

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

Involvement of the Anterior Segment of the Eye in Inflammatory  
Bowel Disease

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# **1. Introduction**

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease that can affect multiple organ systems. Extra-intestinal manifestations (EIM) occur in 5-50% of IBD patients and usually cause significant problems, often even bigger than IBD itself. The severity and prevalence of EIMs and their correlation with IBD bowel disease activity vary. Most EIMs are directly related to IBD, others are independent of IBD activity. EIMs may develop before or after an IBD diagnosis and experience shows that the presence of one EIM increases the likelihood of developing further EIMs.

IBD is a complex disease with a number of manifestations inside and outside the digestive tract, which can be a challenge for health professionals. As such, it requires the collaboration of different disciplines, which should, ideally, coordinate their activities, communicate openly and work together as a cohesive interdisciplinary team. Prompt recognition, assessment and management of EIMs in IBD are essential to improve patients' quality of life and reduce morbidity.

## **1.1. Objectives**

The two main areas of our research are the analysis of the symptoms of dry eye disease (DED), the most common secondary ocular manifestation of IBD in patients diagnosed with and treated for the disease and the detailed characterization of the anterior segment of the eye in patients with IBD. Consequently, the following objectives were defined:

1. To perform detailed objective clinical tests for Dry Eye Disease (DED) in IBD patients as well as in the control group, and then to compare the results.

2. To assess the subjective DED complaints of IBD patients, and compare them with those of the control group.

3. To define the parameters of the anterior eye segment of patients with IBD via Pentacam examination, and compare the results with those of the control group.

- 4 To assess the correlation between the anterior segment scores and some other clinical variables of particular relevance to DED.

## 1.2. Inflammatory bowel disease (IBD)

Two of the most important forms of inflammatory bowel disease, ulcerative colitis (UC) and Crohn's disease (CD), occur in approximately equal proportion in both sexes. However, the incidence and prevalence of IBD vary according to geographical region and ethnic group, with an upward trend in recent decades. The highest incidence rates are found in Europe (UC: 24.3/100,000, CD: 12.7/100,000), Asia, the Middle East (UC: 6.3/100,000, CD: 5.0/100,000), and in North America (UC: 19.2/100,000, CD: 5.0/100,000). The highest prevalence values are found in Europe (UC: 505/100,000 inhabitants; CD: 322/100,000 inhabitants) and North America (UC: 249/100,000 inhabitants; CD: 319/100,000 inhabitants). While the incidence and prevalence of IBD in Northern Europe and North America are relatively constant, they have been rising in Southern Europe and Asia, possibly due to the 'westernization' of dietary habits and lifestyle in these areas. According to domestic studies, there is also a steady increase in the number of IBD patients in the Hungarian population. In a prospective, population-based study in Veszprém county between 1977 and 2001 a significant increase in the incidence of IBD was observed. The incidence of UC increased from 1.66 per 100,000 to 11.01 per 100,000 persons, and the incidence of CD from 0.41 per 100,000 to 4.68 per 100,000 persons, and besides, the UC/CD ratio decreased from 4.0 to 2.3. The incidence of IBD continued to increase in the studies conducted between 2002 and 2006.

IBD is a polycausal disease, whose development involves the interaction of hereditary factors, environmental effects, the gut microbiome and the mucosal immune system (Lakatos et al., 2006). Consequently, the genetic and environmental (microbiological, toxicological etc.) factors may play an important part in predisposing to the disease and are supposed to determine the course of the disease and the efficacy of treatment in both CD and UC. No studies have identified any single factor yet that is sufficient in itself to cause the disease. Thus, it is likely that several etiological factors in complex interaction with one another are involved in the development of IBD.

The exact cause of IBD is not known, so the aim of treatment is to achieve and maintain remission, improve the quality of life and prevent potential complications. The guidelines for treatment in our country are also summarised in the European Crohn's and Colitis Organisation (ECCO) recommendations.

The realisation that chronic and untreated inflammation (even if the patient is

asymptomatic) ultimately leads to a poor outcome has recently led to a paradigm shift in medically treating and monitoring the disease.

It is widely accepted today that early intervention and intensive monitoring can prevent complications. Grouping patients according to their prognostic risk factors and individualising therapy are key steps to optimise patient management. The choice of drug therapy is influenced by a number of factors. The choice of treatment regimen should take into account disease activity, extent, phenotype, as well as the efficacy, side effects and extraintestinal manifestations of previously administered treatments/drugs.

If the 'step up' approach is followed, the exacerbation of the disease is first treated with aminosalicylates (in ulcerative colitis) or corticosteroids such as prednisolone and budesonide. If unsuccessful, or steroid-free remission is to be achieved, immunomodulators, biologic agents and small molecule inhibitors (in ulcerative colitis) are considered. There is also growing evidence in favour of a 'top-down' approach in certain cases with poor prognostic outcome.

Steroids are effective drugs for the induction of remission in patients with moderate to severe CD and UC, but they cannot be used to maintain remission in the long run.

In UC patients with mild to moderate activity, several studies have demonstrated the efficacy of 5-aminosalicylate (5-ASA) in achieving or maintaining remission, but taking a single or multiple daily doses did not affect the achievement of remission. There are two types of 5-ASA, sulfasalazine and mesalazine, which have similar efficacy in active UC, although mesalazine is better tolerated than sulfasalazine. For CD, the ECCO recommendation does not justify the use of 5-ASAs since they have not proved to be more effective in achieving and maintaining remission compared to placebo or budesonide.

In immunosuppressive treatment, azathioprine (AZA) can be used in mild to moderate CD and UC to maintain remission, and in CD to induce remission, but only as adjunctive treatment due to the slow onset of action. Methotrexate is indicated in CD patients who have failed or are intolerant to anti-TNF therapy or azathioprine. It can also be used to induce and maintain remission in active CD. It is not effective in maintaining remission in UC. In severe steroid-resistant UC patients, cyclosporine treatment has proved effective.

In the case of biological therapy, infliximab (IFX) and adalimumab (ADA) IgG1 anti-TNF monoclonal antibodies are most commonly used. IFX is a human-mouse monoclonal antibody chimera, and ADA is a human anti-TNF- $\alpha$  monoclonal antibody. These antibodies target TNF- $\alpha$ , a central molecule of inflammation. Their efficacy in the treatment of IBD has been demonstrated in several studies. The benefit of using a combination of immunosuppressive agents was supported by the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) study, which described that patients with naive CD achieved a higher rate of clinical remission and mucosal healing (by week 26 of therapy) with infliximab therapy combined with AZA treatment than patients receiving IFX or AZA monotherapy. IFX treatment was also shown to be effective in UC patients: significantly more of the moderately or severely active UC patients initially receiving steroid therapy had achieved steroid-free clinical remission by week 30 after IFX treatment compared to placebo. Also in UC patients, combined AZA-IFX treatment was shown to be more effective compared to IFX monotherapy. Weekly and biweekly adalimumab treatment in CD patients also showed positive results, with significantly higher clinical remission and mucosal healing rates at week 26 of therapy compared to placebo therapy. In UC patients, adalimumab treatment was also shown to be more effective compared to placebo, with 13.3% of patients receiving steroid therapy at baseline got in steroid-free clinical remission at week 52.

Currently available biologic drugs are monoclonal antibodies that target different inflammatory pathways, such as tumour necrosis factor-alpha (anti-TNF- $\alpha$ ), interleukin 12/23, anti-integrins and small molecule Janus kinase (JAK) inhibitors such as tofacitinib, as detailed above. Choosing which biological agent is most appropriate for each patient can sometimes be challenging, especially in the presence of concurrent extraintestinal manifestations (EIM).

### **1.3. Ocular manifestations of inflammatory bowel diseases**

IBD-related inflammatory manifestations occur in 1.6-4.6% of patients with UC and 3-5.6% of patients with CD. Ocular manifestations are classified into primary, secondary and incidental categories. Primary complications are associated with temporal worsening of IBD and usually resolve with systemic treatment of IBD. These include episcleritis, scleritis and keratopathy, with less common complications being

peripheral keratitis, retinitis, choroiditis, papillitis. Secondary complications usually arise from primary complications or develop as a result of IBD treatment. Examples include cataracts and glaucoma due to corticosteroid treatment, scleromalacia due to scleritis treatment, and the development of hypovitaminosis A due to dry eye disease (DED) following bowel segment removal. Incidental complications are not exclusively associated with IBD but are more common in IBD patients than in the healthy population in population-based studies. Such complications include conjunctivitis, recurrent corneal erosions and corneal ulceration.

These ocular manifestations can cause significant visual morbidity. Although IBD is specific to the intestinal tract, it is a systemic inflammatory disease affecting multiple organs including the eye. Therefore, it is important to detect possible ocular manifestations and to develop appropriate treatment to significantly reduce the risk of developing vision-threatening conditions.

The most common ophthalmic manifestations associated with IBD are episcleritis, scleritis and uveitis anterior. Episcleritis is characterised by painless inflammation of the sclera and conjunctiva without loss of vision. Some studies have shown that episcleritis closely reflects the active phase of IBD and responds well to anti-inflammatory treatments in IBD.

Uveitis may first appear in a subacute and then in an acute form, the disease is often asymptomatic, but there may be redness of the eyes, rarely pain, blurred vision. There is no change in visual acuity unless the posterior uveal structures or the retina are affected. The temporal association of anterior uveitis with IBD is less predictable and its occurrence may precede the diagnosis of IBD. Patients with uveitis should be treated immediately with systemic or topical steroid therapy to prevent the development of blindness.

There are few publications on the relationship between IBD and DED. Felekis and colleagues measured tear film break-up time in 60 IBD patients (37 UC and 23 CD), used Schirmer's test and rose-bengal corneal staining to investigate DED. They found that 50% of patients had DED, one of the most common secondary ocular manifestations of IBD. Another study involving 48 CD, 40 UC and 24 control patients found that ocular manifestations were common in patients with IBD and that DED was present in 44% of them. In addition, they also found a strong association between 5-ASA use (>3g/day) and DED. In contrast, Cloché et al. found no association between IBD medications and DED, but they also classified DED as a secondary manifestation of the disease. Another

study looked at 36 patients with CD and 25 with UC and found that the most common incidental ocular extraintestinal manifestation was DED, supported by a prevalence of 57%, compared with 21.3% in the control group. Studies by Li and colleagues in a Chinese population showed that in patients with IBD the incidence of ocular extraintestinal manifestations (including DED) was 2%, which is quite lower than the rates reported in studies in European and American countries.

## **2. Patients and methods**

### **2.1. Objective clinical symptoms and subjective complaints of DED in patients with IBD**

#### *2.1.1. Patient and control group*

The patients are outpatients of the Department of Gastroenterology of the Clinical Centre of the University of Debrecen. The diagnosis of the disease was based on the Montreal classification. Secondary Sjogren's syndrome did not occur in any of the patients at inclusion or during the one-year follow-up. All patients underwent at least one colonoscopy during the duration of the disease and were IBD inactive during the study. Patients' age, duration of the disease and medications taken within six months prior to the study and during the study were recorded.

Exclusion criteria for both the patient and control group included eye drop use - on the days of the study and in two weeks prior to the study - eyelid abnormality, contact lens wear and treatment with corticosteroids. During this time, patients were not receiving immunosuppressive treatment.

The healthy control group was selected from individuals who matched the patient group in gender and age, presented for routine examination with minor refractive errors ( $\pm 1.0$  diopter), and had no history of digestive disorder, autoimmune, systemic or connective tissue diseases.

#### *2.1.2. Ophthalmic examinations*

Both groups underwent a detailed ophthalmic examination, during which visual acuity was determined using a Snellen chart. During the slit-lamp examination, the anterior segment of the eye, the refractive media and the fundus were examined. It was followed by taking the intraocular pressure (IOP) with a non-contact tonometer.

Ocular Surface Disease Questionnaire (OSDI) The best known and most widely used OSDI questionnaire consists of 12 questions and is used to assess the symptoms associated with DED and the impact of these symptoms on vision. The questions ask about patients' eye complaints in the past week, such as light sensitivity, nerve damage, eye pain and blurred vision. The test can be used to analyse the functional impact of dry eye complaints (reading, computer use, complaints while watching TV) and the possible

role of environmental factors (windy weather, dry air in rooms, air conditioning use). Respondents rate the frequency of complaints they experience on a 5-point Likert-type scale (0 - none of the time, 1 - small part of the time, 2 - half of the time, 3 - most of the time, 4 - all of the time). The total OSDI score is calculated using the following formula:

$$\text{OSDI} = \frac{\text{the sum of the scores of the questions answered} \times 25}{\text{the sum of the number of questions answered}}$$

The resulting score was marked on a scale from 0 to 100, with a higher score indicating a higher subjective complaint. The OSDI score was based on the ocular surface discrepancy:

normal:	0-12 points
mild:	13-22 points
moderate:	23-32 points
serious:	33-100 points.

Measurement of tear film stability, tBUT (tear film break-up time). A drop of 0.9% sterile saline was dropped onto the fluorescein strip used for the measurement, and then briefly touched to the inferior conjunctival fornix of the eye under test. Stimulation of the eye during the test should be avoided. After a few blinks, the tear film was examined with a slit lamp under cobalt blue illumination. The time interval from the last blink to the appearance of a dark, dye-free spot indicating the rupture of the precorneal tear film was used as the tear film rupture time in seconds. The measurement was performed on both eyes of each subject and the mean of the 3-3 tBUT measurements obtained was recorded.

Measurement of tear production (Schirmer-I test) Tear production was measured without prior anaesthesia, i.e. with the Schirmer-I test. The folded end of a standardized measuring paper was placed at the border between the middle and temporal third of the lower eyelid of the subjects, avoiding touching the cornea. After carefully closing the eyelids, the patients were asked not to move their eyes. 5 minutes after insertion, the length of the wet-out measuring paper was determined in millimetres (mm/5min). In some cases the average of the two eye measurements was taken, in others they were treated separately.

Lysamine green (LG) staining. Lysamine green is a water-soluble, vital dye that shows damage to the conjunctiva and cornea. Pre-impregnated test paper was used to

perform the test. A drop of sterile physiological saline was dripped onto the test strip and touched to the bulbar conjunctiva near the inferior fold. Then, after one or two blinks of the patient, we increased the brightness of the slit lamp gradually, as suggested by Foulks. LG staining thus visualized, which we could observe. Grading was performed according to Bron grading (Oxford Grading Charts): 16x magnification with a Haag-Streit slitlamp. The grading we used is as follows.

Grade 0: 0-9 staining points on the bulbar conjunctiva (nasal and temporal parts are graded separately)

Grade 1: 10-32 staining points

Grade 2: 33-100 staining points

Grade 3: more than 100 points.

LIPCOF: Folds formed at the lateral inferior quadrant of the conjunctiva are parallel to the inferior lid margin, which shows a significant correlation in DED. To evaluate the severity of folds parallel to the lid margin, we used LIPCOF definition. During the test, we asked patients to blink a few times and then look straight ahead. The horizontal conjunctival folds in the area from the middle to the temporal third of the lower eyelid were examined with a slit lamp, while the brightness of the slit lamp was gradually increased. The size of the conjunctival folds and the height of the normal tear meniscus were taken into account in the evaluation. The grading we used is as follows.

Grade 0: no persistent folds present

Grade 1: there is a small crease, but it is smaller than a normal tear meniscus

Grade 2: more folds, up to the height of a normal tear meniscus

Grade 3: more folds, which is higher than the normal tear menu.

## **2.2. Analysis of anterior segment parameters in IBD**

### *2.2.1. Patients and healthy controls*

The patients were selected from the patients treated with IBD, specifically with CD and UC, at the Department of Gastroenterology, Clinical Centre, University of Debrecen. The diagnosis and phenotype of CD and UC were established after clinical, imaging, endoscopic and histopathological examinations according to current international criteria. All patients had IBD in an inactive state and had to undergo

colonoscopy at least once during the duration of the disease. The healthy control group consisted of patients who saw an ophthalmologist for a routine examination for minor refractive errors ( $\pm 1.0$  dioptre). These patients were matched in gender and age to the patient group and had no history of autoimmune, other systemic or connective tissue diseases. In addition, the inclusion criterion included that the patient and control group members had not used any eye drops on the days of the study and in the two weeks prior to the study.

For the patient group, frequent extraintestinal manifestations such as episcleritis, corneal infiltrates and posterior segment manifestations were exclusion criteria. In addition, eyelid abnormalities, contact lens wear, glaucoma, uveitis, previous ophthalmic procedures, and lesions in the lacrimal duct drainage system were also exclusion criteria.

Ophthalmological examinations were performed to determine visual acuity and a slit lamp examination was also performed. To evaluate the DED, the tests were performed in the following order: completion of the OSDI questionnaire by the patient, measurement of tear film break-up time, and Schirmer-I test. Then a Pentacam was used to examine the anterior segment of the eye.

### *2.2.2. Examination of the anterior segment of the eye in IBD patients with Pentacam*

The anterior segment of the eye was measured with a Pentacam. The test was performed with an undilated pupil and the average of 3 consecutive measurements was taken for each eye. Using the proprietary software of the high-resolution Scheimpflug camera, the following parameters were measured - where relevant, both on the outer surface (front) and inner surface (back) of the cornea:

- keratometric value in the flattest axis (K1)
- keratometric value in the steepest axis (K2)
- average keratometric value (Km)
- astigmatia (K1-K2) - given for completeness only
- the smallest radius of the cornea (Rmin) - given only for completeness
- pachymetric data (central corneal thickness (CCT), peak, thinnest point and maximum refractive power (Kmax)
- corneal volume (CV)
- anterior chamber volume (ACV)

anterior chamber depth (ACD)  
anterior chamber axis (ACA)  
pupil diameter.

### **2.3. Statistical analysis**

For the statistical analysis of our first study, we used IBM SPSS 24 statistical software (IBM Corp. Armonk, New York, USA / GraphPad Software Inc., San Diego, USA). The Gaussian distribution of the values was tested using the D'Agostino-Pearson test and the Shapiro-Wilk normality test, and then one-way ANOVA was used to compare the values. Pearson's or Spearman's method was used to determine the coefficients characterising the correlation between each quantity. Mean values of the data are shown ( $\pm$ SD). P-values less than 0.05 were considered statistically significant.

In our second study, continuous variables are expressed as mean  $\pm$  SD, while categorical variables are expressed as a percentage of their frequency. The distribution of data was checked by Kolmogorov-Smirnov test. The Student's t-test and Mann-Whitney U test were used to compare continuous variables based on the distribution of data. Chi<sup>2</sup> test and Fisher's test were used to compare categorical data. Pearson or Spearman's method was used to calculate the correlation coefficients between variables. P values less than 0.05 were considered statistically significant.

## 3. Results

### 3.1. Evaluation of objective clinical signs and subjective complaints of dry eye disease in patients with IBD

#### 3.1.1 Demographic characteristics of patients and controls

Of the patients included in the first study, 39 were diagnosed with CD (21 women, 18 men) with a mean age of  $42.26 \pm 12.36$  years and 26 patients diagnosed with UC (7 women, 19 men) with a mean age of  $46.38 \pm 12.75$  years, all of whom were treated at the Outpatient Department of the Department of Internal Medicine, Clinical Centre, University of Debrecen. The mean duration of disease was longer in CD ( $12.74 \pm 6.63$  years) than in UC ( $11.27 \pm 7.34$  years). The control group consisted of 39 healthy volunteers, 24 women and 15 men (mean age  $48.51 \pm 15.92$  years), age and sex matched with the study population. There were no significant differences between the groups in age and sex.

#### 3.1.2. Results of ophthalmic examinations

Mean OSDI scores were  $10.88 \pm 5.54$  in the control group,  $30.59 \pm 16.68$  in CD patients and  $24.67 \pm 23.48$  in UC patients. Subjective ocular symptoms of DED showed a higher significance value in CD patients compared to the control group than in UC patients, but the latter group also showed a significant difference compared to the control group.

When comparing the DED objective parameters of the healthy control group with those of the patient groups, we found more significant differences for CD patients than for UC patients. The healthy control group had significantly more 0 values than the patient groups, indicating a healthier conjunctiva and cornea.

Correlation analysis revealed a weak association between subjective symptoms and patients' age and duration of illness within the two groups of patients. Only for the UC patient group did we find a significant positive correlation between the patients' age and OSDI scores ( $r = 0.5302$ ,  $p = 0.01$ ).

In the healthy control group, the relationship between OSDI scores and objective test scores is significantly correlated. Within the CD group, only LG scores showed a significant positive correlation with OSDI scores, whereas for UC, all the other objective

scores except for tear production scores showed a significant correlation with OSDI scores within the group.

## **3.2. Analysis of anterior segment parameters in IBD**

### *3.2.1 Demographic characteristics of patients and controls*

Among the patients included in the second study, 30 were diagnosed with CD (16 women, 14 men) with a mean age of  $45.80 \pm 11.55$  years and 36 patients diagnosed with UC (14 women, 22 men) with a mean age of  $52.00 \pm 16.05$  years. All of them were patients treated at the Outpatient Clinic of the Department of Internal Medicine of the University of Debrecen. Mean duration of disease was  $12.72 \pm 5.83$  years in CD patients and  $15.94 \pm 10.09$  years in UC patients. The control group consisted of 80 healthy volunteers of the same age and sex as the study population, 39 women and 41 men, with a mean age of  $50.68 \pm 14.62$  years. There were no significant differences between the groups in terms of age or gender.

### *3.2.2. Results of ophthalmic and clinical examinations*

The mean OSDI scores were higher in both CD patients and UC patients compared to the control group ( $25.02 \pm 17.24$ ,  $19.46 \pm 15.02$ ,  $15.55 \pm 9.63$ ), which was significant between CD patients and the control group. In the evaluation of objective symptoms of DED, the right eye tBUT and ST<sub>I</sub> (Schirmer-I test) values were significantly lower in CD patients compared to the control group, while in UC patients only the right eye tBUT value was significantly lower compared to the control group, ST<sub>I</sub> values remained in the normal range, whereas left intraocular pressure was significantly higher in UC patients. These data suggest that CD patients are more prone to develop symptoms of DED. IOP values were within the normal range and BCVA (best corrected visual acuity) values were close to 1.0 among both IBD patients and control group members, however, in CD patients the left eye BCVA value was significantly different compared to the control group. In comparisons of DED objective parameters between UC and CD patient groups, ST<sub>I</sub> values were significantly lower in CD patient group.

### *3.2.3. Analysis of corneal parameters with Pentacam*

All pachymetry values measured with Pentacam were significantly lower in the

patient groups compared to the control group, and the maximum corneal refractive power (Kmax) values were increased in all IBD patients, but significant differences were only observed in the right eye of UC patients. In addition, the CV values of both eyes and the ACD values of the right eye were significantly lower in the UC patient group when compared with the control group.

In CD patients, the anterior mean corneal refractive power (Km) was significantly increased in one eye compared to the control, and there was a significant difference in ACA when comparing the two groups of patients. In UC patients, the Kmax and ACD values of one side were significantly increased compared to the control group, while the right corneal front Rmin values were significantly lower compared to the control.

In the correlation analysis of corneal parameters and tear production measurements, we found a significant negative correlation between CV values and ST<sub>1</sub> values on both sides. While in the left eye, other corneal parameters (pachymetric apex, thinnest and center) also showed a significant negative correlation compared to ST<sub>1</sub> values.

There was a significant difference in the use of immunosuppressants when comparing medication between the two patient groups ( $p=0.040$ ).

## **4. Discussion**

### **4.1. Objective clinical signs and subjective complaints of dry eye disease in IBD**

The present study is the first study to investigate the subjective and objective symptoms of DED in IBD patients, assessing patients' age, disease duration, drug therapy and symptoms. Our results suggest that patients with CD have more characteristic symptoms of DED compared to those with UC, which is supported by the results of our tear film characteristic studies, where we obtained worse scores for CD when comparing patient groups with control group results.

In our study, the OSDI values of the DED healthy control group (as subjective parameters for DED) showed a significant correlation with all objective parameters of tear production and tear film stability. However, the correlation between the subjective and objective parameters was also significant for the UC patient group, with the exception of the comparison of tear production with the subjective test results. When comparing subjective parameters with age and duration of illness, no correlation was observed for the CD patient group, or for the UC group when those parameters were compared with duration of illness. However, a comparison between the OSDI test scores completed by UC patients and their age showed a significant correlation. The correlation between the objective and subjective symptoms in the control group was not observed in the CD group, whereas in the UC group there was a significant correlation between OSDI scores and the results of the measurement.

It is important for clinicians to recognise the ophthalmological problems associated with IBD, as people over 40 are at increased risk of developing these complications, so early diagnosis and treatment can help prevent serious complications that can also compromise vision. For this reason, it is recommended that patients with IBD are regularly checked by an ophthalmologist and that any eye problems are treated in a timely manner.

Ophthalmological manifestations may precede the diagnosis of IBD in some cases, but early diagnosis of IBD is of paramount importance in corneal refractive surgery, as keratorefractive surgery is contraindicated in untreated immune-mediated disease.

Subjective ocular symptoms assessed by the OSDI are more pronounced in CD patients than in UC patients. Nevertheless, all objective tear production parameters show variable values in both CD and UC patients, and it is important to draw the attention of UC patients to the use of DED therapy in order to preserve ocular surface health and vision.

In our study, we found a significant difference in tear film characteristics between CD patients and the control group. With the exception of ST<sub>I</sub> and tBUT values, UC patients' values were closer to normal than those of CD patients. These results confirm the fact that the tear volume values are quite similar to the control values, yet the tear quality deteriorates, which can be explained by its altered composition.

## **4.2. Evaluation of anterior segment parameters in IBD**

It is very important to maintain and preserve the anatomical and physiological characteristics of the cornea, as these can prevent diseases and inflammatory processes of the ocular surface and cornea. In addition, they play a role in the planning of corneal and anterior segment surgery and in the precision of the procedure. It is also important to highlight that immune-related disorders can increase the risk of intra- and postoperative complications during corneal surgery. Corneal changes have a significant impact on the planning of corneal refractive surgery, as well as on post-operative management and wound healing. While autoimmune or immune-mediated diseases are considered relatively contraindicated for corneal laser surgery, there have been successful LASIK procedures to correct refractive defects in 2 patients with CD and arthritis and in 1 patient with UC and arthritis. However, the most important consequence of laser eye surgery for autoimmune patients is that the surgery may cause the development of scarring. Necrotizing keratitis following an uneventful LASIK procedure can be particularly challenging as it can occur even in stable, controlled IBD.

This knowledge underlines the importance of a detailed medical history, particularly in the case of autoimmune diseases, and surgeons often need to work together with immunologists in order to determine the appropriate timing of surgery. Corneal refractive surgery is only recommended in patients who do not require systemic treatment at the time of screening and who do not have any ocular problems associated with autoimmune disease.

According to literature, IBD-related corneal involvement rarely develops. In 1925, Crohn first described corneal involvement - keratomalacia and xerophthalmia - in 2 UC patients. Knox and colleagues presented 4 CD patients with small, bilateral, symmetrical subepithelial infiltration and scarring that did not affect visual acuity due to their peripheral localization. Using the corneal module of the Heidelberg Retina Tomograph, irregularly shaped hyperreflective dots in the basal epithelium of the cornea were detected in 40% of CD patients, which would not have been detected by a normal slitlamp examination. In addition, the activation of stromal keratocytes was observed in the majority of CD patients, also supporting the possibility of subclinical inflammation. Troncoso and colleagues reported some different corneal involvement in a review article. They described in several studies that corneal damage can occur in different layers of the cornea, but it is important to note that in some cases corneal involvement can be quite unusual and may be associated with other inflammatory disorders. Various diagnostic tools have been used to investigate IBD-related corneal involvement, such as videokeratography or confocal microscopy; however, the parameters of the cornea and anterior segment have not been investigated in detail.

In our study, we compared corneal thickness data with the measurements of some other clinical variables. Our results showed that corneal thickness and CV values were significantly lower in all IBD patients than in the controls. We showed that several other anterior segment values were unilaterally worsened in the patients studied, and we also observed a negative correlation between corneal parameters and  $ST_1$ . In our study, we paid particular attention to DED, as it is often associated with IBD and leads to reduced tear film stability scores. Our results show that reduced tear production is not only present in patients with CD, but the development of DED is also more of a co-morbidity specific to CD patients. When examining the correlation between corneal values and DED parameter values in this patient group, a significant negative correlation between tear volume and corneal thickness was found. The correlation between pachymetric values and DED parameters can be explained by the biochemical and ultrastructural changes in corneal collagen due to immunological abnormalities in IBD.

Methotrexate has well known side effects in the anterior segment (corneal lesions, cataracts), while in the posterior segment it may induce cystoid macular oedema, retinopathy or ischaemic optic neuropathy. Immunosuppressants may also be responsible for corneal thinning in CD patients. As we have observed various types of

corneal and anterior segment damage in our studies, it is worth investigating the possible pathophysiological background. Ocular problems of inflammatory origin, typically uveitis, are often associated with IBD along with erythema nodosum and arthritis as extraintestinal manifestations of IBD. We also found a strong association with HLA-B27, B58 and HLADRB1 haplotypes, but the changes we observed did not lead to inflammatory damage.

The analysis of the association between corneal manifestations and IBD reveals a complex pathomechanism in addition to genetic predisposition, including cytokine imbalance, as the cornea is particularly sensitive to biochemical and ultrastructural changes in collagens in immunological disorders. Collagen metabolism, matrix metalloproteinase and extracellular matrix synthesis are altered in IBD, resulting in a reduced collagen network. In the corneal stroma, the interlamellar branches have distinct stretches, and the arrangement and orientation of these collagen lamellae in the anterior stroma differ from those in the posterior stroma. These anatomical features and pathophysiological processes may result in alterations in corneal and anterior segment parameters that may show significant or near-significant differences between IBD patients and controls. Structural changes in the retina and corneal changes may coexist.

As a complex disease, IBD requires a multidisciplinary approach. It is important to identify ocular symptoms in both ophthalmology and gastroenterology, since ocular symptoms can be sensitive markers for disease prognosis. Clinicians need to be aware of the wide spectrum of ocular manifestations associated with IBD and accordingly perform routine eye examinations to protect vision. We would like to emphasise, however, that patients with IBD were included or excluded from the study based on strict criteria, so our results do not apply to all IBD cases.

## 5. Summary

Two of the most important forms of inflammatory bowel disease (IBD) are Crohn's disease (CD) and ulcerative colitis (UC), which are chronic conditions of fluctuating intensity of inflammation of unknown aetiology. A combination of genetic, immunological and environmental factors may play a role in the development of CD and UC. They primarily affect the intestinal tract, but have a number of extraintestinal manifestations that may also affect the eye and its environment.

We focused our research on two areas: on the prevalence of the most common secondary ocular manifestation, dry eye disease (DED) and its association with IBD, and on the morphology of the anterior segment of the eye in IBD patients. Ocular complications can occur at any stage of IBD and can affect the anterior and posterior segments of the eye as well as the periocular tissues. The majority of these lesions can lead to reduced quality of life, sometimes permanent visual impairment or even complete loss of vision.

The subjective ophthalmic parameters (OSDI scores) of the healthy control group showed a significant correlation with all objective parameters of tear production and tear film stability. The correlation between subjective and objective parameters (except tear production) was also significant in UC patients, but not in the CD patient group. The significant correlation of subjective parameters with age observed in the control group was only retained in UC patients but not in CD patients. The correlation of subjective parameters with disease duration was not significant in either CD or UC patients.

It is important to preserve the morphological characteristics of the cornea in order to maintain visual integrity and to avoid intra- and postoperative complications of possible corneal procedures. In IBD, corneal involvement may develop rarely, but little is known about its severity. Our studies revealed that both corneal thickness and volume were significantly smaller in patients with CD and UC, compared with the healthy controls.

In general, the identification of ocular symptoms in IBD is important for the patient's quality of life, but ocular symptoms can also have prognostic value.

## 6. New results

**In our first study** we found that CD patients develop DED more easily than UC patients since their tear film is more damaged.

Although UC patients had tear film characteristics relatively close to the healthy controls (including tear volume), they also had poorer tear quality compared to the healthy controls.

In healthy control individuals and in UC patients, subjective symptoms (OSDI scores) showed a significant correlation with all the objective parameters of tear production and tear film stability. This correlation was much weaker in CD patients (only lysamine green scores correlated strongly with OSDI values).

The severity of DED did not correlate with age or duration of disease in either CD or UC, i.e. individual background characteristics of IBD predominated.

**In our second study** we found that the thickness and volume of the cornea of IBD patients were significantly smaller than those of healthy controls.

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## 8. Publications



**DEBRECENI  
EGYETEM**

**DEBRECENI EGYETEM  
EGYETEMI ÉS NEMZETI KÖNYVTÁR**

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Jelölt: Czompa Levente

Doktori Iskola: Petrányi Gyula Klinikai Immunológiai és Allergológiai Doktori Iskola

### A PhD értekezés alapjául szolgáló közlemények

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