



## Evaluation of the tear clearance rate by dacryoscintigraphy in patients with obstructive meibomian gland dysfunction



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### ABSTRACT

**Purpose:** To measure tear clearance values in patients with meibomian gland dysfunction (MGD) with a dynamic nuclear medicine method, namely, dacryoscintigraphy (DSCI).

**Methods:** Twenty-four MGD patients and 24 healthy volunteers were examined. During DSCI one drop of a solution with 100 MBq/mL <sup>99m</sup>Tc sodium pertechnetate was instilled with a micropipette into the lacrimal lake of both eyes. Measurements were performed according to a dynamic data acquisition protocol, which resulted in summed DSCI images. Data were also evaluated separately in special regions of interest (ROI), and consecutive time activity curves were created. Tear clearance (T<sub>1/2</sub>) values were calculated based on the activity curves. In addition, tear osmolarity measurements, tear breakup time (tBUT), and Schirmer I (ST<sub>I</sub>) tests were performed prior to DSCI examination.

**Results:** The T<sub>1/2</sub> values were 29.91 ± 11.61 min in MGD patients and 6.26 ± 1.5 min in healthy controls. Tear osmolarity parameters were 308 ± 9.41 mOsm/L and 288.9 ± 6.4 mOsm/L, tBUT values were 5.54 ± 2.73 s and 11.4 ± 2.7 s, while the ST<sub>I</sub> test values were 6.17 ± 2.78 mm and 13.58 ± 3.8 mm, respectively. The differences were significant (p < 0.01) in all cases.

**Conclusions:** Although the MGD patients' lacrimal drainage systems were patent their tear clearance values were significantly higher than those of healthy volunteers, which may be caused by decreased drainage of tears from the eyes towards the nasal cavity. The understanding of new features regarding the altered physico-chemical characteristics of MGD tears has been augmented by the results of this study.

### 1. Introduction

Meibomian gland dysfunction (MGD), the leading cause of evaporative dry eye disease (DED), is a chronic, diffuse abnormality of the MGs that may lead to an imbalance in the precorneal tear film (PTF) due to a deficiency of the lipid layer [1,2]. The role of MGs is to synthesize and secrete a complex mixture of various polar and nonpolar lipids, termed meibomian oil or meibum [3], which is delivered via orifices located between the posterior margin and the muscle of Riolan. The term "meibomian gland dysfunction" was introduced by Korb and Henriquez in 1980 to describe a condition of meibomian gland obstruction that is responsible for the reduced delivery of meibum to the lid margin [4]. As of 2011, based on the International Workshop on Meibomian Gland Dysfunction, the condition is considered to be a chronic, diffuse abnormality of the MG, commonly characterized by terminal duct obstruction and qualitative or quantitative changes in the

glandular secretion that may result in symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease [5]. The PTF is responsible for perfect vision and stable ocular comfort and function by providing a protective, smooth, and lubricant layer. Tear film instability promotes the vicious circle of DED. One of the appropriate methods for classifying the overall status of DED is the assessment of tear film instability [6].

The lacrimal functional unit (LFU), composed of the main and accessory lacrimal glands, MGs, the ocular surface, lids, and their interconnecting innervations [7], which constitutes an integrated structure with a tear drainage system that is a strategic factor in the pathogenesis of different types of DED. Examination of this integrated structure is pivotal not only with regard to diagnosing DED but also to evaluate ocular surface processes and assessing the effectiveness of therapies in DED patients during follow-up periods [4]. One of the recent methods to assess tear film instability is tear clearance measurements performed

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routinely in some departments, evaluating the LFU globally and dynamically [9,10]. In its evaluation, dacryoscintigraphy (DSCI) is a readily available, objective, non-invasive and low-radiation-dose nuclear medicine method first described by Rossomondo et al. [11]. DSCI is mainly used to demonstrate the patency of the system and to localize the area of possible obstruction, which can be important for pre-surgical planning of lacrimal system intervention and can also be performed postoperatively to evaluate the success of the surgery [12]. During DSCI, dynamic or static images may be obtained. For dynamic imaging, 10 s/frame is used for 1–2 min followed by 1 min/frame for 15–20 min. In contrast to dacryocystography (DCG), this test is a physiological assessment, and more accurate scans/images can be obtained; moreover, this method provides better contralateral comparison. Visualization of the nasolacrimal sac within 1 min after eye drop instillation with drainage of activity from the nasolacrimal duct into the nasal cavity within 5 min is considered a normal finding [13]. The radiation dose to the eye is expected to be as low as 0.14 mSv/eye for an unobstructed eye and up to 4 mSv in the presence of any obstruction [14].

The elimination of tears from the conjunctival sac, also called tear clearance, is determined by several influences, such as the lacrimal pump, evaporation, and capillary attraction forces on the upper portion of the conjunctival sac, and mostly gravity and residual (Krehbiel) flow in its lower part [15]. Tear clearance measurement is appropriate for investigating tear film abnormalities, and tear clearance is reported to be delayed in eyes with ocular surface inflammation [16]. Although several studies have assessed the flow of the PTF by means of the clearance, most of these studies are fluorescein sodium-based; furthermore, there are scarce data about the turnover of PTF in patients with DED [8,17,18], and no such data involving MGD are documented in the literature. A reduced tear clearance rate has a negative impact on ocular surface health [19], and the presence of delayed tear clearance may generate a vicious cycle that exacerbates the existing abnormalities in MGD [20]. Both tear production and the ocular hydrodynamic system, including tear drainage, have an essential role in the pathological processes of DED. Conventional tear drainage system evaluation methods cannot provide information on subclinical obstructions or functional deficiencies [21], and in addition to treatment ineffectiveness, patients' compliance with long-term medical therapies is also poor [22]. Consequently, tear clearance rate measurement is important in managing obstructive MGD.

For this reason, the aim of the study was to measure the tear clearance rate in MGD patients with a dynamic nuclear medicine method, dacryoscintigraphy (DSCI).

## 2. Materials and methods

### 2.1. Patients and controls

MGD was diagnosed based on the corresponding international criteria [23]. For the diagnosis of obstructive MGD, different MG examination techniques were performed, including the ocular symptom score, lid margin abnormality score, and meibo score, according to the proposed diagnostic criteria for obstructive MGD reported by Arita et al. [24]. To evaluate the ocular symptom score, members of the patient and control group were asked about the occurrence of 14 ocular symptoms: ocular fatigue, discharge, foreign body sensation, dryness, uncomfortable sensation, sticky sensation, pain, tearing, itching, redness, heavy sensation, glare, excessive blinking, and history of chalazion or hordeolum. Symptoms were scored from 0 to 14 according to the number of these symptoms that were present. Lid margin abnormality score estimation included investigations of irregular lid margins, vascular engorgement, plugged meibomian gland orifices, as well as anterior or posterior replacement of the mucocutaneous junction. For the meibo score assessment, both the upper and lower eyelids were everted, and the MGs were surveyed. The following grades were

**Table 1**

Frequency of symptoms in MGD patients and controls. MGD: Meibomian gland dysfunction.

Symptoms	MGD	Control	P value
Ocular fatigue	14	3	<b>0.002</b>
Discharge	12	1	<b>0.0007</b>
Foreign body sensation	11	3	<b>0.0243</b>
Dryness	12	2	<b>0.0034</b>
Uncomfortable sensation	11	3	<b>0.0243</b>
Sticky sensation	7	0	<b>0.0094</b>
Pain	12	4	<b>0.0305</b>
Tearing	12	3	<b>0.0114</b>
Itching	12	3	<b>0.0114</b>
Redness	15	4	<b>0.0027</b>
Heavy sensation	14	3	<b>0.002</b>
Glare	10	2	<b>0.0173</b>
Excessive blinking	14	2	<b>0.0005</b>
History of chalazion or hordeolum	7	0	<b>0.0094</b>

**Table 2**

MGD symptom score, lid abnormality score and meibo score of MGD patients and controls (mean  $\pm$  SD). The MGD symptom scores and lid abnormality scores were computed from the frequencies of 14 ocular symptoms and 4 lid margin abnormalities found in the individuals. MGD: meibomian gland dysfunction.

	MGD	Control	P value
<b>MGD symptom score</b>	6.79 $\pm$ 2.13	1.74 $\pm$ 0.81	<b>&lt; 0.0001</b>
<b>Lid abnormality score</b>	2.33 $\pm$ 1.34	0.46 $\pm$ 0.66	<b>&lt; 0.0001</b>
<b>Meibo score</b>	3.42 $\pm$ 1.38	0.75 $\pm$ 1.03	<b>&lt; 0.0001</b>

**Table 3**

Clinical parameters of MGD patients and controls (mean  $\pm$  SD). MGD: meibomian gland dysfunction; tBUT: tear breakup time.

	MGD	Control	P value
<b>Tear clearance (min)</b>	29.91 $\pm$ 11.61	6.26 $\pm$ 1.5	<b>&lt; 0.0001</b>
<b>Schirmer I test (mm/5 min)</b>	6.17 $\pm$ 2.78	13.58 $\pm$ 3.8	<b>&lt; 0.0001</b>
<b>tBUT (s)</b>	5.54 $\pm$ 2.73	11.4 $\pm$ 2.7	<b>&lt; 0.0001</b>
<b>Osmolarity (mOsmol/L)</b>	308 $\pm$ 9.41	288.9 $\pm$ 6.4	<b>&lt; 0.0001</b>

utilized: 0: in the case of no loss of MGs; 1: if the lost area was less than one-third of the total area of MGs; 2: if the lost area was between one-third and two-thirds of the total area of MGs; and 3: if the lost area was over two thirds of the total area of MGs. Obstructive MGD was diagnosed when any 2 of the 3 scores were abnormal.

During the same period an age- and gender-matched population presenting for routine eye examination with minor refractive errors ( $\pm$  1.0 dioptre) and no history of any systemic diseases such as diabetes mellitus, rheumatic diseases, or connective tissue disorders during the same period was also enrolled in the study as a control.

None of the patients and controls had taken any medications that may have influenced tear secretion or drainage at the time of the measurements, and none of them had used any eye drops two weeks prior to the measurements and during the study days. Other exclusion criteria were abnormal eyelid position and closure, punctal occlusion, contact lens wearing, co-existence of ocular allergies, severe blepharitis or meibomitis, history of any eye surgery, treatment with corticosteroids or immunosuppressive therapy and systemic or ocular diseases that might interfere with tear film production or function. Since MGD may even be a complication of cranial nerve VII (CN VII) palsy [25], this condition was also included as an exclusion criterion.

The study protocol was approved by the local ethics committee and was in full compliance with Good Clinical Practices (GCP) guidelines of the European Union, and the Declaration of Helsinki (1996). By signing a written informed consent form, all patients agreed to have their study

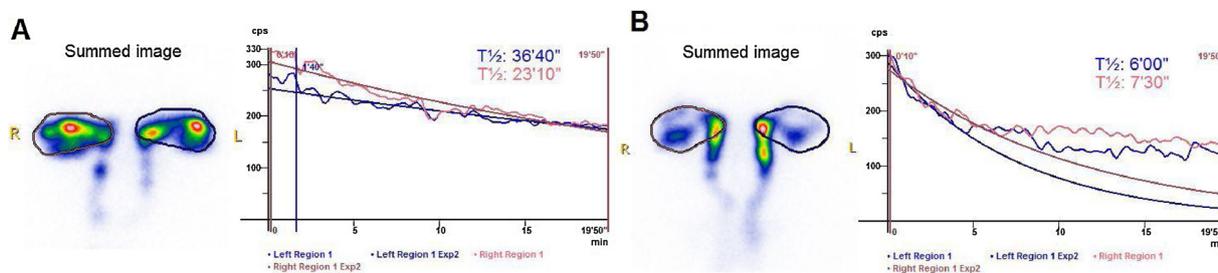


Fig. 1. Special regions of interest (ROI), consecutive time activity curves, and calculated tear clearance ( $T_{1/2}$ ) values. A: Elevated tear clearance value on the right, and normal outflow on the left. B: Normal tear clearance values on both the right and left sides.

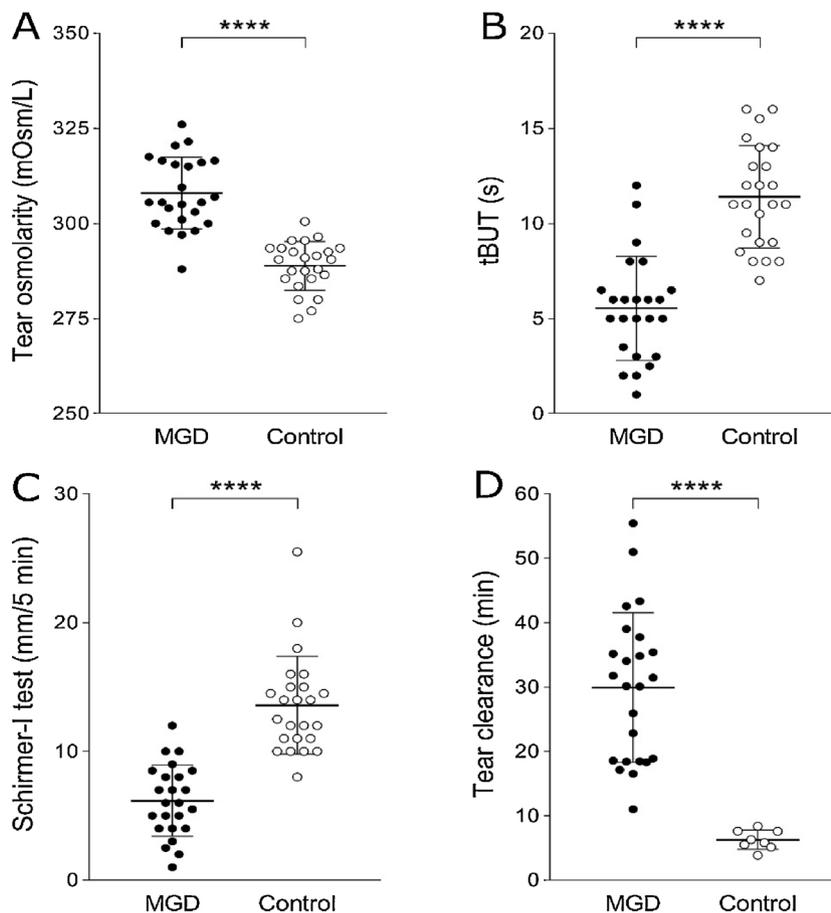


Fig. 2. Osmolarity (A), tBUT (B), Schirmer-I (C), and tear clearance (D) values of MGD patients and controls (mean  $\pm$  SD). MGD: Meibomian gland dysfunction; tBUT: tear breakup time.

results regarding any side effects as well as possible risks and benefits of the study published. Due to the explorative nature of this study, the sample size was not determined in advance.

Before any clinical intervention or score determinations, MGs were examined. To observe MGs, a slit lamp was applied, since biomicroscopy was used to detect notching, telangiectasia, capping and any kind of secretion. To analyse gland secretions a Meibomian Gland Evaluator (TearScience Inc., Morrisville, North Carolina, USA) was applied. Moreover, meiboscopy, a minimally invasive technique during which the lower eyelid is everted over a fibre optic light probe, was also performed.

Prior to DSCI, the following ophthalmological measurements were performed on sequential days, all in one room with constant light, temperature, humidity, and airflow to avoid any ocular surface stress. All clinical examinations were carried out on sequential days. The ambient temperature was  $21 \pm 1.5^\circ\text{C}$ , and the relative humidity was

$60 \pm 3\%$ . Because of the evidence that tear clearance has an intra-day variation [9], measurements were only performed between 9 am and 11 am.

### 2.1.1. MGD symptom score

Fourteen ocular symptoms were assessed in succession: ocular fatigue, discharge, foreign body sensation, dryness, uncomfortable sensation, sticky sensation, pain, tearing, itching, redness, heavy sensation, glare, excessive blinking, and history of chalazion or hordeolum. All of the subjects were scored on a scale of 0–14 according to the frequency of existing symptoms.

### 2.1.2. Lid abnormality score

The 4 lid margin abnormalities that were evaluated and scored from 0 to 4 according to the number of these abnormalities present in each eye were the following: irregular lid margin, vascular engorgement,

**Table 4**  
Correlation of patients' and controls' age with the Schirmer test (ST<sub>I</sub>), tBUT, osmolarity, and tear clearance values. MGD: meibomian gland dysfunction; CI: confidence interval; tBUT: tear breakup time.

	MGD Schirmer test (mm/5 min)	MGD tBUT (s)	MGD Osmolarity (mOsmol/L)	MGD Tear clearance (min)	Control Schirmer test (mm/5 min)	Control tBUT (s)	Control Osmolarity (mOsmol/L)	Control Tear clearance (min)
Pearson's corr. coeff. (r)	0.0382	-0.1451	0.3203	0.1658	-0.02	0.1079	-0.3786	0.5344
95% CI	-0.371 to 0.4349	-0.5182 to 0.2743	-0.09538 to 0.6409	-0.2546 to 0.5335	-0.7146 to 0.6945	-0.6459 to 0.7551	-0.8551 to 0.4447	-0.2731 to 0.9001
R squared	0.0015	0.021	0.1026	0.0275	0.0004	0.0116	0.1433	0.2856
P value	0.8595	0.4987	0.127	0.4387	0.9627	0.7993	0.3551	0.1724

plugged meibomian gland orifices, and anterior or posterior replacement of the mucocutaneous junction.

### 2.1.3. Meibo score

Both the upper and lower eyelids were everted, and the MGs were traced. Partial or complete loss of the MG was scored using the following grades (*i.e.*, meibo score) for each eyelid: 0, no loss of MGs; 1, lost area less than one-third of the total MG area; 2, lost area between one-third and two-thirds of the total MG area; and 3, lost area over two-thirds of the total MG area. Meibo scores for the upper and lower eyelids were summed up to obtain a total score from 0 to 6 for each eye.

### 2.1.4. Osmolarity

Osmolarity was measured in tear samples taken from the lower lateral tear meniscus using the TearLab Osmolarity System (TearLab Corporation, San Diego, CA, USA). The tip of the pen gently touched the inferior tear meniscus. Approximately 50 nL of tear sample was collected from the inferior lateral tear meniscus of the ocular surface to obtain a reading, as per the manufacturer's recommendation [26]. Three measurements in each eye for each participant were made (*i.e.*, both right and left eyes), and the average of the osmolarity values was taken as the mean value.

### 2.1.5. Tear film stability, tBUT measurement

Three measurements in each eye for every participant were made (*i.e.*, right and left eye of each participant), and the average of the tBUT values was taken as the mean value. For tBUT measurement, a strip of fluorescein (Haag-Streit, Koenitz, Switzerland) was moistened with a drop of unpreserved, sterile saline solution (0.9%) from a single-dose ampule, and this strip was then used to touch the inferior fornix for a short time with minimal stimulation. The tear film was observed under cobalt blue-filtered light and wide light. The interval (seconds) between the last complete blink and the first emergence of randomly distributed dry spots was averaged.

### 2.1.6. Tear production: Schirmer I test (ST<sub>I</sub>)

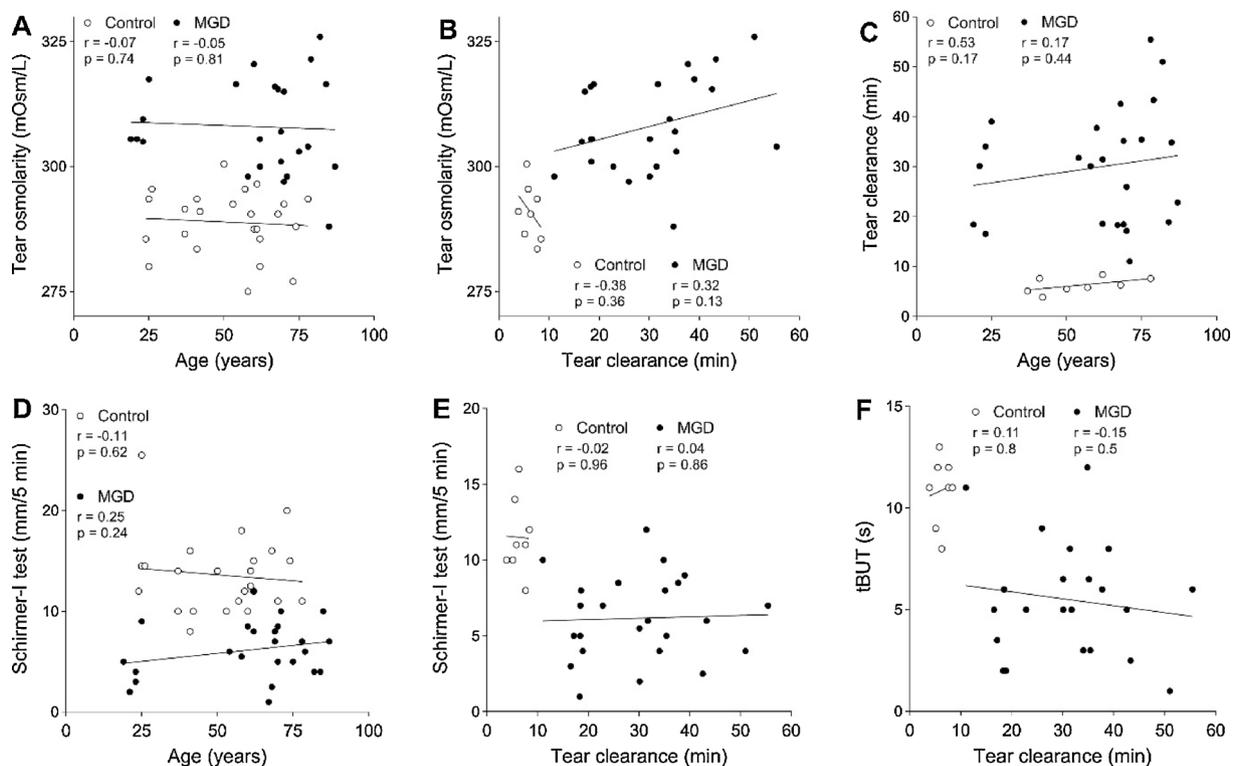
For the estimation of tear production an un-anaesthetized Schirmer test, the Schirmer I test (ST<sub>I</sub>) was performed using standardized strips of filter paper (Alcon Laboratory, Fort Worth, Texas, USA). Without any use of anaesthetic, standard strips were inserted at the lower-lid margin at the junction of the middle and temporal third of both eyes, taking care not to touch the cornea. Patients and healthy volunteers were instructed to gently close their eyelids and not to move their eyes for 5 min; subsequently, the strip was removed and the length of the wet portion was measured (mm/5 min). The average ST<sub>I</sub> values for both sides was taken as the mean value.

All patients' lacrimal drainage systems were checked for patency by syringing prior to DSCI investigation.

### 2.1.7. DSCI

For DSCI, a 100 MBq/mL activity concentration of <sup>99m</sup>Tc sodium pertechnetate as a radioactive tracer with a half-life for gamma emission of 6.0058 h in a saline solution was administered to each eye with a micropipette. Special attention was taken to prevent any contamination of the patient's face with the radioactive drops, which could have interfered with the interpretation of the study. After eye drop administration, the patient was placed in a sitting position in front of a planar camera for imaging. To ensure patient immobilization, the patient's head was secured by a gum strip to obtain optimal imaging. Measurements were performed according to a dynamic data acquisition protocol using a 10 s/frame for 15 min (90 × 10 s), which resulted in summed DSCI images. DSCI was performed using a single head gamma camera (Mediso Nucline TH/22, 128 × 128 matrix) with a low-energy high resolution collimator. After the investigations, both eyes were flushed with saline to help clear any remaining radioactivity.

Data were also evaluated in special regions of interest (ROI)



**Fig. 3.** Correlations between studied values of the MGD patients and controls. A: age (years) and tear osmolarity (mOsmol/L); B: tear clearance (min) and tear osmolarity (mOsmol/L); C: age (years) and tear clearance (min); D: age (years) and Schirmer-I test (mm/5 min); E: tear clearance (min) and Schirmer-I test (mm/5 min), F: tear clearance (min) and tBUT (s); MGD: Meibomian gland dysfunction; tBUT: tear breakup time.

separately, and consecutive time activity curves were created. Tear clearance ( $T_{1/2}$ ) values were calculated based on the activity curves.

## 2.2. Statistical analyses

Data of patients and control persons were compared by means of an unpaired *t*-test with or without Welch's correction (according to the presence or absence of a significant difference between variances of data sets, respectively) after verifying the Gaussian distribution of data with D'Agostino & Pearson as well as Shapiro-Wilk normality tests. The frequency of symptoms and signs in the two groups (patients vs controls) were compared with Fisher's exact-test. Correlation coefficients between variables (*r*) were calculated with the Spearman and Pearson methods. For the sake of an informative appearance in the figures, linear regression was also performed if there was a significant correlation between the investigated data sets. Data are presented as the mean ( $\pm$  SD). P values less than 0.05 were considered statistically significant. For the statistical analysis, GraphPad Prism 7.04 statistical software was used (GraphPad Software Inc., San Diego, CA, USA).

## 3. Results

### 3.1. Characteristics of the MGD patients and controls

Twenty-four MGD patients (18 females and 6 males) aged 60.88 (SD  $\pm$  21.98) years were recruited into this prospective, cross-sectional, observational study. Twenty-four gender- and age-matched volunteers (16 females and 8 males) aged 51.83  $\pm$  16.72 years as healthy controls, who had no history of any autoimmune or ocular surface disorder, or ocular surgery or trauma, or contact lens use were also enrolled. All patients and controls were of Caucasian origin, and their lacrimal drainage systems were patent. There was no significant difference between the ages of patients and controls.

### 3.2. Results of ophthalmologic tests

Frequency of symptoms in MGD patients and control persons are represented in Table 1. There were significant differences in all investigated symptoms.

The average MGD symptom scores were significantly different between the two groups (6.79  $\pm$  2.13 for MGD group and 1.74  $\pm$  0.81 for healthy controls), and so was the average lid abnormality score of 2.33  $\pm$  1.34, and 0.46  $\pm$  0.66, respectively. The average meibo score was 3.42  $\pm$  1.38 in the patients, and 0.75  $\pm$  1.03 in the healthy volunteers group, and the differences between groups were significant for all measurements (Table 2).

To determine obstructive MGD, a cut-off value for each MG examination score was determined as suggested by Arita et al. [24]. An MGD ocular symptom score of  $\geq 3$ , a lid abnormality score of  $\geq 2$ , and a meibo score of  $\geq 3$  were considered abnormal.

Osmolarity was found to be 308  $\pm$  9.41 mOsm/L in MGD patients and 288.9  $\pm$  6.4 mOsm/L in the control group. The tBUT values were 5.54  $\pm$  2.73 s and 11.4  $\pm$  2.7 s, respectively. The mean  $ST_1$  value for MGD patients was 6.17  $\pm$  2.78 mm/5 min, and 13.58  $\pm$  3.8 mm/5 min for healthy controls. The difference between groups was significant ( $p < 0.0001$ ) for all measured parameters (Table 3).

### 3.3. Results of DSCI

The tear clearance was 29.91  $\pm$  11.61 min in MGD patients and 6.26  $\pm$  1.5 min in healthy volunteers. The difference was significant ( $p < 0.0001$ ) (Table 2 and Figs. 1 and 2).

The results of the correlation analysis are shown in Table 4 and Fig. 3.

In general, the association between the tear clearance measurements and measured ophthalmologic variables was weak. However, a tendency towards a negative correlation was found between the tear clearance values and tBUT ( $r = -0.1451$ ), and a slight positive

correlation was revealed between the tear clearance values and the ST<sub>1</sub> and tear osmolarity test values ( $r = 0.0382$  and  $r = 0.3203$ ).

#### 4. Discussion

As far as one can tell from the literature, this is the first study to investigate the diagnostic efficacy of tear clearance measurement in patients with MGD as well as to assess and compare the clinical parameters of MGD patients and normal control subjects. During the patient selection, special attention was paid to prudential diagnosis of MGD, and in the course of this assessment, tear osmolarity, tBUT, fluorescein staining, evaluation of eyelid abnormalities (irregular eyelid margin, vascular engorgement, and plugged meibomian gland orifices), the Marx line, and meibomian expression were measured and recorded according to the International Workshop on Meibomian Gland Dysfunction guidelines [27].

In this study, there was a negative correlation as expected between tear production and age in healthy controls, but in MGD patients, a positive correlation between these factors was detected, which may be due to a certain compensation, as the evaporated tears with increased osmolarity flow slower towards the nasal cavity. Tear clearance values were significantly higher in MGD patients than in healthy volunteers, which may be the result of decreased drainage of the abnormal tears from the eyes towards the nasal cavity. In controls, there was a negative correlation between age and osmolarity and ST<sub>1</sub> values, and in line with this phenomenon, notable positive correlations with tBUT and tear clearance quantities could be detected. Nevertheless, beside a negative correlation between age and tBUT values, positive correlations with osmolarity, ST<sub>1</sub>, and tear clearance parameters were found in MGD patients.

Based on these results attention was drawn to the importance of hyperosmolarity, since this is thought to activate inflammatory pathways, and as a consequence epithelial damage, tear film instability, and ocular discomfort develop [28]. There was no important difference in correlation between age or tear clearance and ST<sub>1</sub> values either in controls or in MGD patients. Despite the fact that ST<sub>1</sub> values were significantly lower in MGD patients than in controls, there was a small-scale increase by age, which may also be due to a compensatory mechanism. Additionally, an association was detected between elevated tear clearance and increased tBUT values in controls, but this association was changed by MGD.

Despite the fact that DSCI has been used to evaluate tear dynamics in different eye disorders for a long time, there are only scant publications available concerning scintigraphic research on DED patients [29–31]. One of the early scintigraphic studies in conjunction with DED was performed by Greaves and co-workers [32]. Their survey compared the precorneal residence of an artificial tear preparation radiolabelled with Tc-99m diethylene-triamine-pentaacetate (DTPA) in patients with keratoconjunctivitis sicca and normal subjects using lacrimal scintigraphy. Precorneal clearance of the artificial tear solution was characterized by bi-exponential kinetics in all cases, and no significant difference was found in tear clearance rates between the two study groups. Twenty-one patients with DED and 12 healthy subjects by lacrimal scintigraphy were investigated by Gencoglu and co-workers and the T<sub>1/2</sub> value was determined to be  $4.16 \pm 1.22$  min for healthy subjects and  $20.59 \pm 1.97$  min for DED patients, but no differentiation among DED subgroups were made [8]. Tear production, distribution and drainage in 23 essential blepharospasm patients suffering from DED were compared by Park et al. and the changes before and 2 weeks after the administration of botulinum toxin A injection by using an artificial tear solution radiolabelled with <sup>99m</sup>Tc were analysed. Delayed tear clearance values in patients were revealed by DSCI. In the interpalpebral fissure, the <sup>99m</sup>Tc T<sub>1/2</sub> clearance time was increased significantly, explained by the absence of contractive forces around the walls of the lacrimal drainage system [33]. In a survey by Erhamamci et al., DSCI was used to evaluate the lacrimal gland function in patients

with early- and advanced-stage primary Sjögren's syndrome (SS). In this study the tear clearance values of patients in advanced-stage disease were significantly delayed compared to those of patients in the early stage of disease and healthy controls. A significant inverse correlation was found in all patients between tear clearance values and both the Schirmer test and tBUT values, whereas there was a positive correlation between both the rose bengal ocular surface staining and Ocular Surface Disease Index (OSDI) scores and tear clearance values [34].

Based on the results of the present study in addition to the existing tear film abnormalities, the tear clearance is also dramatically delayed in MGD, as a consequence of the otherwise inflamed tears, which evaporate faster from the ocular surface and flow slower throughout the nasolacrimal drainage system. Since the main constitutional difference between normal tears and MGD tears is the reduction in the lipid layer in the latter, its significance might be underlined by the examinations, presented here, since the physico-chemical properties of the tear film in MGD is altered because of the lack of this layer. These results augment the understanding of new features regarding the varied physico-chemical characteristics in MGD tears and suggest the significance of lipid layer substitution in MGD for preventing decreased quality of life and avoiding possible serious complications.

The main limitations of the study could be the relatively small sample size from one institute, and the lack of recording more detailed and specific data about the evolution and course of the disease or the physico-chemical parameters of tears. As a consequence, the number of enrolled patients and controls from diverse departments is to be increased, and their data are to be incorporated. Also more specific patient data on factors that may exert an influence on tear clearance processes shall be obtained and analysed.

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#### Conflict of interest

None of the authors has any potential financial interest related to this manuscript.

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#### Contributorship

All authors contributed to performing the study, and they all wrote, edited and reviewed drafts and approved the final version of the manuscript.

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