Abstract of PhD Dissertation
"Infrared Imaging of the Meibomian Gland Structure"
by Laura Rico del Viejo

Dry eye disease (DED) is a multifactorial disease of the ocular surface considered one of the most frequently encountered ocular conditions seen by eye care practitioners. Nowadays, DED is estimated to affect between 5-50% of the worldwide population. Furthermore, the prevalence of DED increases linearly with age which makes DED a growing public health concern as the global population of older people is expected to be more than double its current amount by 2050. According to DED classification, the aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) are the two major DED types and are considered to exist on a continuum rather than as separate entities. Despite this, according to the current DED understanding, an evaporative component is more common than an ADDE component. Currently, the Meibomian gland dysfunction (MGD) is considered the leading cause of EDE. This condition may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation and ocular surface disease. Therefore, any change that occurs in the morphology of the MG or in its secretion has an important clinical impact.

Recently, the non-contact infrared meibography (NIM) has become the most widely used tool for both researchers and clinicians for the assessment of the MG structure. Many studies have confirmed the use of this technology for diagnosis and management of MGD. Indeed, NIM allows the detection of MG abnormalities such as meibomian gland loss (MGL), shortening, dilation and distortion. The MGL or dropout refers to the partial or total loss of acinar tissue and it is one of the most common MG features reported in the literature. Currently, there is no gold standard in the classification of MG assessed by NIM but most of them are based on the MGL. Previous studies found significant correlations between MGL and some tear film parameters (such as tear film break-up time (TBUT), non-invasive break-up time (NIBUT), lipid layer thickness (LLT), Schirmer test, MG expressibility and corneal staining) and subjective symptomatology (Ocular surface disease index questionnaire (OSDI) and McMonnies questionnaire), suggesting its possible diagnostic value. However, other studies concluded that asses the MGL alone as clinical parameter has not enough DED diagnostic value, and it should be interpreted jointly with other clinical parameters.

Additionally, the multifactorial nature of the DED makes difficult for eye care practitioners to carry out a correct diagnosis and monitoring. For this reason, more objective, less invasive and more repeatable methods and technologies have been developed in order to obtain more valuable information for DED diagnosis.
This dissertation is an in-depth work focused on the study of the MG structure revealed by NIM. The main research goals of this work were: 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. Also, 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. 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.

In order to accomplish these objectives, a clinical protocol was designed that included a complete assessment of the ocular surface with classical tests both invasive and non-invasive, as well as some new technology for the ocular surface assessment. The following measurements were included: a clinical anamnesis; tear film osmolarity by TearLab Osmolarity System; automated measurements with the Keratograph 5M (K5M); ocular surface temperature (OST) using a non-contact infrared thermography camera; a slit lamp biomicroscope with ×10 magnification, cobalt blue illumination, a Wratten 12 yellow-barrier filter and fluorescein sodium ophthalmic sterile strips were used to observe ocular surface staining and TBUT. Lissamine Green strips were used to assess lid wiper and the conjunctival staining. Additionally, an assessment of the eyelid was carried out. Furthermore, a meibography image of each eyelid was obtained using the K5M. Finally, the Schirmer test was performed with topical anaesthesia with the eye closed and after 5 minutes the length of the wetting was measured.

This experimental work is organized into four independent studies. In the first study the clinical protocol explained above was applied monocularly to a total of 110 participants (mean age; 44 ± 19 years, 70 females and 40 males) in order to study the first objective of this work. The main results of this study showed elderly population present ocular surface changes when compare to a young population. Although the majority of the ocular surface parameters studied presented a fair correlation with age, these results give us relevant information of the ageing of the ocular surface and how it could affect the DED diagnosis. Additionally, females from this study showed more changes due to ageing than males who presented better ocular surface conditions than those of their age- matched female group.

In the second study a total of 161 participants were included (mean age; 42 ± 17 years, 91 females and 70 males) whom were grouped according to the MGL graded using the subjective scale meiboscore introduced by Reiko Arita et al. 2008. These groups were compared and the relationships between MGL and several ocular surface parameters were evaluated. In addition, age was included as covariant in the relationship between MGL and the ocular surface parameters since the mean age of the participants in this study was higher in those groups with higher MGL. The findings of this study suggest that a MGL higher than 50% is accompanied by signs of increased osmolarity, redness and staining of the ocular surface. Despite this, when age was included as a covariant only the corneal staining was correlated with MGL, emphasizing the influence of ageing on the MG morphology and also on several ocular surface parameters. Overall, these findings suggest that age-matched groups should be compared in order to know the contribution of the MGL on the ocular surface as well as establish a valid cut-off values for DED diagnosis.

The third study of this doctoral thesis consisted of the use of an automated algorithm that analyses infrared images of the MG using image processing techniques (developed by the Department of Biomedical Engineering, Wroclaw University of Science and Technology, Wroclaw, Poland) to obtain objective information about the MG morphology. Several objective MG parameters such as the MGL, gland length, gland width and the gland irregularity (also named as tortuosity or MG distortion) were extracted of a total of 149 meibography images from the everted upper eyelids (UL) from the second study of this work. The main results of this study showed that the majority of the objective MG morphology parameter, which was obtained with the automated algorithm (Objective MGL, length and width of the gland) are highly influenced by age. Therefore, their influence on the ocular surface should be assessed by comparing age-matched groups as previously described in the second study. This study suggests that MG irregularity could represent the

prodromal stage before losing the MG. This means that while the MG is still present (irregular or not) it will continue functioning and only in the presence of high amount of MGL the ocular surface will be affected.

The latest study involved the assessment of the OST of 86 participants (48 healthy and 38 DED eyes, mean age; 39 ± 12 and 49 ± 19 years, respectively) using an infrared thermography camera. The OST of both groups was registered for 40 seconds, allowing subjects to blink naturally. Several OST metrics were proposed in order to study the OST changes during the recording, assessing the first and last complete interblink interval (IBI). The main results of this work showed slightly thermal differences between DED and healthy eyes as well as ADDE and EDE. These differences were not statistically significant when the complete thermal recording was assessed. Indeed, this could be explained since the OST could be regulated by the warming effect provided by the eyelid in each blink. These findings show that the evaluation of the thermal behaviour during the IBI could provide useful information about the thermal changes of the ocular surface in DED and healthy eyes.

Summarizing, this research work provides a new knowledge about the MG morphology and its relationship with several important ocular surface parameters. This could help eye care professional to interpret and carry out a better the DED diagnosis. At the same time, the clinical utility of the infrared thermography to study the tear film dynamics has been used for the study of the tear film dynamics, especially in DED.