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Could Tear Fluid Urate Be a Predictor for Ocular Inflammation in Asymptomatic Hyperuricemia and Gout Patients?

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ABSTRACT

Background: Uric acid is a result of purine metabolism. Hyperuricemia can be caused by either excessive urate production or inadequate elimination. Asymptomatic hyperuricemia is estimated to occur in up to 21% of the general population and 25% of hospitalized patients.

Objectives: This study aimed to investigate the presence of pro-inflammatory cytokines and their relationship to uric acid level in the tear fluid of individuals with hyperuricemia and gout.

Patients and methods: For this investigation, a total of 90 control volunteers, 80 patients with hyperuricemia, including 65 with asymptomatic hyperuricemia, and 15 participants with gout were enrolled. After stimulation, capillary action microcaps were used to collect each patient's tears for analysis. Chemiluminescence was used to gauge the amount of uric acid in the tears. Using an enzyme-linked immunosorbent test, serum & tear interleukin-1beta (IL-1β) as well as tumor necrosis factor alpha (TNF-α) levels were measured. Also, serum & tear urate levels correlation with TNF-α and IL-1β were determined.

Results: In comparison to control group, the hyperuricemia group had significantly higher tear urate levels (0.72±0.17 mg/dl vs. 1.65±0.4 mg/dl, P<0.001) and considerably higher levels of IL-1β (210.0±51.9 pg/ml vs. 143.4±29.6 pg/ml, P<0.001). Tear urate and IL-1β levels were independently positively correlated, according to multiple linear regression analysis (B=0.191, P < 0.001). However, no meaningful relationships between serum or tear urate and TNFα-level were discovered. Furthermore, there were no statistically significant changes in the levels of IL-1β and TNFα in tears between the groups with asymptomatic hyperuricemia and gout.

Conclusions: Patients who had gout and asymptomatic hyperuricemia had higher tear urate levels than controls. Tear uric acid levels had a substantial positive connection with IL-1β levels, suggesting an interaction between hyperuricemia and ocular inflammation.

Keywords: Gout, Hyperuricemia, Uric acid, Tears, Interleukin-1β, TNF-α, Inflammation.

INTRODUCTION

Purine metabolism produces uric acid. Hyperuricemia may result from either excessive urea synthesis or insufficient elimination. Up to 21% of the general population and 25% of hospitalized patients are believed to have asymptomatic hyperuricemia [1]. The most important risk factor for gout development is hyperuricemia, which is also linked to other concurrent conditions such diabetes, hypertension, coronary artery disease, and chronic renal disease [2]. The eye is prone to vascular, metabolic, and inflammatory conditions [2,3]. In those with gout and hyperuricemia, urate crystals have been seen in practically every ocular and adnexal site [4]. The pH difference between plasma and tissue make ocular structures vulnerable to tophi deposition due to their relatively low solvent capacity[5].

As the clinical manifestations are caused by urate deposition-induced inflammation of the affected tissue. Therefore, it is important to research how ocular inflammation varies in people with gout and hyperuricemia. The most frequent ocular manifestation in people with hyperuricemia and gout is red eye, which is generally bilateral and produced by conjunctival and episcleral hyperemic vessels. Early gout has been associated with vascular alterations on the ocular surface, including tortuosity, thickness, congestion, and persistent subconjunctival bleeding [6]. Uveitis, glaucoma, episcleritis and chronic conjunctivitis are other ocular symptoms [7, 8]. As the tear fluid is essential for controlling the physiology of the human eye and mostly composed of proteins, lipids, mucins, and electrolytes. Eye inflammations can change the complicated composition of tears [9]. According to a few recorded studies, TNF-α, NOD-like receptor protein 3 (NLRP3) inflammasome, pro-inflammatory molecules IL-1β, IL-17, and IL-8, and anti-inflammatory factors like IL-10 and IL-37 have all been connected to the inflammatory process that mono sodium urate (MSU) induces in gout. [10].Nonetheless, the presence of cytokines in the tears of gout and hyperuricemia patients is still unknown, and the significance of hyperuricemia as a catalyst for increased cytokine release and subsequent ocular inflammation is yet underappreciated. Therefore, the purpose of this study is to measure the urate level in tear fluid in individuals with asymptomatic hyperuricemia and gout as well as to ascertain its relationship to ocular inflammation and pro-inflammatory cytokines in those patients.

PATIENTS AND METHODS

Study design and patient selection: The Rheumatology, Rehabilitation & Physical Medicine Department of Tanta University Hospital conducted this cross-sectional observational study from

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December 2022 to June 2023. Eighty patients with hyperuricemia or gout.

Inclusion criteria: Age between 18 and 80 years. Serum urate levels greater than 7 mg/dl. History of hyperuricemia or gout flare-ups. The 2015 American College of Rheumatology/European League against Rheumatism diagnostic criteria [11] were used to make the gout diagnosis.

Exclusion criteria: Pregnant or nursing women, severe medical, neurological, or psychiatric conditions, any ophthalmological condition, including infection or allergic conjunctivitis, significant liver or kidney dysfunction, and patients undergoing consistent urate-lowering therapy, NSAIDs, colchicine, corticosteroids, and diuretics within the preceding month.

Ninety five participants with hyperuricemia and 100 healthy controls in total were evaluated for eligibility. A total of 90 controls and 80 patients with hyperuricemia were included for the final analysis after 10 controls and 15 patients were excluded due to insufficient tear fluid sampling.

All participants were subjected to:

1. Clinical assessment: General as well as local ophthalmological examination were done. The participants' height, weight, SBP, and DBP were all recorded along with their demographic data. The formula for calculating the BMI was weight (kg)/height (m^2).

2. Laboratory evaluation:

A) Routine laboratory tests including CBC, ESR, CRP, ALT, AST, BUN, creatinine, FBG, total cholesterol and triglycerides. Serum uric acid level was determined using enzymatic-colorimetric methods (Roche Diagnostics, GmbH, Mannheim, Germany).

B) Tear urate level was determined using chemiluminescence (Nanjing Jiancheng Bioengineering Institute, China).

C) Tear IL-1β and TNF-α concentrations detection were done according to the user manual (R & D systems, USA). The tear fluids were diluted 20 times with PBS to determine the amounts of IL-1 and TNF- using a commercial ELISA kit.

D) Inflammatory cytokines including serum levels of IL-1 and TNF-α were measured by ELISA using ultrasensitive commercial kits (Human Ultrasensitive, BioSource International Inc., Camarillo, CA, USA).

Tear collection: To ensure that there was enough volume, ear fluid was collected while individuals were fasting for about a minute with a microcapillary tube placed into the lower lateral fornix. Tears were collected after activating the sneeze reflex by gently inserting a sterile cotton bud into the nasal passages to stimulate tear production [12]. Participants turned away from the collection, cocking their heads towards it. Blinking was permitted during the operation, and the sample was moved from the capillary tube to a siliconized 0.25 mL microcentrifuge tube, which was then frozen before processing. To remove cellular debris after collection, materials were centrifuged at 4000 rpm for 20 minutes at 4 °C. The supernatants were collected and maintained at -80 °C for storage.

All hyperuricemia and gout patients were followed up during the whole period of the study for any ocular manifestations.

Ethical consideration: The Faculty of Medicine of Tanta University's local ethics committee gave its approval to the research's protocol (approval code: 36170/12/22). We certify that none of the methods used in this study went outside the guidelines outlined in the most recent iteration of the Declaration of Helsinki. While writing this manuscript, we also adhered to the advice of the STROBE standards.

Statistical analysis

Statistical analyses were conducted using the SPSS software program, version 20.0. Categorical data were presented as numerical percentages, whereas continuous variables were given as mean. ± SD. The X^2-test was used to compare frequencies between groups, whereas the Student's t-test was used to compare means in normally distributed data. Spearman's rho coefficient was used to assess correlations. Candidates for the linear regression analysis were found to be variables that were substantially linked with tear urate. The candidate components were fitted into a multivariable linear regression model using the stepwise likelihood ratio technique, with an admission probability of 0.05 and a removal probability of 0.10. ANCOVA was used to evaluate the differences in tear urate between individuals with gout and those with asymptomatic hyperuricemia after adjusting for serum urate levels. For all 2-tailed tests, P values of 0.05 or less were considered statistically significant.

RESULTS

Table (1) showed the patient demographics. The mean age of the hyperuricemia and control groups were 50.5 ± 16.5 and 49.2 ± 12.0 years respectively. Male participants made up 85% & 80% of the hyperuricemia and control groups respectively. Patients with hyperuricemia had overweight (mean BMI; 26.3 ± 4.2) compared to controls (mean BMI; 23.6 ± 3.2). Also, they had higher SBP and FBG levels, as well as lower liver and kidney functioning. We found no significant uric acid deposits in the cornea in any of the individuals. The vast majority of hyperuricemia & gout patients had bilateral dry eye (40% & 53.3%), followed by bilateral red eye (15.4% & 20%) respectively (Table 2).

Analysis of pro-inflammatory cytokines (IL-1 & TNF-α) and uric acid levels in tear fluid: Table (1)

showed the hyperuricemia group had considerably higher tear uric acid levels than the control group (1.65±0.4 vs. 0.72±0.17 mg/dl, P<0.001). Our findings showed that the hyperuricemia group had a considerably greater level of tear IL-1β than the control group did, with respect to the pro-inflammatory cytokines IL-1 and TNF-α in tear fluid (210.0±51.9 pg/ml vs. 143.4±29.6 p g/ml, P<0.001) **(**Table 1). However, there was no discernible difference between the control and hyperuricemia groups' tear TNF-α levels (130.3±31.6 pg/ml vs. 134.6± 32.8 pg/ml, P=0.657) (Table 1).

Table (1): Clinical & laboratory characteristics of healthy controls and hyperuricemia patients

Variable	Hyperuricemia (N=80)	Controls (N=90)	P -Value
No (Male),%	68(85)	72(80)	0.319
Age (year)	50.5±16.5	49.2±12.0	0.384
BMI (kg/m^2)	26.3±4.2	23.6±3.2	<0.001*
SBP (mmHg)	137.8±22.3	127.6±16.6	0.010*
DBP (mmHg)	79.0±13.2	77.0±11.5	0.382
ALT (U/L)	36.6±8.9	24.7±5.7	0.010*
AST (U/L)	27.3±6.4	23.2±5.6	0.362
BUN (mg/dl)	18.48±4.2	13.44±3.08	0.003*
Cr (mg/dl)	1.03±0.25	0.8±0.16	<0.001*
FPG (mg/dl)	118.8±25.2	104.4±23.4	0.040*
TC (mg/dl)	177.61±42.47	189.19±34.75	0.133
TG (mg/dl)	159.29±35.4	132.74±26.55	0.058
s UA (mg/dl)	8.05±1.49	4.91±1.14	<0.001*
t UA (mg/dl)	1.65± 0.4	0.72 ±0.17	<0.001*
t IL1 β (p g/ml)	210.0±51.9	143.4±29.6	<0.001*
t TNF-α (p g/ml)	134.6± 32.8	130.3±31.6	0.657

BMI, body-mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; sUA, serum uric acid, t UA; tear uric acid, t IL1β; tear interleukin 1β , t TNF-α ; tear tumor necrosis factor α .

Table (2): Frequency of ocular manifestations in acute gout& asymptomatic hyperuricemia patients

Ocular manifestations	Gout patients (N=15 ,%)	Hyper-uricemia patients (N=65, %)	Laterality
Dry eye syndrome	8 (53.3%)	26(40%)	Bilateral
Red eye	3(20%)	10(15.4%)	Bilateral
Uveitis	1(6.7%)	3(4.6%)	Unilateral
Glaucoma	1(6.7%)	2(3.1%)	Unilateral
Cataract	2(13.3%)	7(10.8%)	Unilateral

Correlation between serum & tear Uric acid levels and clinical data: Serum urate level substantially correlated with SBP, BMI, ALT, TG, and Cr levels as well as tear urate level had positive significant association with, BMI, Cr, and TG levels (Table 3). The relationship between tear urate level and serum urate level was significantly positive in the whole participant population and the control group, but not in the hyperuricemia group. Additionally, there were positive correlations between tear urate level and tear IL-1 level in both the hyperuricemia group and the entire participant population, but not in the control group. However, neither among all participants, nor among hyperuricemia patients or controls, there were any statistically significant relationships between tear uric acid and tear TNF- level. Furthermore, multivariable linear regression analysis included variables such as BMI, SBP, ALT, Cr, TG, s UA, and tear IL-1 were substantially correlated with tear urate in Spearman correlation analysis (Table 3).

Table (3): Factors correlated with tear and serum urate levels

Variables	Tear urate		Serum urate	
	r	P value	r	P value
Age	0.153	0.107	-0.042	0.667
BMI	0.300	0.001*	0.348	<0.001*
SBP	0.017	0.873	0.237	0.015*
DBP	-0.099	0.281	0.128	0.175
ALT	0.089	0.348	0.270	0.001*
AST	0.048	0.612	0.139	0.107
BUN	0.179	0.060	0.120	0.203
Cr	0.274	0.003*	0.480	<0.001*
FPG	0.149	0.114	0.128	0.172
TC	-0.084	0.373	-0.082	0.350
TG	0.229	<0.001*	0.370	<0.001*
tIL-1β	0.586	<0.001*	0.345	0.002*
tTNF-α	0.175	0.072	0.053	0.580

Tear proinflammatory cytokines & tear urate levels between acute gout and asymptomatic hyperuricemia patients: 15 individuals in the hyperuricemia group had acute gout attacks at the time of study enrolment, however they did not take any medications (i.e., colchicine, NSAIDs, or glucocorticoids). As shown in table (4), the group with asymptomatic hyperuricemia had somewhat higher serum urate levels than the group with gout, while the group with asymptomatic hyperuricemia had significantly higher tear urate concentrations than gout patients. The difference in tear urate levels between the two groups, however there was no longer statistically significant (P 0.054) after controlling for serum urate level. Furthermore, TNF- and IL-1 levels in tears did not differ significantly between the gout and asymptomatic hyperuricemia groups, suggesting that ocular inflammation was overexpressed during the asymptomatic hyperuricemia phase.

Table (4): Comparison of serum & tear urate and pro-inflammatory cytokines levels between asymptomatic hyperuricemia and gout patients

Variables	Asymptomatic Hyperuricemia (N=65)	Gout patients (N=15)	P - Value
sUA (mg/dl)	8.18±1.13	7.37±1.82	0.072
tUA (mg/dl)	1.82±0.44	1.22±0.29	0.054
tIL-1β (p g/ml)	224.3±55.7	182.1±44.7	0.228
tTNF-α (p g/ml)	148.5±36.5	116.1±28.9	0.328

Table (5) it is shown that tear urate was independently correlated with serum urate (B, 0.179; 95% CI, 0.119–0.257; P <0.001) and tear IL-1β (B, 0.191; 95% CI, 0.112–0.274; P <0.001).

Table (5): Multivariable linear regression of confounding factors associated with tear urate level

Variables	B	P value	95%CI	
			Upper limit	Lower limit
sUA	0.179	<0.001*	0.119	0.257
tIL-1β	0.191	<0.001*	0.112	0.274

DISCUSSION

The current research showed that patients with hyperuricemia had tear urate levels that were noticeably greater than those of healthy controls. Tear IL-1β concentration was higher in the hyperuricemia group and substantially correlated with tear uric acid level, suggesting a relationship between eye inflammation and hyperuricemia. However, there were no significant differences in tear IL-1β or TNF-α levels between the acute gout flare and asymptomatic hyperuricemia groups, indicating that eye inflammation may already be present during the asymptomatic hyperuricemia period.

Our investigation found that the mean uric acid level in tear fluid was much lower than that in blood, (0.72±0.17 mg/dl) in control participants and (1.6± 0.4 mg/dl) in hyperuricemia patients, respectively. This comes in line with **Wu *et al.*** [13] who found that uric acid level in tear fluid 0.72 mg/dl vs 1.7 mg/dl in control subjects & hyperuricemia patients respectively compared to serum.

Also, **Horwath-Winter *et al.*** [14] found that, in agreement with our investigation, the mean uric acid concentrations in tears were lower than those in serum (2 mg/dl vs. 5.8 mg/dl). Furthermore, we found that our study's tear uric acid level was lower than that found in previous publications. This might be related to the various methods used for both tear collection and uric acid measurement. As it is already known that hyperuricemia can result in vascular abnormalities, tophi deposits, subconjunctival clear vesicles, and hemorrhage, among other ocular surface abnormalities [15]. Moreover, two of the most typical ocular signs included subconjunctival hemorrhage aggravated by purine consumption and conjunctival hyperemia [4]. The buildup of urate and the ensuing inflammation may have negative effects on other ocular and adnexal tissues, which could endanger one's vision [4].

Furthermore, serum uric acid and IL-1 production are linked according to numerous studies [16]. The etiology of many inflammatory and degenerative eye disorders as well as the search for effective therapies, are both heavily dependent on IL-1 [17]. For example, studies using a rat model of uveitis discovered that during the active stage of ocular inflammation, the expression of the genes for TNF and IL-1 was markedly elevated [18, 19]. IL-1 antagonists have been used to treat uveitis in monogenic autoinflammatory illnesses such as Blau syndrome and cryopyridine-associated periodic syndrome, as well as complicated polygenic autoinflammatory disorders such as Behcet's disease [20, 21]. Likewise, it has also been shown that an IL-1 receptor blocker works well for treating scleritis and episcleritis in a number of rheumatic conditions [22, 23]. As a result, the concentration of IL-1 may be used as a potential marker and therapeutic target for ocular illnesses linked to hyperuricemia. According to the current study, patients with hyperuricemia exhibited noticeably greater tear IL-1 levels. A significant association between tear IL-1 and serum/tear urate levels was discovered, suggesting that higher tear uric acid levels may contribute to the development of ocular inflammation associated with hyperuricemia.

As, the real hyperuricemia cut-off is primarily determined by the uric acid saturation point. Hence, the detrimental effects of cardiovascular disease may manifest at lower levels, according to a recent study [24]. Another study found that 6.3 mg/dl for males and 4.9 mg/dl for women were the ideal cut-off values for blood uric acid to detect metabolic syndrome [25]. These findings highlight the significance of the treat-to-target strategy for decreasing urate levels in individuals with hyperuricemia. The risk of uric acid-induced ocular damage is associated with the uric acid cut-off, however it is unknown and requires further study. However, the level of IL-1β did not significantly differ from that of individuals with acute gout episodes and asymptomatic hyperuricemia. Gout is often understood to be a painful arthritis caused by urate deposition. It can be treated with anti-inflammatory medications on an occasional basis, and some medical societies advise starting urate-lowering treatments only when flare-ups happen frequently [26]. One possible explanation for the common comorbidities linked to gout might be systemic urate accumulation and the persistent inflammation that results [27].

Our findings imply that ocular inflammation may be present as early as the asymptomatic phase of hyperuricemia. The most common ocular abnormality among gout patients was red eye, usually bilateral, caused by conjunctival and episcleral hyperemic vessels, according to **Ferry *et al.*** [6] and **Yülek *et al.*** [8]. Furthermore, vascular changes at the ocular surface, including tortuosity, thickness, congestion, and prolonged subconjunctival bleeding, have been linked to early gout. Gout patients have been recognized to have dry eye syndrome [28], and two investigations revealed that gout patients were more likely to have this condition [29, 30]. However, the link between dry eye syndrome and gout was not discovered in a larger cohort or over a longer period of time [31]. As a result, there is still debate concerning the relationship between dry eye condition and gout history. Inflammatory ocular illnesses also contain high concentrations of cytokines such IL-1, TNF-, and IL-6, which may excite and promote the maturation of monocytes into macrophages.

Additionally, acute anterior ocular inflammation is characterized by macrophage and neutrophil infiltration in the anterior chamber of the eye, as well as pro-inflammatory cytokine production. Studies employing a rat model of induced uveitis found that IL-1 and TNF- gene expression were dramatically upregulated during the period of active intraocular inflammation, together with high intraocular IL-6 levels [32, 33]. Monocytes in patients with a history of acute anterior uveitis produce more TNF-α when exposed to LPS than healthy individuals [34]. Therefore, gout and intraocular inflammation processes both exhibit greater levels of pro-inflammatory cytokines.

Limitations: There are a few limitations to be aware of. First, this study's sample size was modest, particularly for some of the subgroup analyses. Second, the cross-sectional nature of our study makes it impossible to draw conclusions about the persistence or evolution of tear urate and cytokine concentration over time or the peculiarities of the MSU disposition in individuals with hyperuricemia and gout. Third, gout's ocular symptoms are uncommon but varied. We did not see any appreciable corneal urate deposits in this research. Fourth, this study looked into tear IL-1β and TNF-α , but, the levels of many cytokines, including IL-1Ra, IL-33, IL-37, IL-38, and IL-6, were not measured.

CONCLUSION

We found that uric acid and IL-1β are higher in the tear fluid of people with gout and hyperuricemia. Increased levels of IL-1β and tear uric acid in hyperuricemia patients' eyes implied that inflammation mediated by IL-1β may be a plausible mechanism behind the ocular symptoms of gout and hyperuricemia. Furthermore, gout flare patients had the same levels of TNF-α and IL-1β as the group with asymptomatic hyperuricemia, highlighting the need of physicians closely monitoring asymptomatic hyperuricemia. However, further prospective studies with a bigger sample size are required to confirm the results of the current study and look into the connection between elevated cytokines and ocular symptoms in patients with gout and hyperuricemia.

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