Resumen: This thesis is a far-reaching work with the purpose to find a new macro-type biomarker that could be objectively and non-invasively measured as an indicator of DED, specifically at its early stage. To achieve this goal, it proposes new metrics of tear dynamics quantification and explores the pathophysiological role of potential biomarkers in incipient DED, by following visit-to-visit longitudinal trends of these measures over a period of one year, in subjects reported with incipient symptomatology. The hypothesis behind developing the new macro-type biomarkers of DED is that the loss of homeostasis of the tear film, describing the core pathophysiological mechanism of DED, may not only be expressed as disturbed tear film morphology, but also by a lack of equilibrium between hydro-dynamic processes occurring in the tear fluid or tear menisci. These phenomena are in a state of equilibrium regulated by the lacrimal functional unit. A disruption of this subtle
balance will ultimately lead to DED. Based on the abovementioned observation, the tear clearance rate (TCR) was chosen as a potential macro-type biomarker of DED. The multifactorial nature of DED can be expressed by TCR, as it considers all the hydrodynamic phenomena occurring in the tear fluid and was shown to perform well in DED differential diagnosis.

METHODS
This thesis has been divided into two parts: Experimental and Biomarkers trends study. The experimental chapter, in a form of three separate experiments, proposes new methodologies for tear dynamic quantification. The second part describes the one-year-long longitudinal study, arranged to follow the above-mentioned visit-to-visit biomarkers trends.

RESULTS
Fifty-five subjects participated for the whole duration of the study. The group mean age was (mean ± standard deviation) 26 ± 4 y/o (20 to 37 y/o). The limitation of this study was a lack of control in study environment. No statistically significant correlation was noted between laboratory temperature and humidity for any of the ocular measures assessed, except for lid wiper epitheliopathy score. Non-parametric two-way ANOVA showed statistically significant temporal trends in OSDI and DEQ-5 in subjects with incipient symptomatology, in tear osmolarity, non-invasive, objective measures of tear film break-up time, tear meniscus height assessed with dynamic meniscometry and measures of tear clearance and staining with vital dyes, lid wiper epitheliopathy scores, corneal thickness and quantification of Meibomian gland drop-out. Statistically significant difference between Baseline and Control visit was not noted in some measures, suggesting that the temporal changes induced by contact lenses could be short-term. No significant differences were noted in bulbar and limbal redness, which may suggest that changes observed in the study are not inflammatory.

CONCLUSION
Tear osmolarity, tear clearance and dynamic meniscometry could be used as potential biomarkers for supporting DED diagnosis.