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

CHANGES OF THE ANTERIOR SEGMENT OF THE EYE IN PATIENTS WITH SYSTEMIC SCLEROSIS

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ABBREVIATIONS

ACA – anterior chamber angle
ACD – anterior chamber depth
ACV – anterior chamber volume
ANF – antinuclear factor
anti-Scl70 –anti-topoisomerase antibody
CCT – central corneal thickness
CRP – C-reactive protein
CV – corneal volume
dcSSc – diffuse cutaneous systemic sclerosis
DEWS – Dry Eye Workshop
IOL – intraocular lenses
IOP – intraocular pressure
K1 – flattest meridian
K2 – steepest meridian
KCS – keratoconjunctivitis sicca
K_m – mean keratometry value/reading
K_{max} – greatest refractive power
lSSc – limited systemic sclerosis
lcSSc – linited cutaneous systemic sclerosis
LG – lissamin green
MGD – Meibom-mirigy diszfunkció--- Meibomian gland dysfunction
NFC – nailfold capillaroscopy
OSDI – ocular surface disease index
SSc – systemic sclerosis
ST_I – Schirmer-I test
TBUT – tear break-up time
TFOS – Tear Film & Ocular Surface Society

1. INTRODUCTION, LITERATURE REVIEW

1.1. Systemic (SSc) sclorosis

Systemic sclerosis or scleroderma (SSc) is a systemic autoimmune disease. The etiology of the disease is not fully known today, thus it is regarded as a multifactorial disease. SSc is a generalized connective tissue disease characterized by connective tissue proliferation and fibrosis. Its pathogenesis can be defined by the simultaneous presence of three factors: vasculopathy, an altered function of the immune system, and generalized fibrosis.

In addition to skin sysmptoms, SSc can be accompanied by life-threatening complications as peripheral and visceral veins and conseqently internal organs the lungs, heart, the gastrointestinal tract, and the kidneys – are greatly affected. The two main subtypes of the disease are as follows: the more common limited cutaneous SSc (lcSSc) and the rarer but more severe diffuse cutaneous form, (dcSSc). SSc is a rare disease with a prevalence and incidence ranging between rather wide margins: from 4 to 126/1 000 000 and 1.2m to 19.1/1 000000/year, respectively. Prevalence of its occurrence shows geographical distribution: it is lower in Northern-Europe and Japan while both prevalence and incidence are higher in Southern Europe, North-America, and Australia. Female dominance is remarkable, with a female:male ratio of 4,8:1-8:1. The first symptoms usually appear in people's late forties, with the age group between 45 and 65 typically affected.

1.2. Ophthalmological complications of SSc

There are only scarce literature data available concerning the ophthalmological implications of SSc, only a handful of case reports or comprehensive theses can be found in the literature with a small number of patients – despite the fact that the ophthalmological changes involved in the disease are well known in clinical practice.

About one-third of patients with SSc develop ocular complaints, since the face, and hence the periorbital region of the eye, is often affected in both subtypes, and these symptoms can appear at any stage of the disease. The inflammatory processes typical of SSc and fibrosis with the involvement of the eyes and the surrounding tissues cause clinically diverse symptoms such as periorbital oedema, scarring of the eyelids, as well as decreased mobility, ectropium, blepharophimosis, madarosis and blepharitis. Telangiectasias develop on the skin of the eyelids and the conjunctiva with more frequent pinguecula, orbital fat atrophy and resultant enophthalmos.

The most common ophthalmological change is keratoconjunctivitis sicca (KCS), whose prevalence can range between wide margins: 37 and 79%. Development of KCS in patients with SSc is caused by fibrosis typical of the disease since scarring affects the main lacrimal glands and the accessory lacrimal glands in the regions of the conjunctiva.

2. OBJECTIVES

During our research we focussed on two main areas: analysis of KCS symptoms, usually mentioned first among the ophthalmological manifestations of patients with SSc and the detailed examination of the anterior segment of the eyeball.

With the above aspects in mind, we set the following goals.

1. We intended to conduct the detailed clinical tests used during the investigation of KCS among patients with SSc and a control population, and compare the results obtained.

2. It was also our aim to assess subjective complaints related to KCS in patients with SSc and the control group, respectively.

3. We planned to carry out an analysis of objective clinical signs and subjective symptoms that occur during examination of dry eye syndrome in both populations.
4. We intended to determine the parameteres of the anterior segment of the eyeball in patients with SSc using Pentacam (measure) and compare the results with those in the control group.

5. We also set the goal of analysing the relationships between anterior segment parameters in patients with SSc and other clnical vairables typical of SSc (e.g. autoantibodies).

3. PATIENTS AND METHODS

3.1. Patients and healthy controls

We involved 19 patients (17 females and 2 males) with SSc and 19 healthy controls in our first examination while 32 patients with SSc (27 females and 5 males) and 39 controls were recruited in the second. Patients were enrolled from among patients with SSc admitted to and treated at the the outpatient clinic of the Department of Rheumatology, University of Debrecen. Diagnosis of SSc was based on the current international system of criteria. Secondary Sjögren syndrome could be excluded in every examined patient and did not develop during the long follow-up period after the examination, either. The healthy control group was composed of age- and gender matched volunteers with no history of any autoimmune or ocular disorder.

No eye drops were used in the two-week period before the examination either by the patients or by the control group. Eyelid disorder, wearing contact lenses and treatment with corticosteroids were exclusion criteria for participation in the study. The patients did not receive immuno-oppresive treatment during the examinations.

3.2. First study

Examination of the objective clinical symptoms and subjective complaints of dry eye syndrome in patients with SSc.

3.2.1. Ocular Surface Disease Index – OSDI

Analysis of the subjective symptoms suggestive of dry eye disease in patients with SSc and the control group was conducted using the internationally most well-known and most widely used OSDI questionnaire (Allergan, Inc. Irvine, CA, USA). The 12 points of the questionnaire ask about the patient's ocular complaints during the week preceding the examination. The test enables the analysis of the functional effects (complaints occurring during reading, working with a computer or watching television) of dry eye complaints as well as the potential role of environmental factors (windy weather, room with dry air, air conditioner). Frequency of the complaints had to be provided on a 5-point Likert scale.

3.2.3. Measuring tear breakup time, tBUT

To measure tBUT, we instilled 0.9% sterile saline solution onto a fluorescein strip and, with the least possible stimulation, we gently touched the lower conjunctival fornix of the examined eye with it. Then we examined the tear film using a slit lamp with a cobalt blue filter. After asking the patient to blink, we measured the time in seconds that elapsed until the first appearance of dark or dye-free spots signalling the tear of precorneal tear film after a blink. During measuring tear film stability we recorded the avreage of 3 tBUT measurements on both eyes of every examined individual.

3.2.4. Measuring tear production (Schirmer I test)

To measure tear production we used Schirmer-I test without the use of an anesthetic agent: we placed the bended end of a standard size strip of filter paper at the border of the middle and temporal thirds of the lower eye lid in the examined individuals, then, we asked them to carefully close their eyes, not moving their eyes. We determined the length in mm of the wet filter paper after 5 minutes of placement (mm/5 minutes). We used the average of two readings measured on the two eyes.

3.2.5. Lissamine-green (LG) dye

LG is a water-souble, vital dye, which shows damage to the conjunctiva and the cornea. In our examination we used a pre-impregnated test strip instilled with a drop of sterile physiological saline solution and lightly touched the lower palpebral conjunctiva with it. Then we asked the patient to blink a few times, then, gradually increasing the light of the slit lamp, following Foulk's recommendation, we examined the LG staining that had thus become visible. We carried out the evaluation based on Bron's scale (Oxford Grading Charts):16x magnification, using a Haag-Streit slit lamp.

The used scale:

grade 0: 0-9 points of staining on bulbar conjunctiva (nasal and temporal sides separately
grade 1: 10-32 points of staining
grade 2: 33-100 points of staining
grade 3: more than 100 points of staining

3.2.6. Measuring tear film osmolarity

Determination of tear film osmolarity is conducted using an osmometer. The procedure is based on determination of the salt and protein content of tears, which allow us to draw conclusions concerning their respective concentrations. Using the tool enables us to determine the electrical conductivity of the sample and transform it into numerical values. During our examination we used the osmometer of TearLab Osmolarity System to determine tear film. The device showed osmolarity of the sample on the display in mOsmol/L in less than 1 minute.

3.2.7. Determining tear film secretion speed

Using a capillary tube, we collected unstimulated tear film from the temporal part of the tear meniscus of the lower cul-de-sac. We were especially careful not to touch the eyelids or the ocular surface with the capillary tube that we used to take samples for minimal irritation. Tear sampling occurred between 11 a.m. and 16. p.m. in every case.

Time of tear sampling was measured with a stopwatch. The time of sampling lasted until the capillary tube was filled with tears or tear movement ceased. Tear volume was determined based on the height of the liquid column in the capillary tube and the diameter of the tube. Tear secretion speed was calculated based on the ratio of tear volume and tear sampling time.

3.3. Second study

Examination of the parameteres of the anterior segment of the eye in SSc

3.3.1. Evaluation of anterior segment parameteres in patients with SSc using Pentacam

Measurements were made of the anterior segment of the eye with undilated pupils using Pentacam, taking the average of three consecutive measurements into consideration in both eyes. Using the software of the high-definition Scheimpflug-camera. We examined the following parameters:

- keratometry value in the flattest axis (K1)
- keratometry value in the steepest axis (K2)
- mean keratometry value
- pachymetry data (central corneal thickness (CCT), peak, thinnest and és maximal refractive power (K_{max})
- corneal volume - CV
- anterior chamber volume - ACV
- anterior chamber depth - ACD
- anterior chamber axis - ACA
- pupil diameter

3.3.2. Nailfold capillaroscopy (NFC)

Nailfold capillaroscopy (NFC) is a simple, non-invasive, differential diagnostic method used for dignosing autoimmune diseases. A capillary microscope is a light microscope in which the capillary network of the skin can be seen using a halogen

cold light source. On other skin surfaces capillary loops run perpendicular to the skin surface; but at the lateral margins of the nail-bed they run parallel to the skin surface, hence changes can be easily studied in the latter location.

On examination, our results fell into the following categories:

normal capillary microscopy image

early phase – a few enlarged or giant capillaries, minimum amount of capillary bleeding, relatively well preserved capillary distribution, no pronounced capillary loss

active phase – frequent giant capillaries, a great deal of capillary bleeding, moderate capillary loss, mild desorganisation of capillaries with absent or mild capillary branching

late phase – irregular enlargement of capillaries, giant capillaries and bleeding, severe capillary loss, extensive avascular areas, neovascularisation

In SSc patients nailfold capillaroscopy helps not only in early diagnosis but also in assessing the severity of microvascular differences. It enables us to make prognostic inferences as to the severity of pulmonary fibrosis, which can alert the physician to a life-threatening complication.

3.3.3. Laboratory tests

During the laboratory tests the patients' C-reactive protein (CRP) levels and autoantibody profiles were determined from serum, concentrating primarily on anti-centromere, antinuclear factor [ANF], and anti-topoisomerase I [Scl-70] levels.

3.4. Statistical analyses

For the satitistal analysis of our data obtained as a result of our first examination GraphPad Prism 7.02 (GraphPad Software Inc. San Diego, CA, USA) statistical software was used. Gaussian distribution of data was tested using D'Agostine and Pearson as well as Shapiro-Wilk normality tests. Then, to compare values, we conducted an independent samples t-test with or without Welch's correlation, depending on whether there were significant differences between the data. Data are shown as means (±SD). P values less than 0.05 were regaded as statistically significant.

In our second examination patient and control data were compared using independent samples t-test according to Levene's test for equality of variances, after veryfing Gauss data using Kolmogorov-Smirnov normality tests. Data of patients and controls of the second study were compared by means of an unpaired t-test according to Levene's test for equality of variances after verifying the Gaussian distribution of data with Kolmogorov-Smirnov normality tests. In the case of non-parametric distribution, Mann-Whitney U test was used. Using ANOVA, the means of several groups were compared. To compare categorical data Chi2 test and Fisher's exact test were used. Correlation coefficients between variables were calculated using the Pearson or Spearman method (r). Data are shown as mean (± SD). P values less than 0.05 were regaded as statistically significant. For the statistical analysis IBM SPSS 24 statistical software (IBM Corp., Armonk, New York, USA) was used.

4. RESULTS

4.1. First study

Analysis of the objective clinical symptoms and subjective complaints of dry-eye syndrome in SSc.

4.1.1. Demographic features of patients and controls

Mean age of the 19 patients (17 females and 2 males) with SSc included in the first examination was 59.11±7.73 years. Most of them had been suffering from SSc for a long time, with a mean age of 19.79±11.42 years. As controls we used 19 healthy volunteers sex and age-matched in terms of the characteristic features of examined patients population, 17 males and 2 females (mean age was 53.11±18.11 years). There were no significant differences between the two groups in age or in sex.

4.1.2. Outcomes of the ocular examinations

In patients with SSc mean tear production was 6.4±2.76 μL with 14.39±9.36 μL in the control group. Tear velocity was 4.65±1.96 μL/min, and 13.04±6.75 μL/min, respectively. The time of tear sample collection ranged //varied between 28 and 158 s. Mean tBUT value in patients with SSc was 5.16±2.33 s with 11.03±3.75 s in the control group. In patients the Schirmer –I test showed a value of 5,39±3,16 mm/5 minutes while in the control group the same indicator was 14.34±6.39 mm/5 minutes. LG staining score was 2,03±0,89 in patients with SSc and 0,74±0,71 in controls. Mean tear osmolarity was 310.8±14.47 mOsmol/L in patients and 289.9±7.36 mOsmol/L in controls. In our patients with SSc mean OSDI score was 33.6±19.86 compared to 12.8±5.29 in controls.

4.1.2. Correlations between objective symptoms and subjective complaints of dry eye sysndrome

In general, the correlations between objective clinical tests and subjective complaints were weak. In controls, age and tear velocity as objective symptoms, and tBUT showed a significantly negative correlation with the Schirmer I test and a siginificantly positive one with LG scoring. In patients with SSc, analysis of correlations between patients' age or length of disease showed no siginificant correlations with objective symptoms.

In patients the only significantly positive correlation was found between the OSDI score and length of SSc ($r= 0.6031$, $p= 0.0063$).

4.2. Examination of the anterior segment parameters in SSc

4.2.1. Demographic features of patients and controls

Thirty-two patients with SSc, 27 females and 5 males, were included in our second examination, with a mean age of 62,09±12,87 years, and their mean length of scleroderma was 16,56±8,61 years. Twenty-seven of them were suffering from the limited form of the disease while 5 had diffuse cutaneous form. As controls, 39 age- and sex-matched healthy volunteers with the characteristic features of the examined patient population were included, 33 females and 6 males, with a mean age of 62.05±11.25 years. No significant difference was found between the groups in terms of age and sex.

4.2.2. Outcomes of the ophthalmological and clinical examinations

Mean best corrected visual acuity in patients with SSc was 0.84±0.17 in the right eye and 0.81±0.16 in the left eye while in controls it was 0.81±0.16 and 0.81±0.22, respectively. In the patient group mean IOP in the right eye was 15.59±2.47 Hgmm compared with 15.84±2.41 Hgmm in the left eye, whereas in the control group the corresponding values were 16.23±2.93 Hgmm and 15.69±2.61 Hgmm, respectively. No significant differences were found in best corrected visual acuity or IOP.

Mean tBUT score in the right eye of patients with SSc was 4.47±2.55 s compared with 5.09±3.14 s in the left, with the corresponding values in controls being 9.85±2.91 s and 9.9±2.92 s, respectively. Using Schirmer-I test the following values were found: 4.78±3.21 mm/5 minutes in patients' right eye, 5.44±3.21 mm/5 minutes in the left, compared with the corresponding values in controls 10.9±2.32 mm/5 minutes and 10.69±2.35 mm/5 minutes, respectively. OSDI scores were 27.08±12.66 in patients and 14.51±9.11 in controls, respectively.

Mean CRP value/score in patients with SSc was 3.76±3.74 mg/L, and, of the antibodies, mean anti-Scl-70 level was 15.76±14.55 U/mL. Four of the patients (12.5%) showed ACA positivity, while 24 (75%) showed ANF positivity.

We found that thirteen of the 32 patients with SSc had early, 10 active, and 8 had late NFC changes.

4.2.3. Analysis of corneal parameters using Pentacam

All pachymetric values measured using a Pentacam device were significantly lower among patients and maximal corneal refractive power (K_{max}) was significantly

increased. CV measurements taken on the right eye and ACD measurements taken on the left eye showed a decreased level. However, there was no significant difference between patients and controls in terms of ACD and ACA results. Interestingly, these incongruences did not prove bilatereal in every case, instead, in terms of several parameters, they only affected one side.

Based on the correlation analysis we found a significantly negative correlation for patients between pachymetry values and age as well as disease duration, but we found no correlation for objective symptoms of KCS. In general we can conclude that the correlations between measurements taken using Pentacam and clinical variables were weak.

We could demonstrate a significant correlation only between corneal posterior astigmia and ANF positivity as well as between LG score and ACV.

5. DISCUSSION

SSc is a chronic autoimmune disease that affects several organs and tissues, however, few studies, mostly case riports, deal with the examination of the ophthalmological manifestation of the disease. Given that pathomechanism of the disease can be defined as multifactorial, patients with SSc have demonstrated diverse ophthalmological symptoms. These symptoms can appear at any stage of the disease and can involve tissues around the eyes as well as the anterioir and posterior segments of the eyes, and some of them can even cause lasting visual impairment.

Among changes in SSc, in our examinations we analysed the frequent dry eye syndrome and the anterior segment parameters and then compared these values with those of members of a healthy control group.

5.1. Analysis of the results obtained during examination of the objective clinical symptoms and subjective complaints of dry eye syndrome in patients with SSc

Our work team made a thorough/detailed analysis of the objective clinical symptoms and subjective complaints of dry eye syndrome in patients with SSc and then compared them with corresponding indicators of healthy subjects/ individuals. We used several methods to examine the diagnosis of KCS. The results of these examinations led us to conclude that one or two methods are not sufficient to make an unequivocal diagnosis of KCS. We found that while in the control group there was a significant correlation between age and objective functional tear tests, in patients with SSc results of the objective tests were greatly influenced by individual parameters like age or length of disease.

The score based on the OSDI questionnaire, which measured subjective complaints, was 33.6±19.86 in patients with SSc compared with 12.8±529 measured in the control group. The lower OSDI values of the control group may also result from the fact that members of the group consisting of healthy individuals spend most of their time among healthy people hence their quality of life is usually not considerably affected by reduced tear production or impaired objective parameters that ususally come with age. In contrast, patients with SSc suffer from a rare, progressive disease and are likely to spend most of their time with people about the same age but with relatively better ophthalmological status. As a result, they continuously become aware of the ophthalmological differences that accompany their disease and this very fact may have influenced them when they chose /identified higher values on the OSDI questionnaire. Based on the above, OSDI alone should not be chosen for the diagnosis of KCS; instead, it should be used for the follow-up of patients and for the monitoring of the effect of the applied artificial tears.

5.2. Analysis of the examination results of anterior segment parameters

Characteristic features of the anterior segment that can be measured using instrumental methods of examination, including corneal parameters, are of paramount importance in ophthalmological practice. Of the ophthalmological changes, it is these indicators that can provide valuable information about establishing diagnosis when glaucoma or keratoconus are suspected or about monitoring progression of the disease after it has been confirmed. Further, they provide indispensable help in designing intraocular lenses (IOL) or refractive surgeries as well as in analysing the results of the interventions and contact lens fitting.

In our study we analysed anterior segment parameters using Pentacam. The analysis revealed a significant decrease in pachymetry values and, on both sides, a significant increase in the anterior corneal refractive surface power. We found a slight decrease in CV on the right eyes of the examined patients and a decrease in ACD on their left eyes. Statistical analysis revealed a significant negative correlation between pachymetry values and age as well as length of disease. This finding supports the need for an early examination of the anterior segment in patients with SSc with a view to exploring possible ophthalmological manifestations because changes in the cornea occur already in earlier stages of the disease and at a younger age, too.

Autoantibodies were found in 90-95% of patients with SSc. These have a very important role from both a diagnostic and a prognostic aspect, especially in the forms of the disease accompanied by canges in internal organs.

During the analysis of autoantibodies typical of the disease the only significant correlation that we found was between corneal astigmia and ANF positivity. Further studies are needed to find out more about this correlation.

In terms of the variables of the anterior segment and other clinical parameters, in addition to the former, a significant correlation was found exclusively between the LG value and ACV, whose background is not yet clear.

In terms of the clinical relevance of the results obtained by analysing the anterior segments of patients with SSc we need to highlight considerations in connection with laser refractive surgeries since these days these interventions are among the most frequent surgeries worldwide. In addition to refractive surgeries, corneal parameters are not only of high relevance in refractive surgeries but in cataract surgeries as well. As an important factor in IOL design is knowledge of keratometry values, changes

in the structure of the cornea in connective tissue diseases may lead to challenges in the design of intraocular lenses.

In conclusion, some of the changes observed in patients with SSc- (e.g. changes in the eyelids and lacrimal glands) occur partly as a result of damage caused by fibrosis of various organs, especially ones that are rich in connective tissue.- As a result of this damage, the given tissue begins to thicken. By contrast, examination of the cornea using Pentacam revealed lower CCT values. An explanation for the thinning of the cornea, which contradicts the presence of the the well-known fibrosis in SSc, can be the collagen composition of the cornea and the biochemical and ultrastructural changes occurring likely as a result of the collagen composition of the cornea as distinct from the skin and immunological disregulation of collagens. As clinicians we need to be aware of the fact the ophthalmological changes in patients with SSc can cover a broad spectrum. Our results draw attention to the importance of routine ophthalmological examinations, which could enable us to avoid complications that threaten vision or, identifying them at an early stage, start treating them in time. Both during the diagnosis and follow-up of glaucoma and during the design of cataract or refractive surgeries changes observed in the corneal parameters of patients with SSc need to be taken into consideration. The conclusions we have drawn based on our study can also be used outside these surgeries.

6. NEW RESULTS

1. Analysis of the examined objective symptoms of KCS revealed a significant correlation between the values of the patient population with SSc and those of the control group.

2. Analysis of the OSDI questionnaires used to examine the subjective complaints of patients with SSc showed a significantly higher mean score compared with the control population.

3. While, in accordance with literature data, in the control group, a significant correlation was found between age and several objective paramateres of patients with KCS, no significant correlation was found for any of the examined indicators in patients with SSc. With regard to patients with SSc, a significant correlation was found exclusively between the subjective symptoms of KCS and the underlying disease. This fact proves that patients with SSc attach importance to the symptoms of KCS only at later stages of the disease. Thus, the OSDI questionnaire, used to assess subjective complaints, is not sufficient for the diagnosis of KCS alone, it can be important only in the follow-up of patients and in monitoring the effect of the applied treatment with artificial tears.

4. Analysis of the corneal parameters of patients with SSc using Pentacam revealed that several pachymetry values were significantly lower compared with the corresponding indicators in the control group. We often found signficant differences between the two groups in terms of other corneal and anterior segment factors as well. A negative correlation was confirmed between several corneal parameters and patients' age as well as the length of the original disease.

5. Based on the analysis of the correlations between the anterior segment parameters of patients with SSc and the results of the examinations using a capillary microscope and other clinical variables we can generally conclude that these correlations were weak. The only positive correlation was observed on one eye between the astigmatism on the posterior surface of the cornea and ANF, as well as anterior chamber volume and LG score.

7. SUMMARY

Systemic sclerosis (SSc) is a chronic, automimmune conjuntive tissue disease, which can be described by a pronounced microvasculopathy and fibrosis of the skin and the internal organs mainly. Ophthalmological manifestations, which can occur at any stage of the disease, are preesent in about one third od patients with SSc and, as a result of the heterogeneity of the disease, can appear in diverse forms. The ophthalmological changes, which are relatively frequent in patients with SSc, can be regarded either as the systemic manifestations of the disease or the side effects of the given treatment.

The most common ophthalmological change in patients with SSc is KCS, with a wide-ranging prevalence, which is high. Thus, in the first part of our study/work, we examined the objective clinical symptoms and subjective complaints of KCS in patients with SSc together with the correlations between them. While in the control group we found a significant negative correlation between objective tear tests and age, the results of the objective examinations in patients with SSc were significantly affected by individual parameters such as age or length of disease. Analysis of the subjective complaints led us to conclude that patients with SSc attribute importance to KCS sympoms only in later stages of the disease.

In the second part of our study we measured anterior segment parameters using Pentacam. All pachymetry values were found to be significantly lower than in patients. In addition to this, we found significant differences between the values of the patient group and those of the control group. Based on the correlation examinations, with respect to patients, a significant negative corrrelation was confirmed between pachymetry values and age, as well as disease duration. These findings underline the importance of treating KCS and of the examination of the

cornea in earlier stages of the disease. Proper treatment reduces patients' discomfort and helps prevent development of vision-threatening complications.

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List of publications related to the dissertation

1. **Nagy, A.**, Rentka, A., Németh, G., Ziad, H., Szűcs, G., Szekanecz, Z., Gesztelyi, R., Zsuga, J., Aszalos, Z., Szodoray, P., Kemény-Beke, Á.: Corneal Manifestations of Systemic Sclerosis. *Ocul. Immunol. Inflamm. [Epub ahead of print]*, 2018.
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Total IF of journals (all publications): 7,486
Total IF of journals (publications related to the dissertation): 4,183

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *