SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

(PhD)

THE ROLE OF E-SELECTIN AND OTHER PATHOGENETIC FACTOR IN RETINAL DISEASES

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1. INTRODUCTION

Besides age-related macular degeneration and glaucoma, diabetic retinopathy is one of the leading causes of blindness in well-developed countries.

Retinal vascular diseases are found frequently in the background of serious vision failure.

1.1. Retinal vascular diseases

Retinal vascular diseases refer to a range of eye disorders such as retinal vein occlusion (RVO), which can be divided in two groups: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO); central retinal artery occlusion and Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION). These diseases are multifactorial disorders. Cardiovascular disorders, for example hypertension (HT), ischemic heart disease (IHD), atherosclerosis, diabetes mellitus (DM), hyperlipidemia and also smoking can play an important role in their development.

1.1.1. Retinal vein occlusion (RVO)

In retinal vein occlusion (RVO) the central retinal vein (CRVO) or branches of the retinal vein (BRVO) suffer occlusion. The venous congestion also affects the arterial circulation; we distinguish ischaemic and non-ischaemic RVO. Usually, venous circulation, damage in the wall of the retinal vein at the lamina cribrosa, and increased blood coagulation (also known as the triad of Wirchow) together lead to occlusion in the retinal vein.

Main symptoms are slow loss of vision (usually within one to two weeks), relative afferent pupillary defects, visual field defects, and typical ophthalmoscopic findings. Diagnosis is also based on fundus examination. Due to defects of the circulation, it is

frequently associated with papillary and macular oedema. Complications include neovascularization due to hypoxia and secondary glaucoma.

1.1.2. Vascular Endothelial Growth Factor (VEGF)

Several factors contribute in neovascularization and affect the vascular permeability of newly formed vessels. Vascular endothelial growth factor (VEGF) plays an essential role. In humans, VEGF has several isomers; VEGF 121 and 165 isomers of VEGF-A play roles in ocular pathology. Increase of their levels due to hypoxia and vascular congestion increase the permeability of capillary walls, leading to macular oedema, and frequently resulting in severe and irreversible visual impairment.

1.2. Diabetic retinopathy

Diabetic retinopathy might appear early, only a couple of years later than the diagnosis of diabetes. Main risk factors for diabetic retinopathy are the duration of diabetes and glycaemic control of the disease. Severity of retinopathy is graded by the American Academy of Ophthalmology (AAO) based on visual acuity, ophthalmoscopic findings and risk factors; there are no signs of retinopathy in group A, while group B refers to non-proliferative diabetic retinopathy (NPDR) that can be divided into mild, moderate and severe stages, and group C refers to proliferative diabetic retinopathy (PDR), one or both of the following: neovascularisation, vitreous/preretinal haemorrhage.

Diabetic retinopathy might appear early, only a couple of years later than the diagnosis of diabetes. Main risk factors for diabetic retinopathy are the duration of diabetes and glycaemic control of the disease.

An intensive presence of adhesion molecules leads to stronger macrophage and leucocyte adhesion to the capillary endothelium, which can cause capillary obstruction and retinal ischaemia. Severe retinal ischaemia leads to neovascularization and the formation of

proliferative retinopathy, triggered by vasoactive agents (such as VEGF). For this reason, the elevation of the level of adhesion molecules in diabetes might play a role in the formation of diabetic retinopathy.

1.2.1. The soluble E-selectin (sE-sel)

Selectins are adhesion molecules that play an important role in regeneration after tissue damage or inflammation, providing adhesion between leucocytes and vascular endothelial cells. There are three basic types of selectins: L-selectins are presented on the surface of leucocytes, P-selectins on thrombocytes and E-selectins on the surface of vascular endothelium. All selectins have a characteristic extracellular region, which consists of a calcium-dependent lectin domain, an epidermal growth factor-like domain, a short consensus repeat and a transmembrane domain.

Selectin proteins production are strongly and rapidly induced by a variety of inflammatory mediators, including IL-1β, TNF-α, interferon-γ, substance P.

Endothelial dysfunction is well-known in diabetes. Several studies have shown elevated serum levels of circulating adhesion molecules and sE-sel levels in diabetic patients, proving their association with macro-, microangiopathy and neuropathy.

Elevated sE-sel levels were additionally reported in dyslipidemia, atherosclerosis, obesity and in case of smoking. Higher serum sE-sel levels can increase the prevalence of cardiovascular and cerebrovascular diseases (myocardial infarction, angina pectoris, sudden cardiac death, stroke).

2. AIMS

2.1. Measurements of VEGF levels in tear of RVO patients

2.1.1.Our aim was to detect as well as to measure the tear VEGF levels in patients with CRVO and BRVO.

2.1.2. To measure the tear and plasma VEGF levels in RVO patients.

2.1.3. We observed not only the tear and plasma VEGF levels in RVO patients, but also measured the Central Retinal Thickness (CRT) by Optical Coherence Tomography (OCT).

2.1.4. We studied the correlation between tear VEGF levels and macular thickness in RVO patients.

2.2. Measuring plasma sE-sel levels in DM patients

2.2.1. We measured the plasma sE-sel levels in DM patients.

2.2.2. We examined the pathogenetic role of plasma sE-sel levels in the development of DM retinopathy.

2.2.3. We studied the role of sE-sel in the severity of DM retinopathy.

2.2.4. We also measured and analyzed glycated haemoglobin level (HbA1C) levels of the patients.

2.2.5. We observed the correlations between the duration of the DM and the HbA1C levels as well as the other cardiovascular risk factors.

3. PATIENTS AND METHODS

3.1. Patients

Patients were enrolled from the outpatient clinic of the the Department of Ophthalmology, University of Debrecen. Patient enrolment was based on clinical protocols in accordance with international guidelines. All patients with ophthalmological or any other disease that would interfere with the results have been excluded. All enrolled patients gave informed consent and the International Review Board approved the study protocol in accordance with the 1989 Declaration of Helsinki (RKEB/IKEB 3763-2013).

3.1.1. Patients with RVO

During the two years of recruitment in 2013 and 2014, we diagnosed RVO in 15 patients at the outpatient care unit of the Department of Ophthalmology, University of Debrecen. Eight patients (age 70.37 ± 5.24 years: three females and five males) fulfilled our inclusion criteria and participated in the study. Three patients had CRVO (one female, two males) and five patients had BRVO (two females and three males). Our control group consisted of five healthy volunteers (age 63.60 ± 16.24 years: one female and four males) without any concomitant diseases. Demographic and comorbidity data were compared with the Mann-Whitney U and Fisher exact test.

Out of the eight patients, two patients arrived within 24 hours, two patients within a week, one patient after two weeks, and three patients within three weeks after the onset of symptoms.

3.1.2. Patients with DM

On the other hand the study patients were enrolled from 102 patients who attended

regular ophthalmological screening due to their diabetes mellitus at the outpatient care facility of the Department of Ophthalmology, University of Debrecen, in 2014-2015.

Fifty-seven patients were eventually enrolled (37 female and 20 male, aged 61.71 ±12.31 years). We divided the patients into three groups as follows. In group A were 19 patients (12 female and seven male, aged 64.45 ±10.36 years) with no signs of diabetic retinopathy, of which two patients had DM1, while 17 had DM2. The diabetic retinopathy group was subdivided between groups B and C according to the severity of retinopathy: group B comprised 19 patients (13 female and six male, aged 64.05 ±12.42 years) with non-proliferative diabetic retinopathy (NPDR), of which eight patients had DM1, while 11 had DM2; in group C, there were 19 patients (12 female and seven male, aged 56.65 ±12.99 years) with proliferative diabetic retinopathy (PDR), all of whom had DM1. Our control group consisted of 14 age-matched healthy patients (10 female and four male, aged 63.06 ±10.46 years).

3.2. Examinations

All patients underwent a careful ophthalmological examination, including best corrected visual acuity, slit lamp examination, applanation tonometry, ophthalmoscopy with dilated pupil. Fundus colour photography and fluorescein angiography were performed on each patient using Zeiss FF450+IR equipment. In RVO patients were examination by optical coherence tomography (Spectralis OCT). In RVO patients central retinal thickness was also examined by using optical coherence tomography.

3.2.1. Examinations in RVO patients

Plasma and tear samples were obtained at the baseline visit (V1), tear samples were obtained after one week (V2) and four weeks (V3). VEGF levels were evaluated in each

sample. After the baseline visit at diagnosis (V1), we evaluated the patients, and obtained plazma samples and tear samples. After one week (V2) and four weeks (V3), we evaluated tear samples in all eight patients.

3.2.2. Examinations in DM patients

A full medical history was taken from all patients, including type and duration of diabetes, IHD, HT, hypercholesterinaemia (HC)) and current medication. Staging of diabetic retinopathy was conducted using the AAO 2012 classification. Colour fundus photographs and fluorescein angiograms were graded simultaneously by two masked ophthalmologists, and only corresponding classifications were accepted.

3.3. Laboratory methods

3.3.1 Tear sample collection in patients with RVO

Tear samples were obtained by the same examiner by capillary flow with no nasal stimulation or previous installation of drugs or vital dyes. No anaesthetic drops were used; samples were collected non-traumatically from the inferior meniscus without touching the cornea, conjunctiva, or eyelids. The collected amount of tear sample (µl) and collection time (120 sec) were recorded, and samples were centrifuged. All samples were stored at -70°C until measurement in the presence of the protease inhibitor Complete Mini (Roche Diagnostics, Basel, Switzerland).

3.3.2. Measuring the tear and plasma VEGF levels in RVO patients

VEGF levels were quantified by using Human VEGF Quantikine® ELISA kit (R&D Systems, Minneapolis, MN, USA). The ELISA kit was applied according the manufacturer's instructions. Samples were thawed at room temperature, immediately before use. Plasma

samples were measured directly; tear samples were diluted up to 200µl with Calibrator Diluent RD5K (a component of the kit), as amounts collected were small.

3.3.3. Laboratory investigations in DM patients

In each case, routine laboratory investigations and HbA1C test were performed. Venous blood samples were obtained from the antecubital vein via a 21-gauge needle directly into Vacutainer tubes containing 0.105 M sodium citrate (Becton Dickinson, San Jose, CA, USA) with minimal venous stasis.

Blood glucose levels were measured on a Cobas Analyzer (Roche, Mannheim, Germany). HbA1C was measured by HPLC (BioRad, Hercules, CA, USA).

We analyzed the plasma levels of sE-sel by using commercially available ELISA (R&D Systems, Minneapolis, MN) kit following the manufacturer's instructions. All plasma samples were centrifuged immediately at 2000 x g for 15 minutes at RT, aspirated and stored at -70°C until analysis.

3.4. Statistical analysis

3.5.1. Statistical analysis in patients with RVO

For statistical analysis, the program SPSS v 22 (IBM Statistics, Chicago, Illinois) was used. We used paired T test and Pearson correlation analysis, and the level of significance was defined at $p<0.05$.

3.5.2. Statistical analysis in patients with DM

Statistical analysis was carried out using the SPSS for Windows (Version 22.0) and MedCalc (Version 14.8.1) statistical software. The normality of data was tested using the

Kolmogorov-Smirnov test. If normality was rejected, a non-parametric test was performed. For continuous variables, data were expressed as median and a 95% confidence interval (95% CI) for the median. Comparison between two variables was performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for binomial variables. For subgroup analysis, binomial variables were compared with the chi-square test and continuous variables were compared with the Kruskal-Wallis analysis of variance. Correlation between test results was calculated by Spearman's rank test. A p value of <0.05 was considered statistically significant.

4. RESULTS

4.1. Results in RVO patients

We found that VEGF levels in tears of the RVO eyes were significantly higher at each visit, compared to the fellow eye (paired t test: p_1=0.01, p_2=0.02, p_3=0.006, respectively).

We also found alterations over time in tear VEGF levels. In RVO eyes, VEGF levels were significantly elevated after one week (V2 p_{1-2}=0.023) and after three weeks (V3 p_{1-3}=0.050), compared to the baseline (V1). Although V2 levels were higher compared to those of V3, the difference was not statistically significant (p_{2-3}=0.874). In the tears of the fellow eyes, the tendency was similar to that of VEGF levels; however, only the difference between the baseline (V1) and V2 was statistically significant (p_{1-2}=0.038). Differences between the other visits were not significant (p_{1-3}=0.113, p_{2-3}=0.596).

We found that CRT increased significantly after one week; we found a significant difference between CRT values of V1 and 2 (paired t test, p_{1-2} =0.01). The difference between V1 and V3, and V2 and V3, were not found to be statistically significant (p_{1-3} =0.57, p_{2-3} =0.11).

We found that the plasma VEGF levels of RVO patients at baseline were elevated, when compared to an age-matched control group, the difference was strongly significant (p=0.0001).

Correlations were found between plasma and tear VEGF levels at V1 (r=0.33, p<0.05), and between plasma and tear VEGF in the fellow eye (r=0.21 p< 0.05).

We compared tear VEGF levels with OCT findings in RVO eyes; however, none of the results were statistically significant.

4.2. sE-sel levels in the plasma of patients with DM can play a role in the development of diabetic retinopathy

Regarding age and gender, patient groups were homogenous according to the Mann-Whitney U test, with p=0.64 and p=0.86, respectively.

The sE-sel level was found to be higher in the diabetes patient group, compared to controls (p=0.03). The HbA1C level was higher in the diabetes group compared to controls and, therefore, the difference was highly significant (p<0.0001).

Strong correlation was found between the duration of diabetes and the presence of retinopathy (p<0.0001).

We found significant association with HT (p<0.0001) and IHD (p=0.007) in the diabetic patient group according to Fisher's exact test compared to controls. No similar association was found regarding HC (p=0.84).

Dividing the diabetic patient group by the presence of retinopathy into groups A, B and C, as described above, we found the following results: the mean sE-sel level in the control group was 26.55 ng/mL (20.40-33.22 ng/mL 95% CI) and 31.6 ng/mL (25.81-36.50 ng/mL 95% CI) in group A; 36.90 ng/mL (27.00-47.80 ng/mL 95% CI) in group B; and 32.60 ng/mL (25.05-39.19 ng/mL 95% CI) in group C. The difference between the subgroups individually is not statistically significant.

However, if we compare sE-sel levels in patients without retinopathy (controls and diabetic patient group A) with patients in whom diabetic retinopathy is present (diabetic patient groups B and C), we found that the sE-sel level is significantly higher with the presence of retinopathy (p<0.05).

4.2.3. Statistical analysis in the DM subgroups

By Spearman correlation analysis the following results were found in the diabetes subgroups A, B and C.

In group A, sE-sel level was shown an elevating tendency with the duration of diabetes and HbA1C levels; however, Spearman's correlation test did not find the observation statistically significant, showing r=0.39, p=0.1 and r=0.31, p=0.18, respectively.

Regarding co-morbidities, significant negative correlation was found between sE-sel level and HC (r=-0.48, p=0.04); however, no such correlation was found with HT and IHD (r=0.04, p=0.86 and r=0.38, p=0.11, respectively). Strong and significant positive correlation was found with the Spearman test between the duration of diabetes and IHD (r=0.55, p<0.01), although similar correlation was not observable between the duration of diabetes and HT or HC (r=0.21, p=0.40 and r=-0.4, p=0.09, respectively).

In group B, correlation was not found between sE-sel levels and duration of diabetes (r=0.16, p=0.50) or HbA1C levels (r =0.14, p=0.55). Regarding co-morbidities, significant positive correlation was found with HC and IHD (r=0.8, p<0.0001).

There was no correlation between the duration of diabetes, HT, HC and IHD (r=0.38, p=0.10; r=-0.30, p=0.21; r=0.01, p=0.96, respectively).

Finally, in subgroup C, a marked correlation was detected between HC and IHD (r=0.45, p=0.05). There was no association between sE-sel levels and the duration of diabetes (r=-0.27, p=0.25) or HbA1c levels (r=-0.02, p=0.92). Regarding co-morbidities,no association was found between sE-sel levels and HT, IHD or HC.

5. DISCUSSION

5.1. VEGF levels in tears of patients with RVO

Elevated VEGF serum levels have been associated with several pathologies, such as heart failure, atherosclerosis, cardiac diseases, and ischaemic strokes. It has been also associated with inflammatory diseases, like arthritis, and several malignancies. Mysliwiec et al. found significantly higher level of blood serum HbA1C, VEGF in patients with DM, with retinopathy in comparison without retinopathy. In ophthalmological diseases, there were reports on elevated VEGF tear levels in corneal neovascularization and after refractive surgery procedures.

Several studies have shown elevated VEGF levels in the aqueous humour and vitreous body of patients with RVO. Other authors investigated VEGF levels in the vitreous body in BRVO and CRVO and found elevated levels, suggesting its relation with the concomitant macular oedema. They also found that both VEGF levels are higher in the vitreous gel of patients with ischaemic BRVO/CRVO than in the non-ischaemic form, and found a correlation between the levels and the severity of macular oedema. Boyd et al. found a correlation between VEGF levels in aqueous humour in CRVO and the severity of iris neovascularization.

The aim of our study was to investigate VEGF levels in tears of patients with RVO. According to our knowledge, we are the first to describe these findings.

In our pilot study, we investigated the tears and serum of eight RVO patients. We found that VEGF level increases in the tears of RVO eyes, compared to the fellow eye, at all examined time points (V1, V2, and V3). We found similar changes in BRVO and CRVO, but did not divide the RVO patients into subgroups because of the small sample size.

In our study, we found associations between tear VEGF levels and the severity of macular oedema (central retinal thickness measured by OCT). Our results are similar to the results of other authors, who found correlations between VEGF level in aqueous humour, vitreous body, and central retinal thickness in RVO. Noma et al. also found a correlation between aqueous humour and vitreous gel VEGF levels and the increase of CRT in CRVO and in BRVO.

Our results lead to similar findings, but an association was found between tear VEGF levels and OCT findings. This association might lead to the conclusion that there might be a correspondence between the hypoxia-induced VEGF level rise due to the RVO and the degree of macula oedema.

As our study design was a prospective pilot study, we were able to investigate the changes of VEGF levels in tears and the severity of macular oedema over time.

We had two patients (Patients 3 and 7) who presented immediately after the onset of symptoms, meaning that they were ideal candidates for the follow-up evaluation. In both of these cases, we found that VEGF levels were relatively low at baseline (V1) and tear VEGF levels were increasing over time, reaching an intermediate level by V2 and were highest by V3. As the other subjects were enrolled later in the course of the disease, coming for their first visit one to three weeks after the presentation of the symptoms, we found the highest VEGF levels in tears at V2, with a modest decrease by V3.

Regarding macular oedema, we found that CRT reached its maximum level by V2, except for Patient 7, in which case CRT was continuously increasing until V1-V3; this patient was probably investigated immediately after the onset of the disease.

5.2. sE-sel levels in the plasma of patients with DM can play a role in the development of diabetic retinopathy

Elevated serum levels of soluble adhesion molecules in DM have been previously described. Their role in diabetic macro-, microangiopathies, and retinopathy has been also suggested. Increased adhesion molecule levels have also been previously identified in the vitreous gel of diabetic patients.

Well known that diabetic retinopathy is caused by capillary occlusions that result from microvascular thrombi formed by red blood cells, platelets and leukocytes. Platelets can play an important role in this vascular occlusive process.

Our aim was to investigate the sE-sel levels in the plasma of patients with DM to determine whether there is a correlation between their levels and the presence or severity of retinopathy. We also investigated their association with the duration of diabetes and HbA1C levels, as well as general risk factors and co-morbidities, such as HT, IHD and HC.

The HbA1C has also been found to be significantly higher in the DM group. IHD and HT were more frequently associated with DM than were present in the control group. Disease duration correlated significantly with the presence and severity of retinopathy.

An elevated sE-sel level has been found in the plasma of DM patients compared to the control group.

In the subgroups of diabetic patients, sE-sel levels were also found to be higher compared to the control group. However, when we regrouped patients by the presence of retinopathy (group A and controls vs. groups A and B), the sE-sel level was significantly higher in the retinopathy group.

An association between the duration of DM and the HbA1C-, and sE-sel levels could be observed, although the correlation was not statistically significant. These results suggest

that an elevated sE-sel levels might play a role in the formation of diabetic retinopathy, but that it has no effect on severity. Severity is more likely to be affected by the present co-morbidities, such as HT, IHD or HC. In patient groups A, B and C, an elevating tendency of sE-sel levels has been observed; however, we could not identify a statistical significance that can also be explained by sample size.

In the NPDR group (group B), we could not identify association between sE-sel levels and disease duration and HbA1C levels.

We found significant positive correlation with HC and IHD. These results might suggest that the duration of disease and the presence of comorbidities, together with the elevated sE-sel levels, might play a role in the formation of retinopathy.

In the proliferative group (group C), we did not find any association with the sE-sel levels. We, therefore, suggest that, at this stage, sE-sel have no or only a minor role, such that neovascularization can be defined by other mediators, such as VEGF.

Our results are in accordance with the findings of Boulbou et al., who also found elevated sE-sel levels in DM patients but no association with the severity of retinopathy. Matsumoto et al. also found significantly elevated sE-sel levels in DM patients who had either micro- or macroangiopathy, further suggesting that sE-sel might play a role in the formation of diabetes-associated vascular disease.

However, they did not investigate the sE-sel levels in different stages of diabetic retinopathy or their association with co-morbidities and their effect on the formation of retinopathy.

We found association between the presence of retinopathy and elevated sE-sel levels, yet our findings suggest that sE-sel has no or only a minor effect on the severity of retinopathy.

We conclude that sE-sel levels ought to be measured in the plasma of DM patients without retinopathy, while elevated levels might be treated by sitagliptin or miglitol therapy in order to reduce the risk of the formation of diabetic retinal disease. Proper treatment of co-morbidities, such as HT, IDH and HC, also plays a role in the prevention of diabetic retinopathy.

6. SUMMARY

6.1. VEGF levels in tears of patients with RVO

6.1.1 Our pilot study could be a milestone establishing that tear analysis in RVO also has its role, as a non-invasive method that can be performed easier than the sampling of aqueous humour or vitreous body. In our pilot study we were able to detect VEGF in the tears of RVO patients; its level was significantly elevated in the affected eye compared to the fellow eye.

6.1.2. We found that the plasma VEGF levels of RVO patients at baseline were elevated in comparison to an age-matched control group, and that the difference was strongly significant.

6.1.3. In accordance with the elevation of VEGF level in tears, we found similar changes (retinal thickening) in the macula, which were represented as an increase in CRT on OCT maps. We were able to investigate the changes of VEGF levels in tears and the severity of macular oedema over time.

6.2. Correlation between plasma sE-sel level and the severity of retinopathy in DM patients

6.2.1. The sE-sel level in the plasma was significantly higher in patients with diabetes compared to controls. Dividing patients into groups by the presence of retinopathy, the sE-sel level was also significantly higher in the retinopathy group. When we examined diabetic patients by the severity of retinopathy (groups A, B and C, by the guidelines of the AAO),

however, we did not find any significant difference in sE-sel levels, although it tended to be higher in group B.

6.2.2. According to our study it seems that the increased sE-sel plays a pathogenetic role in the early stage of DM.

6.2.3. sE-sel levels showed significant increase until the retinopathy developed. However, it counts less in the development of proliferative retinopathy.

6.2.4. To summarize, the increased blood glucose, HbA1C, cardiovascular risk factors (HT, IHD, HC) and increased sE-sel as atherosclerotic agents play a role in the early stage of DM and the development of non-proliferativ retinopathy. However, after the impairment of capillary endothelial cells and luminal narrowing these agents lose significance.

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Subject: PhD Publikációs Lista

Candidate: Márta Kasza
Neptun ID: KYYP91
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Kasza, M.**, Meleg, J., Várdai, J., Nagy, B., Szalai, E., Damjanovich, J., Csutak, A., Ujhelyi, B., Nagy, V.: Plasma E-selectin levels can play a role in the development of diabetic retinopathy. *Graefes Arch. Clin. Exp. Ophthalmol. 255* (1), 25-30, 2017.
   DOI: http://dx.doi.org/10.1007/s00417-016-3411-1
   IF: 1.991 (2015)
2. **Kasza, M.**, Balogh, Z., Bíró, L., Ujhelyi, B., Damjanovich, J., Csutak, A., Várdai, J., Berta, A., Nagy, V.: Vascular endothelial growth factor levels in tears of patients with retinal vein occlusion.
   Graefes Arch. Clin. Exp. Ophthalmol. 253, 1581-1586, 2015.
   DOI: http://dx.doi.org/10.1007/s00417-015-3030-2
   IF: 1.991

List of other publications

3. Balogh, Z., **Kasza, M.**, Várdai, J., Reznek, I., Damjanovich, J., Csutak, A., Berta, A., Nagy, V.: Analysis of optic disc damage by optical coherence tomography in terms of therapy in non-arteritic anterior ischemic optic neuropathy.
   Int. J. Ophthalmol. 9 (9), 1352-1354, 2016.
   DOI: http://dx.doi.org/10.18240/ijo.2016.09.20
   IF: 0.939 (2015)
4. Nagy, V., Balogh, Z., **Kasza, M.**, Ujhelyi, B., Csutak, A., Reznek, I., Damjanovich, J., Berta, A., Pfliegler, G.: Cardiovascular and thrombophilic risk factors in retinal vein occlusion.
   Exp. Clin. Cardiol. 20 (1), 238-244, 2014.

5. Nagy, V., Kolozsvári, B. L., Balogh, Z., Csutak, A., **Kasza, M.**, Nagy, B., Kardos, L., Berta, A., Pfliegler, G.: Increased level of platelet P-selectin in nonarteritic anterior ischemic optic neuropathy.
Graefes Arch. Clin. Exper. Ophthalmol. 251 (3), 917-922, 2013.
DOI: http://dx.doi.org/10.1007/s00417-012-2196-0
IF: 2.333

6. Losonczy, G., Fekete, Á., Vokó, Z., Takács, L., Káldi, I., Ajzner, É., **Kasza, M.**, Vajas, A., Berta, A., Balogh, I.: Analysis of complement factor H Y402H, LOC387715, HTRA1 polymorphisms and ApoE alleles with susceptibility to age-related macular degeneration in Hungarian patients.
Acta Ophthalmol. 89 (3), 255-262, 2011.
DOI: http://dx.doi.org/10.1111/j.1755-3768.2009.01687.x
IF: 2.629

7. **Kasza, M.**, Berta, A., Pfliegler, G., Nagy, V.: Az Eales-betegség klinikai tünetei, differenciáldiagnosztikai problémái, kezelése.
Szemészet. 144, 92-94, 2008.

8. Módis, L., **Kasza, M.**: A száraz szem tünetei, diagnosztikája és kezelése.
Praxis. 15 (5), 33-34, 2006.

Total IF of journals (all publications): 9,883
Total IF of journals (publications related to the dissertation): 3,982

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

13 March, 2017

7. LIST OF OTHER PUBLICATIONS

7.1. List of oral presentation related to the thesis

- *M. Kasza, Z. Balogh, L. Biro, B. Ujhelyi, I. Reznek, J. Várdai, A. Berta, V. Nagy*
  Vascular endothelial growth factor levels in tears of patients with retinal vein occlusion
  114 th Meeting of German Ophthalmology Society (DOG), 25-28. September 2014, Leipzig as been addressed with a Travel award

7.2. List of other presentations

- *Kasza M., Módis L.*:
  Immun stromalis keratitis esetbemutatás
  Immunológiai-, szemészeti közös kongresszus, Budapest, 2010. április 24.
- *V. Nagy, Gy. Pfliegler, M. Kasza, M. Fodor, A. Berta*:
  The role of ophthalmologist in the identification of orphan disease
  Amsterdam, Netherlands: 17th Congress of SOE, 2009 június 13-16.
- *Kasza M., Gáspár B., Németh G., Kerek A.:*
  Blepharospasmus kezelése Botulinum A toxinnal és a száraz szem
  Magyar Szemorvostársaság 2008. évi kongresszusa, Pécs
- *Kasza M., Módis L.:* Impressziós citológia a szárazszem diagnosztikájában
  Magyar Szemorvostársaság 2007. évi kongresszusa, Debrecen
- *Kasza M.:* A szemfenéki vascularis történések tünetei, rizikófaktorai
  Az ér-, és ideghártya betegségei, Továbbképző tanfolyam, 2006. okt. 13-14.