SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Investigation of the obstructive and inflammatory disease of the lacrimal funcional unit and lacrimal drainage system using nuclear medicine methods

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1. Introduction

The adequate volume and the appropriate, well-balanced composition of tears are of paramount importance for the maintenance of ocular surface health. Precorneal tear film has several essential functions including protecting the cornea from drying, contributing to the refractive power of the eye, or defending the structures inside the eye against infections. These roles are regulated by the lacrimal functional unit (LFU) that consists of the tear production system involving the main and accessory lacrimal glands, the interconnecting innervations, fluid flow, tear evaporation, and last but not least tear outflow through the lacrimal drainage system (LDS). LFU is assumed to be a strategic factor is the development of different obstruction-related eye disorders.

Given that epiphora, either evoked on the basis of tear overproduction or diverse anatomical malformations, including stenosis or obstruction of the LDS is considered to be an escalating health problem, the need for the introduction of precise and non-invasive imaging modalities is warranted for appropriate treatment planning. Differentiation between epiphora-related anatomical (obstruction in the LDS) or functional (stenosis) inadequate tear drainage is indispensable for the determination of appropriate therapeutic approach. Another obstruction-associated ophthalmic symptom is the evaporative dry eye disease (DED) that is most commonly caused by the Meibomian gland dysfunction (MGD). This condition is supposed to be a chronic, diffuse abnormality of the MG, characterized by terminal duct obstruction and qualitative or quantitative changes in the glandular secretion. The role of MGs is to synthesize and secrete a complex mixture of various lipids, named meibomian oil or meibum.

As for the evaluation of the LFU, besides the widely available clinical tests such as the measurement of tear film instability, tear break up time (tBUT), Schirmer, Jones dye tests, syringing, nasolacrimal probing, and the conventional radiological imaging methods (X-ray, dacrycystography (DCG), CT, or magnetic resonance imaging), nuclear medicine may not fall short here as we have much to offer. Dacryoscintigraphy (DSCI) is a readily available, objective, non-invasive and low-radiation-dose nuclear medicine method that provides an objective and precise assessment of functional and partial obstruction, more detailed information regarding its localization and better contralateral comparison as well. Further, time activity curves generated during dynamic DSCI make the measurement of tear clearance rate possible. However, DSCI excels in the assessment of LDS patency during diagnostic work-up, and in the evaluation of tear outflow after lacrimal surgery, DSCI allows solely planar, two-dimensional images, consequently its sensitivity and specificity need to be improved. Application of DSCI together with SPECT/CT and CT-DCG resolves the anatomical details of the bony lacrimal duct system leading to more sensitive outcomes. 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.

Attributed to the fact that conventional tear drainage system evaluation methods cannot supply satisfactory information on subclinical obstructions or functional deficiencies, less-invasive, objective imaging modalities that are capable of detecting subtle functional impairments are gaining traction in the management of obstructive ophthalmic alterations.

2. Aims of the study

1. We also evaluated the clinical utility of simultaneous DSCI and single-photon emission computed tomography/computed tomography (SPECT/CT) combined with computed tomographic dacrycystography (CT-DCG) in the evaluation of lacrimal drainage system (LDS).

2. We aimed at measuring tear clearance rate in MGD patients applying a dynamic nuclear medicine method, dacryoscintigraphy (DSCI).

3. Materials and Methods

3.1. Study participants

For the first part of this prospective, cross-sectional, observational study twenty-four MGD patients (18 females and 6 males) aged 60.88 (SD±21.98) years, while for the second section of the study fifty-seven participants (45 women and 12 men) aged 54.25 (±18.26) years with epiphora as a major complaint were selected. Age- and gender-matched healthy control subjects (24 vs. 32 subjects in the first and second part of the study, respectively) were was also recruited for both study parts selected from patients presenting for routine eye examination with minor refractive errors (±1.0 diopter), and no history of any tearing problem.

Neither prior application of medications influencing tear secretion or drainage, nor the use of eye drops was allowed two weeks before the measurements and on the days of the examinations. Exclusion criteria included the following as well: abnormal eyelid position and closure, punctal occlusion, contact lens wearing, co-existence of ocular allergies, presence of ocular infection, severe blepharitis or meibomitis, inflammation of the sclera, episcleral layer and uvea, trauma of the eye, corneal haze, peripheral or central corneal melting, history of any eye surgery, treatment with corticosteroids or immunosuppressive therapy, systemic or ocular diseases, and cranial nerve VII (CN VII) palsy. The study protocols were approved by the local ethics committee (Regional and Institutional Research Ethical Committee [DE RKEB/IKEB 4779-2017]) together with the National Institute of Pharmacy and Nutrition [OGYEI/37752/2017] and was in full compliance with Good Clinical Practices (GCP) guidelines of the European Union, and the Declaration of Helsinki (1996). Informed consent was collected from all patients involved.

For the diagnosis of obstructive MGD, the below detailed MG examination techniques were performed in the first section of the study: 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. In addition, osmolarity, tear film stability, tBUT measurement and tear production were also assessed before DSCI (detailed below). During the second part of the study, DSCI was followed by SPECT/CT and CT-DCG examinations. The aforehead mentioned ophthalmologic measurements were performed on sequential days, all in one room with constant light, temperature, humidity, and airflow to avoid any ocular surface stress. The ambient temperature was 21±1.5 °C, and the relative humidity was 60±3%. Because of the evidence that tear clearance has an intra-day variation, measurements were only performed between 9 am and 11 am.

3.1.1. MGD symptom score/Ocular symptom score

In order to evaluate the ocular symptom score, both the participants of the patient and control groups were asked about the occurrence of the following fourteen 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. According to the number of symptoms that were present, patients were scored from 0 to 14.

3.1.2. Lid abnormality score

The following lid margin abnormalities were also assessed and scored from 0 to 4: irregular lid margins, vascular engorgement, plugged meibomian gland orifices, as well as anterior or posterior replacement of the mucocutaneous junction.

3.1.3. Meibo score

As for the meibo score assessment, both the upper and lower eyelids were everted, and the MGs were surveyed. The following grades were utilized: 0: in case of no loss of MGs; 1: the lost area was less than one-third of the total area of MGs; 2: the lost area was between one-third and two-thirds of the total area of MGs; and 3: the lost area was over two thirds of the total area of MGs. Meibo scores for the upper and lower eyelids were summed up to obtain a total score from 0 to 6 for each eye.

3.1.4. 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). 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. 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.

3.1.5. 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.

3.1.6. Tear production: Schirmer I Test (ST_I)

For the estimation of tear production an un-anaesthetized Schirmer test, the Schirmer I test (ST_I) 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/5min). The average ST_I 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.

3.1.7. DSCI

First a massage was applied on both lacrimal sacs in order to remove any debris out of the upper part of tear drainage system. For dynamic investigation of the regions of the eye and LDS, one drop (20 µL) of 100 MBq/mL concentration, effectively 2 MBq activity of ^{99m}Tc sodium pertechnetate as a radioactive tracer with a half-life for gamma emission of 6.0058 hours 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, patients were 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 (90x10 sec), which resulted in summed DSCI images. DSCI was performed using a single head gamma camera (Mediso Nucline TH/22, 128x128 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) separately, and consecutive time activity curves were created. Tear clearance (T½) values based on the activity curves were generated for both study parts, while for the second part of the study T_{max} values were measured as well. All DSCI results were evaluated by two experienced observers, who were familiar with DSCI and unaware of other clinical data. The final evaluation was made by consensus.

3.1.8. SPECT/CT and CT-DCG examinations in patients

During the second section of the study after DSCI, SPECT/CT examination was carried out in supine position applying the following protocol: 32 frames per detector head, each with a duration of 20 s, 360°, and acquisition matrix size of 128 x 128. 2D OSEM (Ordered Subset Expectation Maximization) reconstruction method was used. CT acquisition was conducted right after the SPECT acquisition with these parameters: image matrix size: 128 x 128, tube voltage 120 kV and 50 mAs (AnyScan FLEX SC, Budapest, Hungary). Following the administration of 2% xylocaine eye drops to locally anaesthetize the conjunctival sac, 0.5–1 mL of contrast material (ioversol, Optiray 350, Guerbet, France) was syringed into the affected LDS by a trained ophthalmologist. Contrast CT scans were parallelly acquired applying the previous protocol. Data were

obtained as axial images and then reconstructed into 2D and 3D coronal and parasagittal planes along the major axis of the LDS. Due to ethical reasons, healthy volunteers did not undergo SPECT/CT and DCG modalities.

3.1.9. Statistical analyses

Data of patients and control subjects 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, Shapiro-Wilk and Kolmogorov-Smirnov normality tests as well. The frequency of symptoms and signs in the two groups (patients vs. controls) were compared with Fisher's exact test. In the second section, both eyes of the patients and one randomly selected eye from each control were selected for the statistical analyses. Tracer disappearance times were expressed in seconds as mean values and standard deviations (±SD), whereas categorical variables were expressed as frequencies and their percentages. Correlation coefficients between variables (r) were calculated with the Spearman and Pearson methods. A nonparametric (Wilcoxon) test was used to compare groups. Kappa test was used to compare interrater reliability between different methods. Linear regression was also performed if there was a significant correlation between the investigated data sets. P values less than 0.05 were considered statistically significant. For the statistical analysis IBM SPSS 24 statistical software (IBM Corp., Armonk, New York, USA) and GraphPad Prism 7.04 statistical software were applied (GraphPad Software Inc., San Diego, CA, USA).

4. Results

There was no significant difference between demographic data of patients and controls.

4.1. Results of ophthalmologic tests

Significant differences were found between the MGD group and the control group regarding the investigated symptoms. The average MGD symptom scores were significantly different between the two groups (6.79±2.13 for MGD group and 1.74±0.81 for healthy controls), and so was the average lid abnormality score of 2.33±1.34, and 0.46±0.66, respectively. The average meibo score was 3.42±1.38 in the patients, and 0.75±1.03 in the control group. Osmolarity was found to be 308±9.41 mOsm/L in MGD patients and 288.9±6.4 mOsm/l in the control group. The tBUT values were 5.54±2.73 sec and 11.4±2.7 sec, respectively. The mean ST_I value for MGD patients was 6.17±2.78 mm/5 min, and 13.58±3.8 mm/5 min for healthy controls. The differences between groups were significant ($p<0.0001$) for all measured parameters.

Negative correlation was found between tear production and age in healthy controls, while in MGD patients, a positive correlation between these factors was detected. In addition, there was a negative correlation between age and osmolarity and ST_I values in the control group. Further, in the MGD group a negative correlation was depicted between age and tBUT values.

4.1.2. DSCI outcomes, Part one

The tear clearance was 29.91±11.61 min in MGD patients and 6.26±1.5 min in healthy volunteers. In general, correlation analysis revealed weak association between tear clearance measurements and measured ophthalmologic variables. However, a tendency towards a negative correlation was found between the tear clearance values and tBUT (r=-0.1451). Further, slight positive correlation was revealed between the tear clearance values and the ST_I and tear osmolarity test values (r=0.0382 and r=0.3203). Additionally, positive correlations with osmolarity, ST_I, and tear clearance parameters were found in MGD patients.

4.1.3. DSCI, SPECT/CT and CT-DCG findings, Part two

Concerning DSCI outcomes in the second part of the examinations the difference calculated between mean $T_{1/2}$ values in the eye region both for tearing, fellow and control eyes and mean T_{max} values for tearing and fellow eyes was significant. Interestingly, in the nasolacrimal duct region mean T_{max} value was the most decreased for the tearing eye with a higher value for the fellow eye, and the highest for the control eye. The difference was statistically also significant.

The association between T_{max} values of the tearing and the fellow eyes was weak. Correlation coefficient was significant between T_{max} values of the LDS regions for the tearing and the fellow eye. Concerning sensitivity, SPECT/CT proved to be the most sensitive method (87.72%), followed by CT-DCG (78.95%), and DSCI (68.42%). While combining the techniques the sensitivity values were as follows: DSCI with SPECT/CT: 96.49%, DSG with CT-DCG: 92.98%, and SPECT/CT with CT-DCG: 94.73%, respectively. Specificity of DSCI was found to be higher when compared to SPECT/CT technique. The kappa coefficient used to test interrater reliability was 0.315 between CT-DCG and SPECT/CT with the difference being statistically significant, while it was -0.020 between DSCI and SPECT/CT, and 0.019 between DSCI and CT-DCG with no statistical significance.

5. Main findings and Conclusion

1. Due to the fact that currently there are only scant objective modalities for the diagnostic assessment of LDS abnormalities, subjects with epiphora as a major complaint are most commonly diagnosed via clinical data, external ophthalmic examination and simple tear measurement tests.

2. DSG is a widely employed effective modality in diagnosing abnormalities of the LDS which can provide relatively objective data on LDS impairments. However, DSG allows solely planar, two-dimensional images, consequently its sensitivity and specificity need to be improved. Surgical indication can only be determined on the basis of images supporting the diagnosis. In addition, detailed imaging makes the precise localization of the obstructions possible. Consequently, simultaneous application of DSG, SPECT/CT combined with CT-DCG can provide precise localization of the obstruction leading to more sensitive final results.

3. Since the already existing surveys dealing with DSG only assess the affected eye of the patients with epiphora, the major advantage of our study is the evaluation of control eyes with this technique. Another point to consider is the wide range of imaging modalities compared in our study. Major limitations, however could be the relatively small sample size and – due to ethical reasons- the lack of SPECT/CT and DCG examinations of the control eyes as well.

4. 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.

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List of publications related to the dissertation

1. **Barna, S.**, Garai, I., Kukuts, K., Gesztelyi, R., Tóth, L., Kemény-Beke, Á.: Clinical utility of SPECT/CT and CT-dacryocystography-enhanced dacryoscintigraphy in the imaging of lacrimal drainage system obstruction.
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