Getting ahead of the curve: Epidemiology and biomarkers of keratoconus

On June 19, 2020, Sashia Bennett defended her thesis, "Keratoconus - epidemiology and changes in biomarkers," at the Department of Clinical Medicine, Faculty of Health, Aarhus University, Denmark. The PhD project was conducted at the Department of Ophthalmology, Aarhus University Hospital. The main supervisor was Professor Jesper Hjortdal, and the co-supervisors were Associate Professor Anders Ivarsen and Professor Cecilia Ramlau-Hansen.

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Keratoconus causes an imbalance in the optic system in which curvature of the cornea is too steep, the central cornea becomes too thin, and, with time, central scarring creates opacities. Despite continued research, many aspects of the disease remain elusive. In this PhD project, we aimed to gain more knowledge of keratoconus in a Danish population, investigating the hypothesis that the disease goes beyond the pathology seen in the cornea. The project included several approaches:

Using national Danish registries, the sociodemographic factors, associated diseases, and mortality of 2,679 keratoconus patients were compared to 26,790 healthy controls. The most novel finding was that patients with keratoconus were more likely to be diagnosed with depression. Furthermore, keratoconus patients differed from controls on several sociodemographic factors, including source of income, highest level of education achieved, and civil status. Patients diagnosed with keratoconus had a higher risk of allergic rhinitis, asthma, atopic dermatitis and migraine. Finally, keratoconus patients did not have increased mortality after excluding patients diagnosed with Down syndrome.

Data from the registries also showed an increase in the incidence of keratoconus during the last 10–15 years. We largely attributed this increase to more complete registration in the National Patient Register (NPR). We propose that the increased availability of corneal cross-linking has affected referral practices from primary-sector ophthalmologists and likely resulted in more keratoconus patients being referred to the hospital and included in the NPR. In addition, a survey of primary sector ophthalmologists indicated that the registration of keratoconus patients in the NPR is, at present, very close to complete. Together, these results form a solid basis for the continued study of keratoconus incidence and prevalence in Denmark.

In the clinical study, tear fluid, saliva, and plasma were collected from 147 untreated keratoconus patients and compared to those of 60 healthy controls. The analysis showed that keratoconus patients had a significantly lower level of prolactin-induced protein (PIP) in all three fluids compared to the healthy controls, irrespective of age, gender, and keratoconus severity. These changes in these diverse fluids highlights the systemic aspect of keratoconus. The receiver operating characteristic curve analysis showed that PIP levels in tear fluid had the highest ability to discriminate between individuals with and without keratoconus, indicating that PIP levels in tear fluid may be a clinically relevant biomarker for keratoconus.

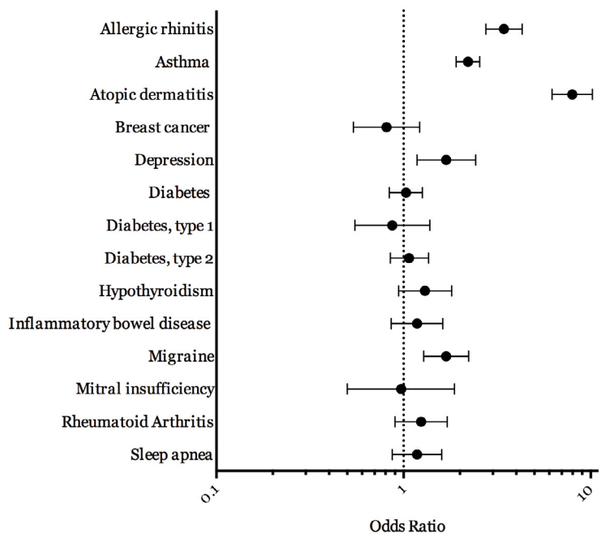

Figure 1. Odds ratios with 95% CI for keratoconus patients being diagnosed with different diseases. Adjusted for ethnicity

Patient-reported outcomes have received increasing attention during the last years, as the doctor's perspective on the success of a treatment is not always shared by patients. However, because there was not yet a validated questionnaire in Danish to study quality of life among keratoconus patients in particular, the study became more methodological and focused on cross-cultural validation of the Keratoconus Outcome Research Questionnaire (KORQ), applying Rasch analysis. The revised Danish KORQ largely fulfilled the Rasch model, though improvements may still be added through future studies.

Key points:

- Danish keratoconus patients displayed higher likelihood of depression, allergic rhinitis, asthma, and atopic dermatitis than controls.
- Prolactin-induced protein (PIP) may be a clinically relevant biomarker for keratoconus.

Remaining questions:

- Further studies to understand the pathophysiology behind the statistical association between keratoconus and other diseases
- Continued studies of developments in the incidence and prevalence of keratoconus in Denmark
- Further optimization of the KORQ to obtain a valid and specific patient reported outcome with which measure to study the impact of keratoconus on quality of life

Articles in the dissertation

1. Bak-Nielsen S, et al. A nationwide population-based study of social demographic factors, associated diseases and mortality of keratoconus patients in Denmark from 1977 to 2015. *Acta Ophthalmol*. 2019;97(5):497-504.
2. Bak-Nielsen S, et al. Incidence and prevalence of keratoconus in Denmark - an update. *Acta Ophthalmol*. 2019;97(8):752-755.
3. Sharif R, Bak-Nielsen S, et al. Prolactin-Induced Protein is a novel biomarker for Keratoconus. *Exp Eye Res*. 2019;179:55-63.
4. Bak-Nielsen S, et al. The Keratoconus Outcome Research Questionnaire: A Cross-Cultural Validation Study of the Danish Version. *Cornea*. 2020;39(8):998-1005.