Int Ophthalmol (2019) 39:991–1001
https://doi.org/10.1007/s10792-018-0901-7

ORIGINAL PAPER

Could corneal densitometry be used as a diagnostic and screening tool for ocular involvement in patients with gout?

Pinar Kosekahya · Kadir Gokhan Atilgan · Cemile Ucgul Atilgan · Kemal Tekin · Mustafa Koc · Mehtap Caglayan · Deniz Ayli · Pelin Yilmazbas

Received: 10 October 2017 / Accepted: 16 March 2018 / Published online: 21 March 2018

Abstract

Purpose To evaluate the corneal and tear film characteristics in patients with gout and compare these data with those of healthy subjects and to investigate the correlation of corneal densitometry with uric acid value and duration of disease.

Methods Forty-one eyes of 41 patients with gout (group 1) and 40 eyes of 40 healthy subjects (group 2) were included in this study. Detailed ophthalmologic examinations were performed on all participants. Corneal tomographic analyses were performed with the Pentacam HR Scheimpflug imaging system (Oculus, Wetzlar, Germany). Maximum keratometry (K_{max}), central corneal thickness (CCT), corneal volume (CV), and corneal densitometric values were compared between groups. Tear function tests including Schirmer, tear breakup time, and fluorescein staining were performed and compared between groups.

Results Groups were similar in terms of age and gender. K_{max}, CCT, and CV values were similar between groups. The outcomes of tear function tests were similar between groups. Corneal densitometric values for the 0–2 and 2–6 mm zones of the anterior and center layers were significantly higher in group 1 compared to group 2. This densitometric increase was positively correlated with uric acid levels and gout duration.

Conclusions Corneal densitometry values of the 0–2 and 2–6 mm zones of the anterior and central layers were higher in patients with gout than those of the control subjects, and the densitometric values increased as uric acid level and disease duration increased.

Keywords Corneal densitometry · Gout · Tear film tests

P. Kosekahya (✉) · C. U. Atilgan · M. Koc · P. Yilmazbas
Department of Ophthalmology, Ulucanlar Eye Training and Research Hospital, Ulucanlar Street, Number: 59, 06240 Ankara, Turkey
e-mail: drkosekahya2@gmail.com

K. G. Atilgan · D. Ayli
Department of Nephrology, Diskapi Yildirim Beyazıt Training and Research Hospital, Ankara, Turkey

K. Tekin
Department of Ophthalmology, Kars State Hospital, Kars, Turkey

M. Caglayan
Department of Ophthalmology, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey

Introduction

Gout is a type of inflammatory disease and is caused by monosodium urate (MSU) depositions in extracellular fluids, primarily in the joints [1]. Hyperuricemia is the main risk factor for the development and

recurrence of gout and is typically defined as serum urate concentration of $\geq$ 6.8 mg/dL [2]. Although it results from elevated uric acid (UA) levels, some people with hyperuricemia never develop gout [3]. Dietary risk factors include excessive consumption of alcohol, meat (including red meat, giblets, and fast foods), seafood, sugar-sweetened soft drinks, and foods and drinks that are high in fructose [4]. The clinical manifestations of gout are recurrent acute arthritis, UA nephrolithiasis, uric acid nephropathy, and MSU deposits, known as tophaceous deposits, in the ligaments, soft tissues, periarticular areas, and osseous tissues [5–7].

The prevalence of gout ranges from 1 to 4% in the USA and Western Europe, and males are more commonly affected than females [3, 8]. However, there are large geographical variations in global prevalence, which may be due to genetic and cultural differences [9]. An almost twofold increase in worldwide gout prevalence occurred between 1990 and 2010 [10]; one reason for this may be the increase in the prevalence of obesity, which is a common and preventable public health problem [10]. The number of studies conducted on gout has also shown a threefold increase between 2005 and 2015, which is in direct proportion to the increased prevalence [11].

Ocular tophi have been reported in the upper eyelid, lateral canthus, cornea, orbit, iris, and anterior chamber of the eyes in gout patients [12–15]. Corneal tophi have previously been reported in the corneal epithelium and stroma [16, 17]. MSU crystals were confirmed in the cornea with polarized light microscopy in two case reports [18, 19], and histopathological examination confirmed gouty tophi in the latter report [19].

Corneal densitometry analysis has recently gained popularity in the noninvasive and objective evaluation of corneal transparency. It has been used to evaluate the effect of CXL and corneal surgeries [20, 21]. It has also been investigated for quantification of corneal deposits in monoclonal gammopathies and amiodarone keratopathy [22, 23].

Gout is a chronic MSU deposition disease, and MSU depositions have been revealed in some ocular tissues including the cornea. We hypothesized that subclinical MSU accumulation may have been demonstrated in the corneas of the patients with gout and that corneal densitometry might represent a helpful tool for monitoring uric acid tissue levels and disease course in patients with gout. To achieve this goal, this study aimed to evaluate corneal densitometry and tear film tests in patients with gout by comparing the data with those of healthy controls and to investigate the correlation of corneal densitometry with uric acid value and duration of disease.

Methods

Subjects

This clinical prospective comparative study was conducted on the Turkish Caucasian participants in the nephrology and ophthalmology departments of two tertiary care hospitals of Ankara (Turkey). The study protocol was approved by the ethics committee of Ankara Numune Training and Research Hospital, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical gout inclusion criteria were based on the 2015 American College of Rheumatology/European League Against Rheumatism classification criteria for gout [24]. These criteria require the occurrence of at least 1 episode of peripheral joint or bursal swelling, pain, or tenderness. The presence of MSU crystals in a symptomatic joint/bursa (i.e., synovial fluid) or in a tophus is a sufficient criterion for classification of the subject as having gout and does not require further scoring. The domains of this classification criterion include clinical (pattern of joint/bursa involvement, characteristics and time course of symptomatic episodes), laboratory (serum urate level, MSU crystals in synovial fluid aspirate), and imaging (double-contour sign on ultrasound or urate on dual-energy computed tomography, radiographic gout-related erosion) characteristics. Serum UA level is not a necessity in the diagnosis, but it is important in the clinical scoring and management of gout.

Systemic exclusion criteria were diabetes mellitus, any systemic disease other than gout, cancer, chronic renal disease, cardiac disease, and the systemic use of drugs that can increase UA levels. Ocular exclusion criteria were a history of previous ocular surgery, trauma, uveitis, corneal scar or ectasia, contact lens wearers, topical medication usage, high spherical (< -6.0 D or $> +6.0$ D) or cylindrical (< -3.0 D or $> +3.00$ D) refractive errors, optic nerve diseases,

glaucoma, and a lack of sufficient cooperation with regard to the Scheimpflug system examinations.

A total of 150 consecutive patients with gout who were examined in the department of nephrology from May 2016 to December 2016 were recruited for the study. One hundred and nine of these 150 patients were excluded for the reasons shown in the flowchart in Fig. 1. Additionally, 19 of the excluded individuals were taking diuretic agents, and 87 were taking antihypertensive agents. Ultimately, 41 gout patients were included (group 1) and referred to the department of ophthalmology for ophthalmologic examinations.

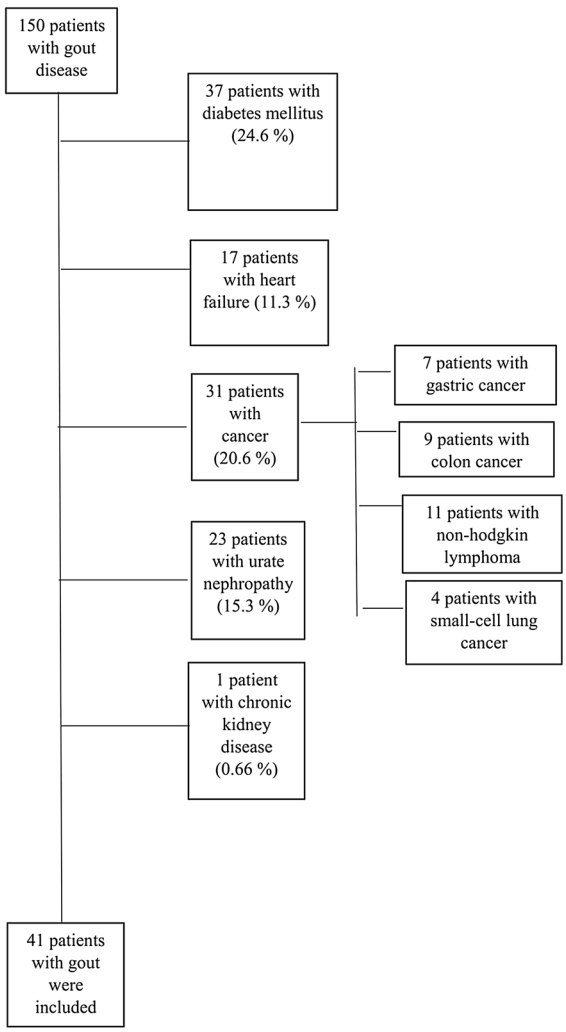

Fig. 1 Flowchart of patients with gout who met inclusion/exclusion criteria for the study

The control participants (group 2) consisted of 40 consecutive age- and gender-matched healthy individuals who had applied to the department of ophthalmology for a routine ophthalmologic examination. They had no signs or symptoms of any ocular and systemic disorder or any topical and systemic medication use.

All gout patients were taking daily oral low-dose colchicine (0.5–1.5 mg/day) and allopurinol. Allopurinol dosing was established as 150 mg/every other day when the UA level of the patient was below 6.8 mg/dL. When the urate level of the patient exceeded 6.8 mg/dL, allopurinol was administered at doses of 150–300 mg/day [2]. Febuxostat, another licensed treatment for gout, cannot be used because no payback is available for the drug. Antihyperlipidemic agents (statins) were administered for 3 of 41 patients in whom non-alcoholic fatty liver disease was confirmed with ultrasonography.

Ophthalmologic examination

All participants underwent a comprehensive ophthalmic examination including tear film tests, best-corrected visual acuity (BCVA) tests using the Snellen chart, intraocular pressure (IOP) measurements via Goldmann applanation tonometry, slit-lamp biomicroscopy, and dilated fundus examination.

Corneal tomography

Corneal tomography was performed using a non-contact, noninvasive rotating Scheimpflug camera system. Prior to a Pentacam examination, the participants had not undergone any contact ocular examination, such as tonometry, gonioscopy, or pupil dilation. The Pentacam generates a three-dimensional model of the cornea and anterior segment. Corneal tomographic analyses were performed by the same blinded experienced clinician, who used the same Pentacam HR Scheimpflug imaging system (Oculus, Wetzlar, Germany), and all measurements were taken under standard dim-light conditions. Three measurements were taken per eye, and the measurement with the best alignment and fixation was selected for data analysis. Distorted images caused by high reflection were not included. The maximum keratometry (K_{max}), mean keratometry (K_m), central corneal thickness

(CCT), and corneal volume (CV) values were recorded as corneal topographical parameters.

Corneal light backscatter measurements were recorded via the densitometry software of the Pentacam HR. This program automatically located the corneal apex and analyzed a surrounding area of 12 mm in diameter. This area was further divided into four concentric zones as follows: the first consisted of a circular 2-mm-diameter area at the center of the cornea, the second was the 2- to 6-mm annular area around the first zone, the third was the 6- to 10-mm annular area, and the fourth zone was the 10- to 12-mm annular area (Fig. 2). These analyses also provided corneal densitometric values at three different depths. The anterior layer consisted of the superficial 120 µm region, and the posterior layer consisted of 60 µm of the innermost cornea; the central corneal layer lies between these two layers (Fig. 2). Corneal densitometry values are expressed as the pixel luminance per unit volume in the Scheimpflug image, and these are given in grayscale units. The measurements ranged from 0 (maximum transparency, no corneal haze) to 100 (totally opaque cornea), with regard to the degree of backscattering light from the cornea.

Tear function tests

The tear breakup time (TBUT) test, corneal epithelial staining with fluorescein (FS), and Schirmer tear test (without topical anesthesia), were, respectively, carried out in all participants.

In order to measure TBUT, a fluorescein sodium strip moistened with a drop of non-preserved saline solution was applied to the inferior palpebral conjunctiva and then removed. The participant was asked to blink three times and then look straight ahead. The precorneal tear film was examined under cobalt blue illumination, and the elapsed time before the initial breakup, rupture of the tear film, or formation of tiny dry spots was recorded. The TBUT was measured three times, and the measurements were averaged [25].

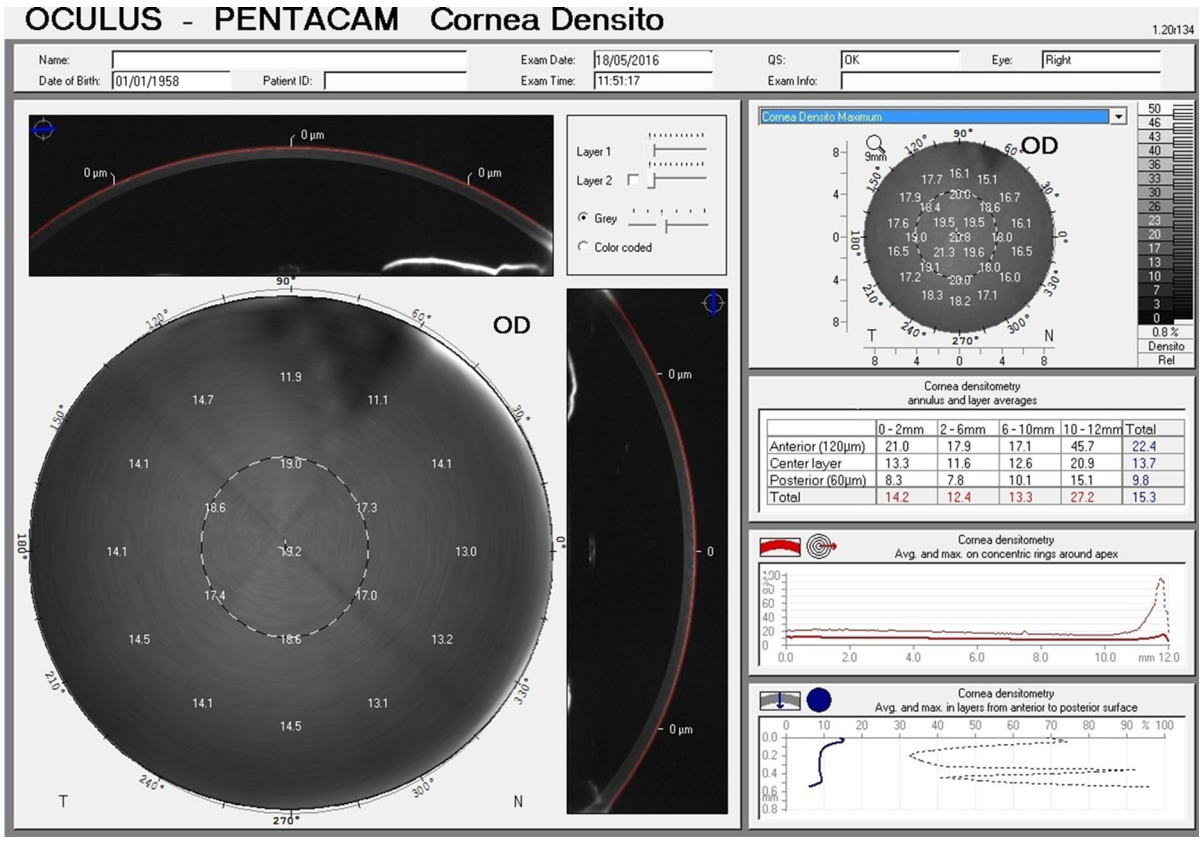

Fig. 2 Corneal densitometric analysis of a participant

Consequently, corneal FS was assessed under cobalt blue illumination. The type of staining (severity/location) was graded as follows [26]: grade 1, none-to-mild; grade 2, variable staining; grade 3, marked central staining; grade 4, severe punctate erosions.

Finally, a standard Schirmer test strip was placed in the lower fornix at the junction of the lateral and middle third, attempting to avoid touching the cornea. Five minutes later, the strip was removed and its wetted length was measured in mm to determine the Schirmer tear test score [27].

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation (SD), frequency distributions, and percentages. The normal distribution of the variables was tested via the Kolmogorov–Smirnov and Shapiro–Wilk tests. Independent-samples *t* tests were used for normally distributed data comparisons, and Mann–Whitney *U* tests were used for non-normally distributed data comparisons. Chi-square tests were used in the analysis of categorical variables, and Pearson and Spearman correlation analyses were performed for normally and non-normally distributed data correlations. The level of statistical significance was set at $p < 0.05$.

Results

The demographical characteristics of all participants, duration of disease, and the laboratory test results of group 1 are summarized in Table 1. The two groups were similar in terms of age and gender ($p = 0.91$ and $p = 0.11$, respectively). The mean values of BCVA and IOP were also similar between the groups ($p = 0.43$ and $p = 0.57$, respectively).

The mean duration of gout disease was 4.44 ± 2.93 (range 1–15) years. All patients were in the intercritical period and were not suffering from a gout attack, gouty arthritis, or a tophus at the time of the ocular examinations. Acute gout attack frequency was low in these patients because they were following a regular treatment protocol, which included colchicine and allopurinol use, and were also on a low-purine diet. ESR and CRP levels were in the normal range in all patients at the time of the examinations. The mean UA level in blood plasma was 8.55 ± 2.14 (range 3.09–11.37) mg/dL, while the normal laboratory values were 3.5–7.2 mg/dL. There was not any participant consuming alcohol. There were 14 smokers and 27 non-smokers in gout group and 12 smokers and 28 non-smokers in control group. Smoking status was similar between groups ($p = 0.68$) (Table 1). The mean values of the TBUT, FS, and Schirmer tests were similar between the two groups (Table 2).

No corneal or conjunctival crystal deposits were present in the slit-lamp examination in any of the gout patients. The corneal topographical parameters data of all participants are summarized in Table 3, and the mean values of the K_{max}, K_m, CCT, and CV values were similar between the two groups.

Table 4 summarizes the corneal densitometry values of all participants. The highest values were obtained in the anterior layer, followed by the central and posterior layers in both groups. The values for the 0–2 mm zones of the anterior ($p = 0.002$) and central layers ($p = 0.004$) were significantly higher in group 1 than in group 2, as were the values for the 2–6 mm zones of the anterior ($p = 0.02$) and central layers ($p = 0.03$). The corneal densitometry values of the posterior 0–2 and 2–6 mm zones were similar between the groups ($p = 0.71$ and $p = 0.74$, respectively), as were the values of the 6–10 and 10–12 mm zones of all layers ($p > 0.05$ for all values). The UA levels were positively correlated with the densitometry values of the 0–2 mm zones of the anterior, central, and total corneal layers. Positive correlations were also found between UA levels and anterior 2–6 mm, anterior total, central total, and overall total densitometric values ($p < 0.05$ for all correlations). Gout disease duration was significantly and positively correlated with the values of the 0–2 and 2–6 mm zones of the anterior and central layers (Table 5). Correlation graphic shows the relationship between uric acid value and overall total densitometric value in patients with gout (Fig. 3).

Discussion

The evaluation of corneal deposits and corneal haze is an essential part of ocular examination and is

Table 1 Demographical characteristics of groups and clinical characteristics of the patients with gout

Characteristics	Group 1	Group 2	*p* value*
Age (years) mean ± SD	59.92 ± 7.62	60.11 ± 7.96	0.91
(range)	(41–75)	(44–71)	
Gender (female/male)	12/29	16/24	0.11
Smoking status (smoker/non-smoker)	14/27	12/28	0.68
BCVA (decimal) mean ± SD	0.83 ± 0.18	0.91 ± 0.05	0.43
IOP (mm/Hg) mean ± SD	13.4 ± 3.6	15.6 ± 2.7	0.57
Duration of gout (years)	4.44 ± 2.93		
mean ± SD (range)	(1–15)		
Uric acid level (mg/dL) mean ± SD	8.55 ± 2.1		
(range)	(3.09–11.37)		
ESR (mm/hour) mean ± SD	12.99 ± 9.46		
(range)	(2–22)		
C-reactive protein (mg/L)	1.16 ± 1.05		

BCVA best-corrected visual acuity, *IOP* intraocular pressure, *ESR* erythrocyte sedimentation rate

SD standard deviation

*Chi-square test

Table 2 Mean values of tear function tests in the groups

Variables (mean ± SD)	Group 1	Group 2	*p* value*
Tear breakup time test (s)	4.54 ± 1.7	4.96 ± 1.87	0.67
Schirmer tear test (mm)	14.39 ± 8.14	15.63 ± 7.56	0.81
Fluorescein staining	0.03	0.02	0.34

mm millimeters

SD standard deviation

*Independent-samples *t* test

Table 3 Mean values of corneal topographical parameters in the groups

Variables (mean ± SD)	Group 1	Group 2	*p* value*
K_{max} (D)	45.03 ± 1.68	44.74 ± 1.71	0.46
K_m (D)	43.56 ± 2.12	42.78 ± 1.85	0.83
CCT (μm)	546.97 ± 31.01	542.58 ± 27.95	0.52
CV (mm^3)	59.92 ± 4.31	59.08 ± 3.00	0.60

K_{max} maximum keratometry, K_m mean keratometry, *CCT* central corneal thickness, *CV* corneal volume, *D* diopters, *μm* micrometers, *mm* millimeters

SD standard deviation

*Independent-samples *t* test

frequently performed via slit-lamp examination. However, even documented with photography, this is a subjective and observer-dependent method. Pentacam, which is a relatively new corneal tomographer, is superior to slit-lamp biomicroscopy in many aspects, as it yields objective, valid, repeatable, and reproducible data regarding the entire cornea [28]. Corneal densitometry provides information relating to the clarity—transparency—of the cornea; a clear cornea does not absorb visible light; and light scattering is minimal. Corneal clarity is maintained with the regular arrangement of collagen fibrils in the stroma, very precise organization of the extracellular matrix

Table 4 Mean values of corneal densitometry parameters in the groups

Variables (mean ± SD)	Group 1	Group 2	*p* value*
Anterior 120 μm (GSU)			
0–2 mm	25.2 ± 4.0 (18.1–36.2)	19.2 ± 1.4 (16.9–23.3)	**0.002**
2–6 mm	20.4 ± 3.6 (16.2–33.1)	17.8 ± 1.4 (15.7–21.3)	**0.02**
6–10 mm	25.9 ± 6.5 (15.3–41.8)	25.0 ± 6.7 (14.7–41.3)	0.50
10–12 mm	38.1 ± 9.5 (15.2–54.4)	38.0 ± 11.0 (19.2–62.0)	0.24
Total diameter	23.9 ± 4.4 (16.6–34.1)	23.6 ± 3.8 (16.7–30.3)	0.78
Central (GSU)			
0–2 mm	14.0 ± 0.7 (11.3–15.1)	12.4 ± 2.0 (10.7–14.6)	**0.004**
2–6 mm	13.2 ± 0.8 (10.7–14.1)	11.6 ± 0.8 (10.0–13.7)	**0.03**
6–10 mm	17.8 ± 5.2 (10.9–35.5)	17.1 ± 4.2 (10.4–25.7)	0.80
10–12 mm	22.4 ± 4.0 (11.9–29.3)	21.8 ± 4.2 (12.9–29.4)	0.41
Total diameter	15.2 ± 2.2 (11.6–21.1)	15.2 ± 2.1 (11.3–18.9)	0.99
Posterior 60 μm (GSU)			
0–2 mm	11.5 ± 0.8 (9.0–12.1)	10.5 ± 0.8 (9.0–12.6)	0.71
2–6 mm	10.8 ± 0.8 (8.6–13.2)	10.1 ± 0.9 (8.4–12.3)	0.74
6–10 mm	16.0 ± 2.7 (9.3–19.3)	15.0 ± 3.1 (9.7–21.6)	0.15
10–12 mm	18.2 ± 3.0 (11.1–22.6)	17.7 ± 3.3 (11.4–24.1)	0.52
Total diameter	13.3 ± 1.5 (10.0–15.5)	13.0 ± 1.8 (10.0–16.6)	0.43
Total thickness (GSU)			
0–2 mm	16.9 ± 1.4 (13.3–20.4)	14.0 ± 0.8 (12.5–16.5)	**0.003**
2–6 mm	15.9 ± 1.3 (12.4–18.7)	13.2 ± 0.9 (11.4–15.1)	**0.02**
6–10 mm	20.1 ± 4.3 (12.1–29.6)	19.0 ± 4.5 (11.6–29.4)	0.40
10–12 mm	26.6 ± 5.0 (12.7–34.9)	25.8 ± 5.6 (15.0–37.6)	0.33
Total diameter	17.2 ± 2.4 (12.8–23.4)	17.2 ± 2.3 (12.7–21.7)	0.98

GSU Grayscale units, *μm* micrometers, *mm* millimeters

SD standard deviation

*Independent-samples *t* test

Boldface, statistically significant values, $p < 0.05$

surrounding these collagen fibrils, and balanced keratocytes [29].

Any systemic or local inflammation and infection may disrupt collagen matrix organization, resulting in a loss in corneal transparency and an increase in light scattering, even in the absence of any visible corneal haze or deposit [30]. There are three studies examining the relationship between corneal densitometry and systemic diseases, which are monoclonal gammopathies, diabetes mellitus, and rheumatoid arthritis [22, 31, 32]. Studies concluded that corneal densitometry values were higher than control subjects in patients with monoclonal gammopathies, diabetes mellitus, and rheumatoid arthritis [22, 31, 32]. In our study, we have excluded the patients with systemic diseases either than gout to minimize the confounding factors. Smoking and alcohol consuming status of participants were also similar between groups.

In a study investigating corneal backward light scattering in patients with dry-eye [33], corneal backward light scattering was greater in dry eyes than in normal eyes. Thus, the consideration of densitometric values without tear function tests may not be adequate. Tear function tests were performed in all participants in the present study, and it was revealed that the two groups were similar in terms of tear function tests. Therefore, it can be claimed that the densitometric outcomes of the study were not affected by tear functions.

In the present study, corneal characteristics were investigated in 41 patients with gout, and the data were compared with those obtained from 40 healthy individuals. Corneal topographical parameters were similar between the two groups. Corneal densitometric analysis revealed increased densitometric parameters at the 0–2 and 2–6 mm zones of the anterior and central corneal layers in patients with gout compared to healthy individuals. Corneal densitometric increases were positively correlated with uric acid values and disease duration in patients with gout.

Table 5 Correlation analyses between corneal densitometric values and uric acid levels and gout duration in group 1

	Uric acid values	Disease duration
Anterior 120 μm (GSU)		
0–2 mm	***r* = 0.51, *p* = 0.002**	***r* = 0.39, *p* = 0.04**
2–6 mm	***r* = 0.41, *p* = 0.013**	***r* = 0.42, *p* = 0.01**
6–10 mm	$r = 0.21$, $p = 0.21$	$r = 0.25$, $p = 0.14$
10–12 mm	$r = 0.20$, $p = 0.25$	$r = 0.16$, $p = 0.34$
Total diameter	***r* = 0.47, *p* = 0.004**	$r = 0.23$, $p = 0.18$
Central (GSU)		
0–2 mm	***r* = 0.45, *p* = 0.006**	***r* = 0.59, *p* = 0.004**
2–6 mm	$r = 0.31$, $p = 0.06$	***r* = 0.32, *p* = 0.04**
6–10 mm	$r = 0.27$, $p = 0.11$	$r = 0.21$, $p = 0.21$
10–12 mm	$r = 0.31$, $p = 0.06$	$r = 0.01$, $p = 0.50$
Total diameter	***r* = 0.38, *p* = 0.002**	$r = 0.14$, $p = 0.39$
Posterior 60 μm (GSU)		
0–2 mm	$r = 0.19$, $p = 0.26$	$r = 0.25$, $p = 0.14$
2–6 mm	$r = 0.31$, $p = 0.06$	$r = 0.001$, $p = 0.99$
6–10 mm	$r = 0.30$, $p = 0.07$	$r = 0.16$, $p = 0.35$
10–12 mm	$r = 0.17$, $p = 0.30$	$r = 0.24$, $p = 0.15$
Total diameter	$r = 0.31$, $p = 0.06$	$r = 0.19$, $p = 0.25$
Total thickness (GSU)		
0–2 mm	***r* = 0.51, *p* = 0.002**	$r = 0.30$, $p = 0.07$
2–6 mm	$r = 0.32$, $p = 0.05$	$r = 0.27$, $p = 0.11$
6–10 mm	$r = 0.24$, $p = 0.15$	$r = 0.31$, $p = 0.10$
10–12 mm	$r = 0.27$, $p = 0.10$	$r = 0.22$, $p = 0.24$
Total diameter	***r* = 0.46, *p* = 0.002**	$r = 0.19$, $p = 0.27$

GSU Grayscale units, *μm* micrometers, *mm* millimeters

SD standard deviation

r Pearson correlation coefficient

r^2 Coefficient of determination

Boldface, significant values, $p < 0.05$

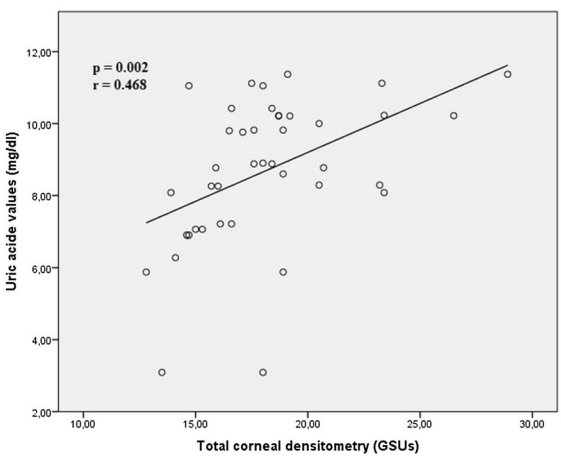

Fig. 3 Correlation graphic showing the relationship between uric acid value and overall total densitometric value in patients with gout

Gout can affect the ocular system as an end-organ containing high blood flow, lower temperatures, and a relatively low solvent ability [34]. The most common ocular symptom in patients with gout is red eyes, which can result from scleritis [35], episcleritis [36], iritis [37], and conjunctival disorders, while the vision-threatening complications of gout are uveitis, increased IOP [12], optic disk edema [38], central retinal vein occlusion, branch retinal artery occlusion [39], and cataract [40]. These manifestations have been generally cited in case reports or obtained from general epidemiologic data, but the exact nature of their relationships with gout remains unclear. In the present study, no ocular tophus, red eye, or vision-threatening complication was observed in the 41 patients with gout at the time of the ocular examination.

Corneal involvement in gout has been reported in several previously published case reports, and corneal tophus locations have included the epithelium, stroma, and Bowman's layer [16, 17]. Corneal deposits were refractile, needle-like, or punctate, and were the

densest in the palpebral fissure. Band keratopathy is a calcific degeneration of Bowman's membrane, and one case report has described band keratopathy in gout [17]. However, it is now clear that while the crystalline deposition in gout can be confused with band keratopathy, it is not a true band keratopathy; depositions are brownish in gout and are whitish gray in band keratopathy [41].

In the study which investigated corneal densitometry in monoclonal gammopathies, corneal backscatter was elevated both in patients with visible proteinemic keratopathy and in patients without visible corneal deposits in the slit-lamp assessment [22]. Corneal deposition may remain as a micro-deposit and may not develop into a visible deposit in all gout patients. Therefore, a more reliable and objective indicator for the screening of ocular involvement in gout is required.

In a report of Slansky et al. [16], the corneal depositions observed were superficial and densest in the palpebral fissure. In the present study, the corneal densitometric increase was more prominent in the 0–2 and 2–6 mm zones, and when the densitometric increase was investigated with respect to corneal layers, anterior and central layer increases were more prominent than posterior layer. These results may indicate that MSU deposition in gout disease might proceed from the central to the peripheral cornea and also from the anterior to the posterior cornea. In the Enders et al.'s study, corneal densitometry was investigated in monoclonal gammopathies, and they concluded that corneal density increase was more evident in the anterior corneal layers in the peripheral annular zone [22]. They have suggested that, as immunoglobulin deposits are likely to originate from the limbal vascular plexus, peripheral corneal density increase is not unexpected [22]. It can be hypothesized that corneal densitometric values could also increase in the posterior layer and in peripheral zones of cornea as the deposition increases. This hypothesis must be confirmed by microscopic and histopathological analyses to verify the MSU depositions, and also to explain the micro-deposit preference with regard to corneal locations by grouping the patients with gout according to disease duration.

In the study which investigated corneal densitometry in diabetic patients, anterior total corneal densitometry measurements showed positive correlation with the duration of diabetes [31]. In a study evaluating corneal densitometry parameters in patients receiving amiodarone therapy, densitometry values were correlated with cumulative dose and duration of amiodarone treatment [23]. So, corneal densitometry may be a useful and objective screening tool for the monitoring of the diseases and/or medications with storage disorders. In the present study, the densitometric increases were correlated with UA levels and disease duration. Although a threshold uric acid value of < 6.8 mg/dL was intended for all gout patients, it cannot be possible for all patients. So, long-term exposure to high serum uric acid levels might result in trapped MSU in the cornea, where it may accumulate to excess levels. The acute attack rates, long-term follow-up of UA levels can give more clues about the association between gout course, disease control, and corneal densitometry. By this means, the role of corneal densitometry as a monitoring tool in the follow-up of patients with gout might be further revealed.

A limitation of our study is its sample size, which was considerably smaller than planned. In fact, a total of 150 gout patients were analyzed, but only 41 of these met the inclusion criteria. However, our exclusion of other systemic diseases ensures the reliability of the results. Second, gout patients were taking oral low-dose colchicine and allopurinol, and their possible effects on corneal densitometry values are unknown. Third, the blood samples could not taken from the control subjects because of the ethical restrictions. Therefore, the data about the UA, ESR, and CRP levels of control subjects could not been presented in our study. Although all the control subjects were selected from systemic disease-free consecutive participants, unknown and/or undetected systemic disorders of the control subjects might have affected the corneal densitometry values and thus acted as confounding factors. However, despite these limitations, we believe that this study provides relevant information about the corneal densitometric analysis in patients with gout.

In conclusion, in eyes with gout, the corneal densitometry values of the 0–2 and 2–6 mm zones of the anterior and central layers were higher than those of the control eyes. Corneal densitometry values of the 0–2 and 2–6 mm zones of the anterior and central layers were correlated with UA levels and disease duration. Histopathological confirmation and expansion of the sample size with patients in different gout

stages, and prospective follow-up of gout patients, would be of further interest.

Compliance with ethical standards

Conflict of interest The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Li EK (2004) Gout: a review of its aetiology and treatment. Hong Kong Med J 10:261–270
2. Dalbeth N, Merriman TR, Stamp LK (2016) Gout. Lancet 388:2039–2052
3. Zhu Y, Pandya BJ, Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum 63:3136–3141
4. Singh JA, Reddy SG, Kundukulam J (2011) Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol 23:192–202
5. Cameron JS, Moro F, Simmonds HA (1993) Gout, uric acid and purine metabolism in paediatric nephrology. Pediatr Nephrol 7:105–118
6. Akizuki S (1982) A population study of hyperuricemia and gout in Japan—analysis of sex, age and occupational differences in thirty-four thousand people living in Nagano Prefecture. Ryumachi 22:201–208
7. Anton FM, Garcia Puig J, Ramos T, Gonzalez P, Ordas J (1986) Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 beta (E2) on the renal handling of urate. Metabolism 35:343–348
8. Bardin T, Bouee S, Clerson P, Chales G, Flipo RM, Liote F, Perez V, Poiraud T, Schaeverbeke T, Richette P (2016) Prevalence of gout in the adult population of France. Arthritis Care Res 68:261–266
9. Kuo CF, Grainge MJ, Zhang W, Doherty M (2015) Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 11:649–662
10. Terkeltaub R (2010) Update on gout: new therapeutic strategies and option. Nat Rev Rheumatol 6:30–38
11. Singh JA (2016) Gout: will the "King of Diseases" be the first rheumatic disease to be cured? BMC Med 14:180
12. Morris WR, Fleming JC (2003) Gouty tophus at the lateral canthus. Arch Ophthalmol 121:1195–1197
13. Ferry AP, Safir A, Melikian HE (1985) Ocular abnormalities in patients with gout. Ann Ophthalmol 17:632–635
14. Topping NC, Cassels-Brown A, Chakrabarty A, Cronin P, Ross S, Russell J, Tesha P (2003) Uric acid crystals presenting as an orbital mass. Eye (Lond) 17(3):427–429
15. Coassin M, Piovanetti O, Stark WJ, Green WR (2006) Urate deposition in the iris and anterior chamber. Ophthalmology 113(3):462–465
16. Slansky HH, Kubara T (1968) Intranuclear urate crystals in corneal epithelium. Arch Ophthalmol 80(3):338–344
17. Fishman RS, Sunderman FW (1966) Band keratopathy in gout. Arch Ophthalmol 75(3):367–369
18. Bernad B, Narvaez J, Diaz-Torné C, Diez-Garcia M, Valverde J (2006) Clinical image: corneal tophus deposition in gout. Arthritis Rheum 54(3):1025
19. Sarma P, Das D, Deka P, Deka AC (2010) Subconjunctival urate crystals: a case report. Cornea 29(7):830–832
20. Alnawaiseh M, Rosentreter A, Prokosch V, Eveslage M, Eter N, Zumhagen L (2016) Changes in corneal densitometry in patients with Fuchs endothelial dystrophy after endothelial keratoplasty. Curr Eye Res 3:1–5
21. Alnawaiseh M, Rosentreter A, Eveslage M, Eter N, Zumhagen L (2015) Changes in corneal transparency after cross-linking for progressive keratoconus: long-term follow-up. J Refract Surg 31:614–618
22. Enders P, Holtick U, Schaub F, Tuchscherer A, Hermann MM, Scheid C, Cursiefen C, Bachmann BO (2017) Corneal densitometry for quantification of corneal deposits in monoclonal gammopathies. Cornea 36(4):470–475
23. Alnawaiseh M, Zumhagen L, Zumhagen S, Schulte L, Rosentreter A, Schubert F, Eter N, Mönnig G (2016) Corneal densitometry as a novel technique for monitoring amiodarone therapy. Ophthalmology 123(11):2294–2299
24. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D et al (2015) 2015 gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatol 67:2557–2568
25. Lemp MA (1973) Breakup of the tear film. Int Ophthalmol Clin 13:97–102
26. Lemp MA et al (2007) The definition and classification of dry eye disease: Report of the Definition and Classification Subcommittee of the international Dry Eye WorkShop (2007). Ocul Surf 5(2):75–92. https://doi.org/10.1016/S1542-0124(12)70081-2
27. Halberg GP, Berens C (1961) Standardized Schirmer tear test kit. Am J Ophthalmol 51:840–842
28. Shankar H, Taranath D, Santhirathelagan CT, Pesudovs K (2008) Anterior segment biometry with the Pentacam: comprehensive assessment of repeatability of automated measurements. J Cataract Refract Surg 34:103–113
29. O'Donnell C, Wolffsohn JS (2004) Grading of corneal transparency. Cont Lens Anterior Eye 27:161–170
30. Meek KM, Knupp C (2015) Corneal structure and transparency. Prog Retin Eye Res 49:1–16
31. Özyol P, Ozyol E (2016) Assessment of corneal backward light scattering in diabetic patients. Eye Contact Lens Oct 3. [Epub ahead of print]
32. Anayol MA, Bostancı B, Şekeroğlu MA, Şimşek M, Günaydın S, Yılmazbaş P (2017) Assessment of corneal densitometry in rheumatoid arthritis patients. Turk J Ophthalmol 47(3):125–129
33. Koh S, Maeda N, Ikeda C, Asonuma S, Mitamura H, Oie Y, Soma T, Tsujikawa M, Kawasaki S, Nishida K (2014) Ocular forward light scattering and corneal backward light

scattering in patients with dry eye. Invest Ophthalmol Vis Sci 55:6601–6606
34. Coassin M, Piovanetti O, Stark WJ, Green WR (2006) Urate deposition in the iris and anterior chamber. Ophthalmology 113:462–465
35. Sousa JM, Trevisani VF, Modolo RP, Gabriel LA, Vieira LA, Freitas D (2011) Comparative study of ophthalmological and serological manifestations and the therapeutic response of patients with isolated scleritis and scleritis associated with systemic diseases. Arq Bras Oftalmol 74:405–409
36. Serpell G (1978) Ophthalmic gout. Aust J Opthalmol 6:77–79
37. Muenzler WS, Gerber M (1963) Uveitis associated with hyperuricemia. Am J Ophthalmol 55:289–291
38. Yulek F, Cagil N, Orhan N, Midillioglu IK, Erten S, Simsek S (2009) Gout attack with unusual ocular complications. Rheumatol Int 29:557–559
39. Kwok AK, Yam JC, Ting J, Ng DS, Kwok VO, Chen Y (2015) Simultaneous central retinal vein occlusion and branch retinal artery occlusion in a young patient with gout. J Clin Exp Ophthalmol 6:3
40. Luo C, Chen X, Jin H, Yao K (2017) The association between gout and cataract risk: a meta-analysis. PLoS ONE 12:0180188
41. Burgos F, Capone RC (1996) Ocular and systemic manifestations of gout. Clin Eye Vis Care 8:155–163