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Review Report on the PhD thesis

submitted to WROCLAW INIVERSITY OF SCIENCE AND TECHNOLOGY

Author: LAURA RICO DEL VIEJO

Title: "INFRARED IMAGING OF THE MEIBOMIAN GLAND STRUCTURE"

Scientific Supervisors: D.David Robert Iskander, D.David Madrid Costa, D.Jose Manuel Benitez Del Castillo

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. DED is considered one of the most frequently encountered ocular conditions seen by ophthalmologists and optometrists. Meibomian gland dysfunction (MGD), a main contributor to evaporative DED (EDED), is considered the leading cause of dry eye in clinic and population based studies. The reported prevalence of MGD rates based on clinical signs in populations over the age of 40 ranged from 38 to 68%

Prevalence of DED in studies involving symptoms with or without signs ranged from approximately 5% to 50%. Studies where the diagnosis was based primarily on signs generally reported higher and more variable rates of disease, up to 75% in certain populations. The reason for reported differences in following studies is the heterogeneity of the DED itself and also the poor standardization of the past data with a lack of well-defined diagnostic criteria of clinical tests in common use.

The PhD dissertation by Laura Rico del Viejo is focused on the study of the meibomian gland structure revealed by non- contact infrared meibography (NIM) – the main and most important cause of DED. The main research goals were: to study the relationship between the (MGL) revealed by NIM and the ocular surface parameters
in order to update MGD classification based on the MG structure. Also to assess the effect of ageing on the ocular surface parameters since it has been reported to be a risk and relevant factor for MG and the ocular surface. In addition, to study the relationship between new objective MG morphology parameters and the ocular surface parameters. Finally, to study and compare the thermal characteristics of DED and healthy subjects using infrared thermography.

Based on above data, I state that the background and concept of the research project by Laura Rico del Viejo is of a significant meaning and originality for the next generation of dry eye clinicians and scientists. It is worth underlying, that currently, there is no gold standard in the classification of MGD assessed by NIM. Also, there is an urgent necessity for introduction objective, non- invasive and repeatable methods and technologies in order to obtain more valuable information for DED diagnosis making process.

The main and secondary objectives of the research project are clearly and precisely defined and formulated based on the in-depth knowledge regarding MDG and DED diagnosis.

The selection of methods presented by Laura Rico del Viejo is the result of a conscious and reflective research process and proves that the PhD candidate clearly understands the MGD and DED pathophysiology. The methodology part is precisely written. The clinical protocol is visualized with the flow diagram as well as with adequate, excellent quality figures and the figure legends.

The results of the research project are impressive and add a considerable novelty into understanding of DED.

The presented results which prove other published thesis results and are consistent with previous studies regarding following issues are as follows:

1. The effect of aging and sex on ocular surface parameters - moderate and positive correlations (bulbar redness (BR), limbal redness (LR), corneal and conjunctival staining and tear meniscus height using Keratograph (TMHk), respectively) and negative correlations (tear break-up Time (TBUT) and Schirmer test, respectively) were found with age. These results are consistent with previously published studies.
2. The impact of MGL on the results of the ocular surface parameters. Other authors also proved the role of the MGL on the ocular surface, although this matter is quite controversial and also future studies should be conducted since different studies with different aims have considered both or only one eyelid.

The new observations reported by Laura Rico del Viejo are as follows:

1. The novel objective, automated algorithm which provides a three-class classification that enables differentiation between gland, inter-gland and areas of MGL. The algorithm provides a detailed estimation of the MGL area and as well, other morphological parameters of MG such as mean length, mean width, number of glands and especially, the irregularity. Automatic quantifying of the MG morphology could have a significant meaning regarding MGD diagnosis and progression analysis.

2. The new information on the ocular surface temperature (OST) changes (both DED and healthy eyes) and the effect of blinking by assessing several OST metrics and specifically the interblink interval (IBI). The IR thermography has shown to be a promising technology to assess the tear film dynamic which should be considered for future studies on MGD.

The above observations have a high potential contribution to the discipline with implications for clinicians as well as for future scientific projects. In my opinion significantly important conclusions include:

1. The influence of age on the MG morphology and the ocular surface, which has been highlighted in this work. Future studies must consider age and use only age-matched study groups due to its great influence on the MG morphology.
2. The necessity of the automatic approach in the study of the MD morphology in order to obtain more reliable information and reduce the time of the clinical evaluation. Future studies should incorporate an automatic method to assess the MG morphology.

Concerning the theoretical and experimental part of the thesis I would like the candidate to answer the following minor points during the defence:

1. According to TFOS DEWS II guidelines, currently a two layered tear film model of the tear film's structure is preferred over the traditional three layered model, with a mucoaqueous gel layer lying beneath, but at least partly integrated with, an overlying lipid layer. The three layer model from Figure 6 should be replaced with the two layer model for future publications. The development of a novel holistic model of tear film structure and function and changes that occur during dry eye is one of the latest achievements of current research and hopefully will help us understand the DED pathophysiology.

2. In the part of the results "The effect of ageing on the ocular surface parameters" I lack the information on prevalence of DED, preclinical state and predisposition to DED according to age. In my opinion presenting the results also in this more general fashion would be useful for clinicians.

The writing style of the PhD dissemination is clear and concise, without unnecessary duplication or repetition. The reference list is complete and accurate and proves in-depth knowledge of the PhD candidate regarding DED prevalence, risk factors, diagnosis and management.

The PhD dissertation consists of 6 chapters, 61 figures and 28 tables and compromises 201 pages. The various chapters of the thesis are connected in a logical and rational fashion. Figures, figure legends, tables and tables legends are properly presented and clear for the reader. The thesis structure is deliberate and transparent.

It is worth mentioning, that the PhD candidate proposes a new methodological approach of MGD diagnosis by creating new paradigms that bring together non-contact meibography results and clinical assessment of ocular parameters analysis.

Summarizing, the candidate for PhD degree Laura Rico del Viejo obtained new original, significant results which broaden the understanding of DED especially of EDED caused by MGD.

In conclusion, I am convinced that the thesis fulfils the provision of Art.13, par 1, of "The act on academic degrees and academic title as well as degrees and title in the field of art (Journal of Laws of 2016, item 882, 1311)" and the candidate can be admitted to the public defence. Taking into consideration the high scientific level and outstanding conclusions with a significant impact on the discipline, I apply for the distinction of the PhD thesis.

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