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Review of Ph.D. thesis "Development of objective non-invasive techniques for the assessment of the ocular surface and tear film dynamics acting as biomarkers for early diagnosis of dry eye disease" by Izabela Katarzyna Garaszczuk

In the submitted thesis Ms. Izabela Garaszczuk presents results obtained during project performed within frames of European Dry Eye Network Initiative (EDEN) concerning development of non-invasive diagnostic tools and, specifically, biomarkers for early diagnosis of dry eye disease (DED). Since DED is a multifactorial disease which etiology is not clearly understood, there is a need for sensitive and highly specific biomarkers that would ease its early diagnosis.

Ms. Garaszczuk in her Thesis puts the hypothesis that homeostasis of the tear film is more likely to be disturbed in the development of DED and therefore, parameters derived from observation of tear film, or tear meniscus, may be useful in development of abovementioned biomarkers. Two such parameters were chosen, namely tear clearance rate and tear turnover rate, and a number of methods to measure and quantify them was used during the study.

During the project of Ms. Garaszczuk new methods to quantify the tear film were proposed and tested. Next the new methods were compared with methods already established in a one year longitudinal study involving human subjects.

The construction of the dissertation is clear and comprehensive. It spans over 250 pages and is composed of four chapters, introduction, summaries in three languages and list of tables. The reference list counts almost 300 items and appendices contain documentation used in the longitudinal studies.

The introductory chapter gives the reader background of the dry eye disease, while the **first chapter** provides information on tear film and related parameters including existing methods to measure them, their limitations and literature values.

The second chapter introduces three experiments to assess tear film related parameters.

The first technique uses corneo-scleral fluorescein profilometry to measure tear turnover rate (or, in that particular case, its analogous parameter: tear fluorescein washout rate TFWR).

Ms. Garaszczuk provides a simple model to estimate the decay of fluorescein content in the tears and describes in detail methodology required to obtain the information about the decay constant. Obtained results show that the TFWR parameter correlates somehow with the McMonnies Questionnaire (McMQ) score, although the correlation is not very high. What is somehow surprising is that having immense amount of data (the Author mentions 2GB per pession) only that simple parameter is calculated. Maybe more sophisticated model would give a parameter with higher correlation to McMqQ.

The second technique uses OCT images to extract size of the tear meniscus. The experiments are performed in static mode (single image) and dynamic mode (time lapse). From the image of meniscus three parameters are derived: height, depth and area of the meniscus. Correlations between the parameters are given and compared with existing technique of meniscus height measurement provided by commercially available K5M Keratometer. OCT clearly provides more information than the K5M device, but the results are not really compared, as only the mean values, standard deviation and range are given for the K5M and the correlations of results with the OCT based ones are not shown. Additionally, static and dynamic OCT parameters are very weakly correlated with each other. Only interclass (static to static and dynamic to dynamic) correlations are high. This is not really surprising as area is not independent on depth and height. Several questions arise immediately. Are these results repeatable for different OCT frames chosen for static analysis? What are the correlation between static parameters from different frames? Why is the correlation negative for height an area in dynamic mode, while it is positive in static mode?

The third technique uses OCT to estimate tear clearance in early phase after application of saline solution. Decays of meniscus area, height and depth in dynamic mode are observed as expected. Correlations between depth, height and area are again observed, but are surprisingly low as for dependent parameters, suggesting that depth and height are not the only possible measures to quantify the meniscus. Surprisingly, the meniscus parameters are not correlated with tear fluoresceine washout rate from the previous part of the chapter.

Although, the experiments proposed by Ms. Garaszczuk provide new parameters, it is a pity that there is no common reference to which all of them are compared. I was not able to find answer to question which of the parameters correlates best to a chosen, established DED marker. Only in case of TFWR the correlation to McMQ score gives such kind of information. The other parameters are only compared between others, what does not give much information, especially that the correlations between them are week or statistically insignificant.

The third chapter provides meticulous description of longitudinal study of trends in biomarkers induced by contact lens wear. In the yearlong study 55 subjects were involved. Patients were given

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and fitted standardized soft contact lenses, and during quarterly follow-up visits a large number of parameters, including the ones proposed by Ms. Garaszczuk, were gathered. The correlations between all the parameters are provided by the author. Since the eye, it is physiology and pathology are extremely complex, it is not very surprising that only the dependent parameters (like ones mentioned in chapter 2) have correlation higher than 0.4. Again it is a pity that the results are not compared to a any reference parameter, like for example the McMQ score or other. Therefore, in my opinion the claims in the summary, that osmolarity, TCR and TMH parameters are expected to be good macro-type biomarkers of DED, although general true, must by subject of further studies.

It has to be noted that the side effects of the study, like the reduction in tear osmolarity in case of patients with hyperosmotic tears, or normalization of lipid layer thickness related to healthier contact lens wear habits has value to general public and should be emphasized.

The doctoral thesis presents the results of a huge scientific effort of Ms. Garaszczuk. The choice of subject, that involves very complex organ that is human eye as target of research, the scale of conducted research including not only design of new parameters, but also preparation of the experiments and all the methodology of longitudinal studies, followed by data collection and processing as well as detailed statistical analysis may impress. Ms Garaszczuk was also active in dissemination of her work. She published three articles in JCR listed journal (Contact Lens and Anterior Eye, IF = 1.99), with three more to appear in the near future and one in national journal. She also presented the results in several international conferences.

In conclusion, I am convinced that the thesis fulfils the provisions of Art. 13, par. 1, of "Ustawa o stopniach naukowych i tytule naukowym oraz o stopniach i tytule w zakresie sztuki (Dz. U. z 2016 r. poz. 882, 1311.)".

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