurs due to an accumulation of uric acid crystals in the tissues. The association between the Ketogenic diet and uric acid concentration has been poorly established. This study aims to evaluate and assess the association of Serum uric acid and other variables with ketogenic diet among Gout patients in comparison with Healthy control subjects. A case-control observational study. Subjects were grouped into Group I (Gout patients-103 individuals) and Group II (healthy Subjects-55 individuals). Parameters of Serum creatinine, blood urea, and uric acid were assessed for both groups. The study population included 51.3% of male and 48.7% of female participants, with an age range of 20-74, with a mean of 35.72±13.69 years old. Ketogenic and meat-rich diet as strong risk factors for Gout were higher among all case groups (45.6%) and (92.2%), respectively. The Pearson's correlation coefficient of serum uric acid with other variables showed that the relation between serum uric acid with age, and weight among gout patients was found to be a weakly positive correlation and statistically significant (r=0.24, P= 0.013), and (r=0.22, P=0.026) respectively. This prospective study confirms that a ketogenic diet and a diet rich in meat have been associated with an increased incidence of gout. Indeed, results have shown that the ketogenic diet might have an increasing effect on serum uric acid. The frequencies of comorbidities have been constantly shown to be increased in gout.

Keywords: Ketogenic diets, Hyperuricemia, Gout.

1. Introduction

Gout is a longstanding inflammatory joint disease tha has been widely recognized for many years [1]. It is some times known as "men's disease" since it affects men more frequently than women. According to epidemiologica investigations, the prevalence of gout varies between 1% and 4% globally, with males estimated to have a four-fold higher occurrence than females [2, 3]. Gout begins with the deposition of Monosodium Urate Crystals (MSU) in articular and non-articular structures, promptly succeeded by the development of kidney stones and accompanied by tophi, which ultimately result in gouty arthritis[4 5]. Persistent stab pain, generally affecting one joint at a time, is among the most common clinical manifestations of gout[6].

Uric acid is the result of the natural breakdown of the nucleic acids adenine and guanine, which occurs in injured, dying, and dead cells, as well as an exogenous source of purines. The most significant risk factor for the onset of gout is a high blood urate content. When it comes to clinical practice and investigation, hyperuricemia is generally defined as a serum urate equal to or higher than (7 mg/dl) [1]. Serum uric acid concentrations are influenced by four primary physiological processes: extra-renal excretion renal reabsorption, renal excretion, and the metabolism of purines [7]. The spectrum of gout illness starts with subclinical high uric acid levels and progresses to abrupt gouty arthritis and, in the end, chronic tophaceous gout [8]. The mainstay of successful gout management is long-term uric acid-lowering medications to counteract hyperuricemia, which effectively dissolves MSU crystals as well as avoids gout flare-ups in the long run [1].

Ketogenic diets, or KDs, have drawn a lot of public attention since are capable of resulting in significant loss of weight in the short term [9]. Under the KD eating pattern, daily carbohydrate consumption is severely limited to fewer than 50 grams per day, while daily fat and protein eating are increased [10], Depriving the body of carbohydrates increases the amount of ketone bodies in the blood by burning down the fatty acids and ketogenic amino acids. Ketones change physiological responses and provide an alternate energy source to carbs [9].

Numerous observational studies have shown that during the ketosis phase of KD, there is an increase in uric acid levels [11]. However, there is insufficient evidence to support the link between the KD and UA concentration. Given the current disparities and paucity of information about the relationship between a ketogenic diet and gout globally, particularly in our area, we set out to evaluate and assess the association between serum uric acid and

* Corresponding author.
E-mail address: kwestan.muhammad@hmu.edu.krd (K. R Muhammad).
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other variables with a ketogenic diet in gout patients in comparison to healthy control subjects.

2. Material and Methods

2.1. Study population and study design

A case-control observational study. The subjects of our study were grouped into two categories:

Gout patients (group I): included a hundred and three patients with Gouty arthritis, who attended surgical specialty hospital- Cardiac Center/ Erbil City-Iraq, Rzgary Teaching Hospital, central Lab, Rozhhalat Emergency Hospital and were confirmed to have gout based on their X-ray diagnosis.

Healthy controls (group II): fifty-five selected subjects served as controls, all were healthy volunteers and had no evidence of gout.

2.2. Collection of blood samples

A total of 158 blood samples were collected from 103 gout patients and 55 healthy controls. The obtained samples underwent a 10-minute centrifugation process at 3500 rpm. The separated serums were used for the measurement of blood urea, S. creatinine, and uric acid.

2.3. Inclusion and exclusion criteria

Both genders, adults aged 20 years and above were included, Exclusion criteria were individuals aged below 2, cancer (being under treatment and/or diagnosed with malignancies), chronic kidney disease stage 3 or higher) and liver dysfunction (including viral hepatitis, cholestasis jaundice).

2.4. Study timeline

The present study was carried out from the (5th of January 2023) to the (28th of November 2023).

2.5. Statistical analysis

All statistical data were analyzed using SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism 9.5 (Graph Pad Software Inc., San Diego, CA, USA). The Shapiro–Wilk test and Kolmogorov-Smirnov test were used to determine whether a random sample was normally distributed. The student t-test for two independent sample groups (e.g., cases and controls). The results are expressed as counts and percentages for the categorical data, and mean ± standard error of the mean for the continuous normally distributed variables respectively.

To examine the significance of relationships between independent and dependent variables, the Chi-Square test was applied. The Receiver operating characteristic (ROC) curve was applied to compare the sensitivity of laboratory parameters in all subjects and asses the diagnostic accuracy for discriminating gout disease. The relationship between uric acid and other variables was evaluated by Pearson's correlation coefficient test. A p-value equal to or less than 0.05 was regarded to be statistically significant.

2.6. Questionnaire form design

The data collection instrument is a structured direct interviewer-administered face-to-face questionnaire that is pretested with modifications made before its use in the study, in conjunction with access to medical records or documents that are individually identifiable, include sensitive personal data, and are not readily available to the public. The questionnaire includes the demographic variables (name, age, gender, home address, time and date, etc.), clinical risk factors of the patient, family history, and smoking habits of the patient.

2.7. Ethical considerations

Ethics committee permission was acquired from Hawler Medical University. Verbally Informed consent was taken from each patient. A Complete explanation of the nature and aim of the study was given to each participant, and reassuring about the confidentiality of the data and their anonymity.

3. Results

3.1. bassline characteristics of the study population

The distributions of selected characteristics are shown in Table 1. A total of 158 individuals were evaluated for this study. 58.5% of them were cases while 41.5% were

Table 1. Bassline characteristics of the study population.

Characteristics	Control (n=55) Frequency (%)	Gout patients (n=103) Frequency (%)	All subjects (n=158) Frequency (%)
Age (in years)			
• 20-34	28 (50.9)	69 (67.0)	97 (61.4)
• 35-44	12 (21.8)	18 (17.5)	30 (19.0)
• 45-54	6 (10.9)	5 (4.9)	11 (7.0)
• 55-74	9 (16.4)	11 (10.7)	20 (12.7)
Gender			
• Male	23 (41.8)	58 (56.3)	81 (51.3)
• Female	32 (58.2)	45 (43.7)	77 (48.7)
BMI			
• Normal weight	35 (63.6)	64 (62.1)	99 (62.7)
• Overweight	13 (23.6)	24 (23.3)	37 (23.4)
• Obese	7 (12.7)	15 (14.6)	22 (13.9)
Smoking Status			
• Smoker	13 (23.6)	56 (54.4)	69 (43.7)
• Non-smoker	42 (76.4)	47 (45.6)	89 (56.3)
Occupation			
• Employer	30 (54.5)	73 (70.9)	103 (65.2)
• Student	15 (27.3)	15 (14.6)	30 (19.0)
• Retired	2 (3.6)	4 (3.9)	6 (3.8)
• Housewife	8 (14.5)	11 (10.7)	19 (12.0)

Results are presented by frequency (percentage). BMI-body mass index

control, and the mean age was 35.72±13.69 with a range of 20-74 years old. Concerning their demographic characteristics, in 103 Gout patients about (61.4%) of the study population were in the 20-34 age group, followed by the 35-44 age group 30(19.0%), 11(7.0%) were aged 45-54 years of age and 20(12.7%) were among 55-74 years of age. Participants with gout were more likely to be male (56.3%), ever smokers (54.4%), to have higher education levels (70.9%) and higher BMI (14.6%) than their counterparts.

3.2. Risk factors of Gout in healthy controls and patients with Gout.

Upon analyzing the risk factor relationship with patients and healthy individuals, the Chi-square test analysis observed that there is a statistically significant difference between the two groups of subjects in most of the risk factors including hyperuricemia, hypertension, Diabetes mellitus, cardiovascular disease, kidney disease, keto diet, smoking, and meat-rich diet, with a *P*-value of (<0.001, 0.028, <0.001, <0.001, 0.001, 0.001, <0.001, and <0.001, respectively. As shown in Table 2.

Furthermore, Incident gout cases also had a higher prevalence of self-reported hypertension at baseline as compared to non-cases in which about 85.4% of the gout patients were Hypertensive, and the frequency of DM was higher (88.3%) among the gout-positive individuals compared to non-gout-subjects. The prevalence of kidney disease was higher among the gout patient group (85.4%) than the control group (61.8%). The ketogenic diet as a strong risk factor for Gout was higher among all case groups which was (45.6%) compared to a smaller population of control groups which was (18.2%). In the era of a meat-rich diet, Participants who developed gout also had higher levels of consumption of total protein, red meat (including beef and lamb), poultry, and fish and shellfish at baseline than those who remained free of gout (92.2%) and (58.2%), respectively.

3.3. A comparison of the mean value of laboratory parameters among Gout patients and non-Gout subjects.

Concerning the lab parameters of participants, there was a significant difference between the mean level of blood Urea among patients and the control group, unsurprisingly the case had a higher level of urea (40.52±1.047) compared to the control (32.27±2.006), with a P-value of <0.001. The Gout patients had a higher Serum Creatinine level (1.37±0.042) compared to the non-Gout subjects (0.98±0.110), this was also highly significant, P =<0.001. The mean uric acid level was found to be higher among the cases (8.90±0.121) than in the control (5.92±0.246), and this was statistically significant, having a p-value of <0.001. As shown in Table 3.

3.4. Receiver Operating Characteristic (ROC) curve analysis of laboratory parameters.

After analyzing the Receiver Operating Characteristic (ROC) curve to determine the diagnostic precision of the lab parameters for establishing and diagnosis of Gout and compare the sensitivity of laboratory parameters in all subjects. The ROC curve of blood urea has an Area Under the Curve (AUC) of 0.753 and is statistically significant with a p-value of <0.001, which means it is a useful test for establishing the diagnosis of Gout. The ROC curve of

Table 2. Comparing the risk factors of the study groups based on the presence of Gout**.**

Risk factors	Patients N (%)	Control N (%)	*P*-value*
Hypertension	88 (85.4)	39 (70.6)	**0.028**
Cardiovascular disease	83 (80.6)	27 (49.1)	**<0.001**
Diabetes mellitus	91 (88.3)	33 (60.0)	**<0.001**
Hookah	39 (37.9)	16 (29.1)	0.270
Alcohol-intake	3 (2.9)	1 (1.8)	0.677
Kidney disease	88 (85.4)	34 (61.8)	**0.001**
Smoking	56 (54.4)	13 (23.6)	**<0.001**
Previous COVID-19	88 (85.4)	44 (80.0)	0.380
Gender (male)	58 (56.3)	23 (41.8)	0.083
Gender (female)	45 (43.7)	32 (58.2)	
Ketogenic-diet	47 (45.6)	10 (18.2)	**0.001**
Meat rich diet	95 (92.2)	32 (58.2)	**<0.001**
Hyperuricemia	102 (99.0)	17 (30.9)	**<0.001**

*Data are analyzed by Chi-square test and results are presented as frequency (percentage).

Table 3. A comparison of the mean value of laboratory parameters among Gout patients and non-Gout patients

Parameters	Subjects	Mean ± SE	P-value*
Blood Urea (mg/dl)	**Gout +**	40.52±1.047	**<0.001**
	Gout -	32.27±2.006	
S.Creatinine (mg/dl)	**Gout +**	1.37±0.042	**<0.001**
	Gout -	0.98±0.110	
Uric acid (mg/dl)	**Gout +**	8.90±0.121	**<0.001**
	Gout -	5.92±0.246	

serum creatinine has an AUC of 0.878 and is statistically significant with a p-value of <0.001 indicating that serum creatinine is an accurate test for diagnosing Gout. The ROC curve of uric acid has an AUC of about 0.9 and a significant p-value <0.001, specifying uric acid as an accurate test for diagnosing Gout. As shown in Figure 1.

3.5. The correlation analysis between Uric Acid levels and other numerical variables.

Regarding the correlation of serum Uric Acid with other variables, a slightly positive correlation and statistically significant was found between Uric Acid with Age and weight, (r=0.24, P= 0.013) and (r=0.22, P=0.026). As shown in Table 4.

4. Discussion

The present case-control study aimed to shed light on the effects of one of the most popular diets, The ketogenic diet, on serum uric acid levels and consequently gout. A pilot investigation was performed to show this possible association between Gout and the ketogenic diet. This research demonstrates that serum uric acid levels were higher among gout patients compared to the healthy control group, several studies support these results [12]. The prevalence of KD was significantly higher in the gout-affected group compared to a non-gout-affected group, in line with these findings, Veech reported that there is an increased risk of gout when entering into nutritional ketosis due to the competitive inhibition of ketones on kidney excretion of uric acid [13]. By contrast, Gohari et al reported data from 267 participants and showed no significant changes in serum UA and consequently no incidence of gout [12].

The development or advancement of gout can be attributed to several common risk factors, such as alcohol use, food, medication use, male gender, the presence of chronic illness, high body mass index, and advanced age. An excessive build-up of triglycerides brought on by a high-fat diet results in an increase in body mass and consequent obesity, the results of this study demonstrate that gout patients were more obese than their counterparts, which is consistent with findings reported by Choi and colleagues, who mentioned that overweight/obesity was linked to 60% of gout cases in a clinical trial of 14,624 adults [14], this may be because purine metabolism is promoted by lipid metabolic disorders, which increase XO activity. Furthermore, approximately two-thirds of gout patients (71.8%) were men, following these results, Engel et al observed that the incidence of gout was greater in men than in women (14.8% vs. 2.8%) [15]. The logical reason for this might be due to the protective effects of female-estrogenic hormones.

Given that age is a significant independent risk factor for gout and that the condition is far more common in older adults than in the general population, cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) and a claims database showed that the prevalence of gout or serum uric acid increased with increased age groups [16]. By contrast, the majority of patients diagnosed with gout were in the younger age range, with 67.0% of them being between 20 and 34 years old.

According to the study's findings, eating meat—especially red meat—increases the chance of developing gout. These findings are in line with other research done on people in the West and Asia. According to research by Choi and colleagues, the incidence risk of gout increased by 21% with every additional daily serving of meat, with a multivariate RR of 1.41 (95% CI, 1.07-1.86) [17]. Similarly, a prospective trial of 28,990 male runners followed up for eight years revealed that a higher meat diet was associated with an increased incidence of gout [18].

The results showed that several comorbidity risk factors, the most prevalent of which are hypertension, renal disease, cardiovascular disease, and diabetes mellitus, coexist in gout patients; nevertheless, it is challenging to isolate the specific impacts of these conditions. Many risk variables may exert their influence via shared inflammatory pathways and/or renal processes of urate excretion [19].Similarly, Bardin and Richette asserted that it has been repeatedly demonstrated that gout is associated with higher frequencies of obesity, peripheral arterial disease, heart failure, hypertension, type 2 diabetes, dyslipidemias, and cardiac diseases (including coronary heart disease, heart failure, and atrial fibrillation) [20], For this reason, it is crucial to screen for and treat these comorbidities in

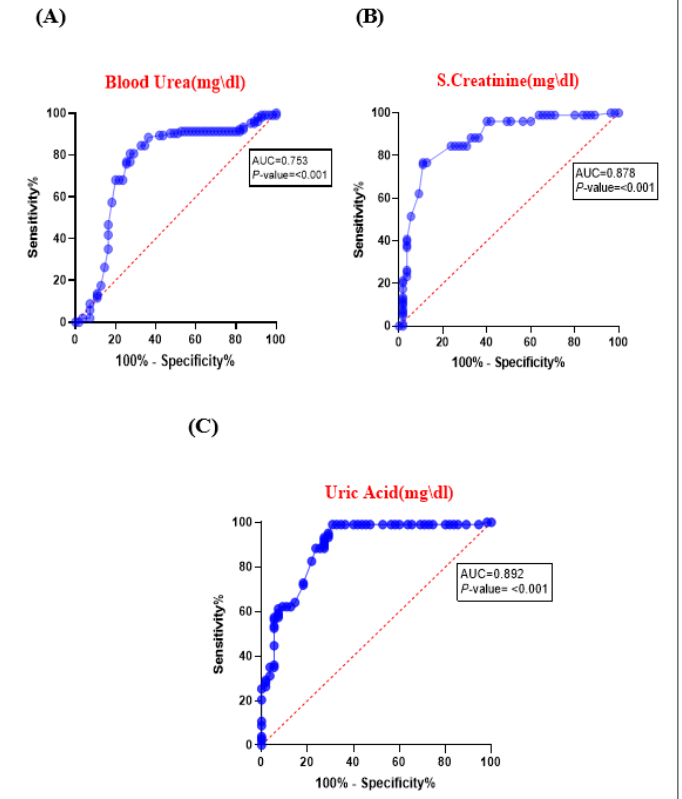

Fig. 1. The ROC curve analyses of Laboratory parameters, A (blood Urea), B (S. Creatinine), and C (Uric acid).

Table 4. The Correlation Analysis between Uric Acid Levels and other numerical variables.

Parameters	Uric Acid Gout patients (n=103)	
	r	*p*-value*
Serum Creatinine (mg/ml)	0.16	0.103
Blood Urea (mg/dl)	-0.03	0.803
Age (years)	0.24	**0.013**
Weight (kg)	0.22	**0.026**
BMI	0.17	0.087

*Data are analyzed by Pearson's correlation coefficient test.

gout patients.

People with underlying gout disease have reported experiencing abnormal kidney function tests linked to the ketogenic diet, The available data have shown that Serum creatinine levels were significantly increased, These findings are in line with the 30-day ketogenic diet in rats that have a 65% composition of fat [21], Another research revealed that gout-affected people had considerably higher mean blood creatinine levels than non-gout-affected subjects [22].

This study's Findings emphasize that Serum uric acid has a significant positive correlation with age according to (Pearson's rho), in agreement with the results of Song and co-authors, who showed that there is a statistically significant positive relationship in uric acid with age among gout patients, and with age advancing the risk of gout increase in both genders [23]. This investigation's findings showed that uric acid levels were significantly linked with weight, similarly, obesity, BMI, and age were predictive factors for incident gout or hyperuricemia in both the Normative Aging Study and a Japanese population [16], Thus, it is important to inform patients who are at risk for hyperuricemia or gout about these variables to lower that risk.

5. Conclusions

To the best of our knowledge, this is the first study assessing ketogenic diet among gout patients in this region. In conclusion, this prospective study demonstrates that a ketogenic diet has been linked to an increased incidence and exacerbation of gout. Indeed, findings indicate a ketogenic diet might increase blood uric acid levels, therefore, Gout patients should take caution when making dietary changes since they might quickly affect their condition.

Under the findings of this study, we conclude that Renal and other comorbidities were frequent in patients with gout. Finally, because there aren't many studies on KD and changes in UA and gout, as well as the studies' findings are so inconsistent, whether KD can affect serum UA concentrations is still debatable and demands more studies.

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Conflict of interests

The author declared that have no competing interests.

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