

The quest for better diagnostics & treatments of dry eye disease



Behzod Tashbayev , PhD,
University of Oslo, Norway
Resident, Department of Ophthalmology,
Region Sörmland, Sweden

On December 18, 2020, Behzod Tashbayev defended his thesis titled "In Search of Diagnostic Markers of Dry Mouth and Dry Eye Disease" at the Institute of Clinical Dentistry, University of Oslo (UiO). The PhD project was conducted at the Institute of Clinical Dentistry, Faculty of Dentistry, UiO, the Norwegian Dry Eye Clinic, and Oslo University Hospital (OUH). The supervisors were Professor Tor Paaske Utheim (UiO, OUH) (main), Professor Janicke Liaen Jensen (UiO), Professor Hilde Galtung (UiO), Xiangjun Chen MD, PhD (UiO), and Sten Raeder MD, PhD (The Norwegian Dry Eye Clinic).

Dry mouth and dry eye disease (DED) are greatly underdiagnosed and undertreated, as both diagnosis and effective management of these conditions are challenging. Dry mouth and DED have not received the attention they deserve, especially considering the high prevalence of these diseases. In this thesis, we aimed to gain a better understanding of dry mouth and DED and, importantly, how these conditions interact. We hoped to pave the path for identifying diagnostic biomarkers in tear film and saliva to contribute to improved diagnosis and treatment of these diseases.

An interdisciplinary approach provided valuable knowledge about both diseases from different perspectives. The subjects studied in this thesis included patients with primary Sjögren's syndrome (pSS), non-Sjögren's syndrome (non-SS) DED, and healthy controls. Overall, six studies were completed using different methodologies, including an evaluation of questionnaires and current diagnostics techniques, metabolomics, and a literature review on a promising new treatment.

This dissertation yielded several conclusions. First, patients with pSS had more severe dry mouth and DED signs than the non-SS group. An interdisciplinary approach can ensure that patients receive need-based treatment. Both patient groups had significantly reduced General Health-Related Quality of Life (GHRQoL) and Oral Health-Related Quality of Life

Key points:

- Patients with dry eye disease (DED), especially non-Sjögren's syndrome, have a significantly reduced quality of life.
- The TearLab osmometer could not accurately predict other parameters of DED.
- In DED diagnosis, the non-invasive measurement of the tear film break-up time could not predict clinical signs of DED in a reference sample of 65-year-olds.
- Metabolomics of the tear film may be important for early detection of biomarkers of DED. Oxidative stress may play a role in the pathophysiology.

(OHRQoL). However, despite having less severe clinical signs, the non-SS group had worse GHRQoL and OHRQoL. In terms of diagnostics, our studies showed that existing methods in the field of dry eye, namely tear osmolarity and non-invasive break-up time (NIBUT), could not accurately predict other parameters of DED. Metabolomic analyses of the tears and saliva showed that patients with evaporative DED had increased levels of certain metabolites including carnitine, spermine, and spermidine. These metabolites have anti-oxidative characteristics, possibly suggesting that oxidative stress may play a role in

evaporative dry eye pathophysiology. Metabolomics may help us understand the pathogenesis of both conditions, which would be important for developing new therapies.

Finally, as a new treatment method of DED, intense pulsed light (IPL) treatment is promising, and future studies could explore its potential for dry mouth treatment. Collectively, this work underlines the importance of interdisciplinary evaluation of patients with dry mouth and dry eye disease, challenges current guidelines in ophthalmology, and points to possibilities for novel diagnostic methods and therapies.

Future directions:

- Optimize settings and expand the indications for intense pulsed light treatment
- Further investigation of tear metabolomics to discover dry eye biomarkers

Articles in the dissertation

1. Tashbayev B, et al. Interdisciplinary, Comprehensive Oral and Ocular Evaluation of Patients with Primary Sjögren's Syndrome. *Sci Rep.* 2017;7 (1):10761
2. Tashbayev B, et al. Patients with non-Sjögren's sicca report poorer general and oral health-related quality of life than patients with Sjögren's syndrome: a cross-sectional study. *Sci Rep.* 2020;10 (1):2063.
3. Tashbayev B, et al. Utility of Tear Osmolarity Measurement in Diagnosis of Dry Eye Disease. *Sci Rep.* 2020;10(1):5542.
4. Tashbayev B, et al. Non-invasive and Fluorescein Tear Film Break-up Time; Comparison and Diagnostic Performance. [manuscript]
5. Tashbayev B., et al. A Pilot Study of Tear and Saliva Metabolomics in Evaporative Dry Eye Disease [manuscript]
6. Tashbayev B, et al. Intense Pulsed Light Treatment in Meibomian Gland Dysfunction: A Concise Review. *Ocul. Surf.* 2020. 18(4): 583-594.