University of South-Eastern Norway
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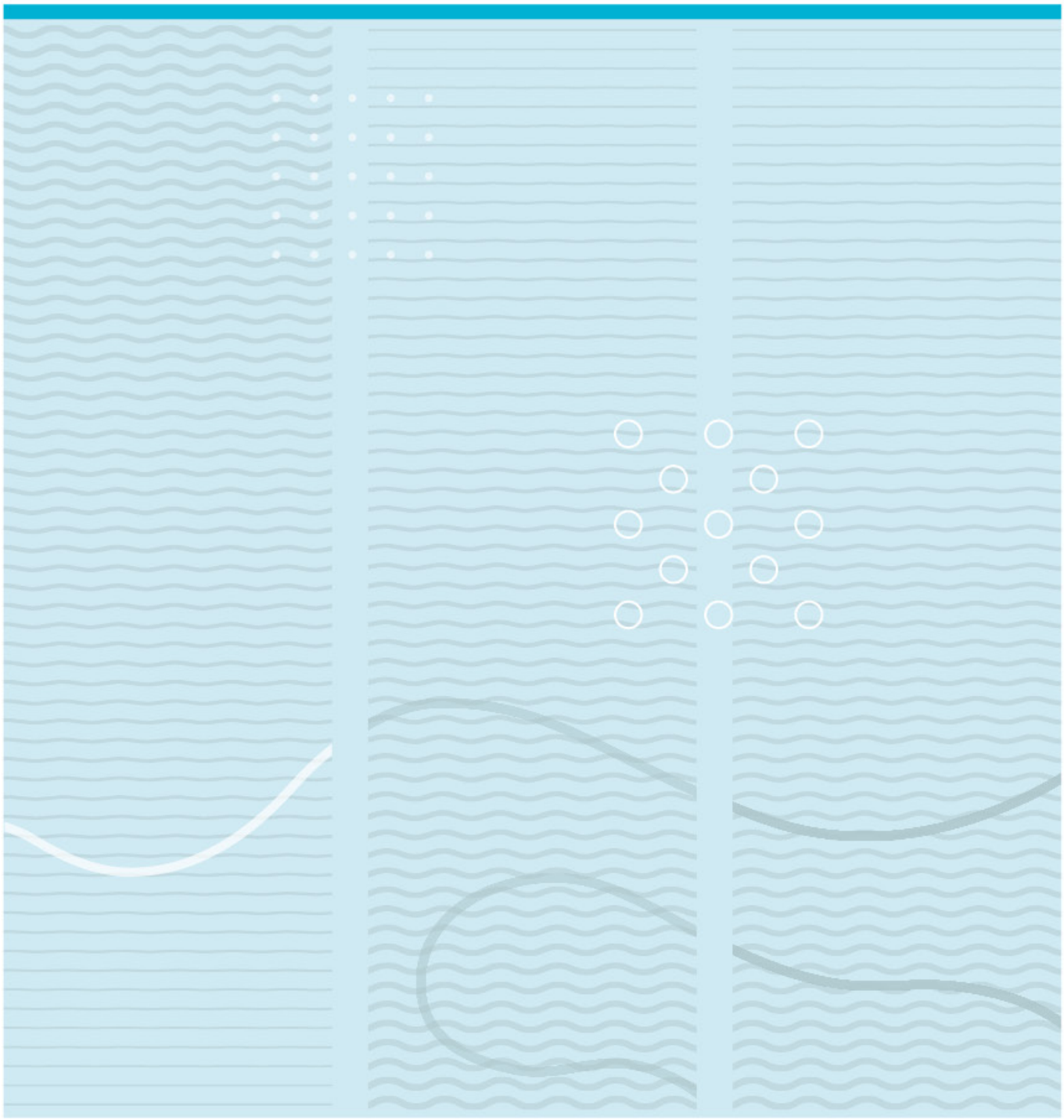
Dry Eye Disease and Visual Quality of Life among Adult Patients seen in a Norwegian Optometric Practice



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This thesis is worth 30 study points

Summary

Purpose

To explore the visual quality of life (VQoL) of patients attending Norwegian optometric practice for a dry eye examination.

Methods

In total 49 patients underwent a thorough dry eye examination at the Norwegian Optometric Clinic Erøy Optikk in the period June - July 2018. The examination included two questionnaires, the Ocular Surface Disease Index (OSDI) and the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) and a range of dry eye tests according to Tear Film & Ocular Surface Society (TFOS) International Dry Eye Workshop 2 (DEWS II) workup scheme. Group differences and associations were analysed using standard parametric and non-parametric statistical tests, a p-value < 0.05 was considered significant.

Results

The patients mean (sd) age was 48 (± 13) years, 29 (59 %) were female. In all, 33 (67 %) had dry eye symptoms (OSDI ≥ 13). Among these, 97 % (n = 32) were diagnosed with DED, of these 41 % had evaporative dry eye (EDE), 34 % had mixed dry eye, 12.5 % had aqueous-deficient dry eye (ADDE), and 12.5 % was unclassifiable. There was no significant difference in the frequency of DED between females and males, and the mean age was not different between patients with and without DED. Reduced score for quality of NEI VFQ-25 general vision (general vision) was moderately correlated with increased dry eye symptoms (OSDI score, $r = - 0.5$, $p < 0.001$); there was no significant difference in the severity of DED symptoms (OSDI) between females and males. Females reported significantly lower on quality of general vision than males, 74 (± 15) versus 84 (± 15) (Wilcoxon's rank sum test, $p = 0.02$). There was strong correlation between NEI VFQ-25 ocular pain score (ocular pain) and dry eye symptoms (OSDI score) ($r = - 0.7$, $p < 0.001$). Moreover, findings of DED were moderately correlated with more ocular pain ($r = - 0.51$, $p < 0.001$). There was no significant difference in ocular pain score between females (68 ± 19) and males (76 ± 22). Twenty-four patients needed some sort of DED treatment; all of them were advised to use artificial tears and/or eye

lubricants, among them, seven patients were started on basic MGD treatment (heat, massage, eyelid-hygiene). Two participants needed referral to ophthalmologist after basic DED treatment.

Conclusion

In this study, patients' VQoL was reduced by DED. Patients with DED experienced more ocular pain and poorer general vision than non-DED patients. These findings suggest that DED and its adverse, negative, effects on VQoL is a public health issue in Norway. We propose that preventing or treating DED is beneficial because it can reduce ocular pain and poor vision, which can be a burden for both the patient and the society, and that DED, should be a subject of sheared-care between optometrists and ophthalmologists. Further studies should explore the prevalence of dry eye in the general population in Norway and the effect of systematic dry eye assessment and treatment in Norwegian optometric practice according to the new diagnostic guidelines given in DEWS II.

Key words: dry eye disease, visual quality of life, ocular pain, NEI VFQ-25

Contents

Number of words: 18173

Foreword

I would like to thank my supervisor Vibeke Sundling for competent and constructive feedback through the process of writing this thesis. I would also like to thank my wife and family for letting me spend so much time digging in to the complexity of dry eye disease and how it effects the lives of my patients. This work has made me a better optometrist and will hopefully inspire other healthcare professionals to learn more about dry eye.

Kristiansand, 20.04.19

Åsmund A. Erøy

Abbreviations

ADDE:	Aqueous Deficient Dry Eye
BCVA:	Best corrected Visual Acuity
DED:	Dry Eye Disease
DEWS:	International Dry Eye Workshop
DEWS II:	International Dry Eye Workshop II
DEQ-5:	Dry Eye Questionnaire
EDE:	Evaporative Dry Eye
ETDRS:	Early Treatment Diabetic Retinopathy Study
FBUT:	Fluorescein Break-up time
FDA:	Food and Drug Administration
HRQoL:	Health-related Quality of Life
KONUS:	Kartlegging og Oftalmologisk Nasjonal Utredning av Framtidig Status [Ophthalmological National Assessment of Future Status]
LogMar:	Logarithm of the Minimum Angle of Resolution
LWE:	Lid Wiper Epitheliopathy
MGD:	Meibomian Gland Dysfunction
NEI VFQ-25:	National Eye Institute 25-Item Visual Function Questionnaire
NEI VFQ-25 general vision:	General vision
NEI VFQ-25 ocular pain:	Ocular pain
NIKBUT:	Non-invasive Keratograph tear-breakup time
NSDE:	Non-Sjögren Syndrome Dry Eye
OSDI:	Ocular Surface Disease Index
PRT:	Phenol Red Thread
QoL:	Quality of Life
REK:	Regional Etisk Komite (the Regional Committee for Medical and Health Research Ethics)
SSDE:	Sjögren Syndrome Dry Eye
TFOS:	Tear Film & Ocular Surface Society
TMH:	Tear Meniscus Height
VQoL:	Visual Quality of Life

1 Introduction

"Dry eye 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" (Jennifer P. Craig et al., 2017). It is one of the most common eye conditions resulting in patients seeking health care (Gayton, 2009). The reported prevalence of dry eye disease (DED) varies from five to 50 % due to application of different definitions and classification criterion of dry eye, as well as regional variations (Stapleton et al., 2017). However, females are more likely to be affected than males and the prevalence of DED increases with age (Stapleton et al., 2017). A recent masters thesis by Ingeborg Sand at the University College of Southeast Norway (2016) found a 28 % prevalence of DED among patients seen in a Norwegian optometric practice (Sand, 2016). Her thesis suggests that better knowledge on the subject among optometrists can raise the quality of the assessment and management to these patients and thereby reduce the number of referrals to ophthalmologists.

In the field of dry eye research, a lot of work has been done the last years to define and establish common diagnosis criterion. The Tear Film & Ocular Surface Society (TFOS) has greatly contributed in this matter. TFOS is a non-profit organization founded to facilitate and advance ophthalmological research, stimulate interactions among members and promote understanding mainly on aspects of the tear film and ocular surface (A. G. Sullivan, 2019). TFOS published their first report in 2007; the 2007 report of the International Dry Eye Workshop (DEWS) (DEWS, 2007). It was followed by; the International Workshop on Meibomian Gland Dysfunction in 2011 (Kelly K. Nichols et al., 2011), and the International Workshop on Contact Lens Discomfort in 2013 (J. J. Nichols et al., 2013). Based on this work, the extensive Dry Eye Workshop II (DEWS II) was published on July 21, 2017 (J. P. Craig et al., 2017). DEWS II involved 150 clinical and basic research experts from 23 countries, and strived through a transparent and evidence-based approach to create a new consensus on several aspects of DED (Nelson et al., 2017). DEWS II updated and refined the definition of DED, included a new classification system, suggested new test procedures, updated the list of preferred instrumentation and renewed the management and treatment advices on DED.

1.1 Dry Eye Disease and Visual Quality of Life

The definition of the term "Quality of life" (QoL) is debated and has been subject to conceptual confusion among researchers (Post, 2014). It has many meanings, and there is no universally accepted definition of QoL (Lavdaniti & Tsitsis, 2015). The terms QoL and Health-Related Quality of Life (HRQoL) are used interchangeably and are commonly known to refer to well-being and ability to function in daily life. QoL measurements are recognized as important in health care to inform patient management and political decisions (Guyatt, Feeny, & Patrick, 1993). It is an important part of health care to investigate how chronic diseases affects patients' QoL. In a QoL article, it is recommended to have a definition of QoL that fits the topic of the study precisely (Post, 2014). Visual Quality of Life (VQoL) is a more specific term describing how visual symptoms and visual impairment affects different generic health domains (Mangione et al., 2001). Chronic diseases in general have a negative effect on mental health, mood and sleep. The pain associated with conditions like diabetes, cancer and cardiovascular diseases are known to deteriorate peoples QoL (Fine, 2011). Studies have found that vision related difficulties could lead to decreased QoL (Finger et al., 2011) and available evidence suggests that DED reduces peoples overall QoL (Stapleton et al., 2017). Studies investigating the effect of DED on VQoL have been performed in the US (Miljanović, Dana, Sullivan, & Schaumberg, 2007) and China (Li, Gong, Chapin, & Zhu, 2012), and Norway (Espelid, 2018). Patients with DED are more likely to report reading difficulties, reduced ability to carry out specific work tasks, using a computer, watching television, driving at day and at night (Miljanović et al., 2007). DED is found to markedly reduce both workplace and non-job related performance (Kelly K. Nichols et al., 2016). Studies confirms a possible correlation between DED and poor mental health, but the exact underlying mechanisms remains unclear (Stapleton et al., 2017). People with DED might avoid places and situations that can trigger their problems, the pain might have psychological and social impacts, and the cost of the treatment can possibly affect their social life. A British study found that patient with severe DED reported it to have nearly the same relative impact on their lives as with dialysis and severe angina (Buchholz et al., 2006). A recent masters thesis by Isabel Espelid at the University of Oslo (2018) assessing QoL in a cohort of DED patients found dry eye symptoms to have substantial effect on QoL (Espelid, 2018).

1.2 Function and biophysical aspects of the tear film

The preocular tear film is the absolute border between the cornea and the external environment. A well functioning tear film forms the primary refractive surface of the eye and it nourishes, protects and moisturizes the cornea. The tear film is an important part of the ocular surface defence mechanism (Bergmanson, 2014), and a stable preocular tear film is a hallmark of ocular health (Willcox et al., 2017). The tear film contains several substances including, proteins, lipids, mucins and electrolytes which all interact to preserve and maintain clear, stable and comfortable vision. The exact interaction between the components is still an object to further research (Willcox et al., 2017).

The precorneal tear film is 2 - 5.5 μm thin (Willcox et al., 2017). It has traditionally been viewed as a three layered model, with an inner mucin layer, an aqueous middle layer and a lipid layer on top (Bergmanson, 2014), but the TFOS DEWS II report suggests that a two layered model is preferred (Willcox et al., 2017). The new model consists of a mucoaqueous inner gel layer, which is partially integrated with an outer lipid layer. The aqueous part of the tear film is produced in the glandula lacrimalis, lipids are extracted with every blink by approximately 35 superior and 25 inferior meibomian glands in the eyelids, and mucin is produced both in the conjunctival goblet cells and glandula lacrimalis (Bergmanson, 2014).

The eyelids distributes the tear film over the ocular surface, wipes away debris, pathogens, allergens, irritants and leads excess tears towards the superior and inferior punctae, where the tears eventually are drained down the pharynx via the canaliculi lacrimalis. The tear film tends to "break-up" or collapse in less than 30 seconds, and needs to be re-established and re-distributed by blinking. In dry eye disease, this break-up time tends to be reduced, mainly because of excessive tear film evaporation, and rapid appearance of regions of localized drying is considered as evidence for tear film disorders (Willcox et al., 2017). Delayed blinking has been linked to higher order aberrations, and reduced tear break-up time is associated with poor optical quality and reduced visual performance in dry eye patients (Liu, Thibos, Begley, & Bradley, 2010).

The transmembrane mucins attached to the epithelial corneal cells make the ocular surface hydrophilic and help the tear film to spread evenly across the surface. The role of the mucoaqueous layer is still a subject to research, but its known to deliver antimicrobial peptides, proteins, and immunoglobulin to the ocular surface that protects the eye from infection, in addition to delivering oxygen, metabolites and electrolytes to the cornea (Willcox et al., 2017). The outer, preocular lipid layer helps the tear film to withstand evaporation by lowering the surface tension.

1.3 Dry eye disease and pain

Reduced tear secretion in DED leaves the corneal epithelium exposed to environmental conditions and can lead to ocular surface inflammation, and damage to the peripheral nerves (Belmonte et al., 2017). The corneal sensory neurons can be sensitized by the ocular surface injury, and cause a sensation of pain to the dry eye patient. Pain is subdivided into nociceptive and neuropathic pain. Nociceptive pain occurs as a response to tissue damage. Neuropathic pain occurs due to lesions within the somatosensory nervous system (Belmonte et al., 2017). Our understanding of ocular pain has evolved, and has parallels to pain in general, which was initially recognized as one of the signs of inflammation (dolor). Ocular pain can have psychological and physical impacts, and the ocular blur caused by DED can affect peoples ability to read, drive, watch TV, and operate smart phones (Stapleton et al., 2017). DED is therefore suggested to impact the social life and the physical and mental health of the public, and thereby reducing peoples QoL (Schiffman et al., 2003).

1.4 Symptoms and diagnosing

1.4.1 Clinical tests and diagnosis

To make the DED diagnose there has to be both dry eye symptoms, confirmed with the Dry Eye Questionnaire (DEQ-5) or the Ocular Surface Disease Index (OSDI) questionnaire, and at least one positive test result of disruption of the tear film homeostasis, defined by non-invasive Keratograph tear-breakup time (NIKBUT), osmolarity or staining (Wolffsohn et al., 2017). Figure 1 shows the DEWS II diagnostic test battery and procedure.

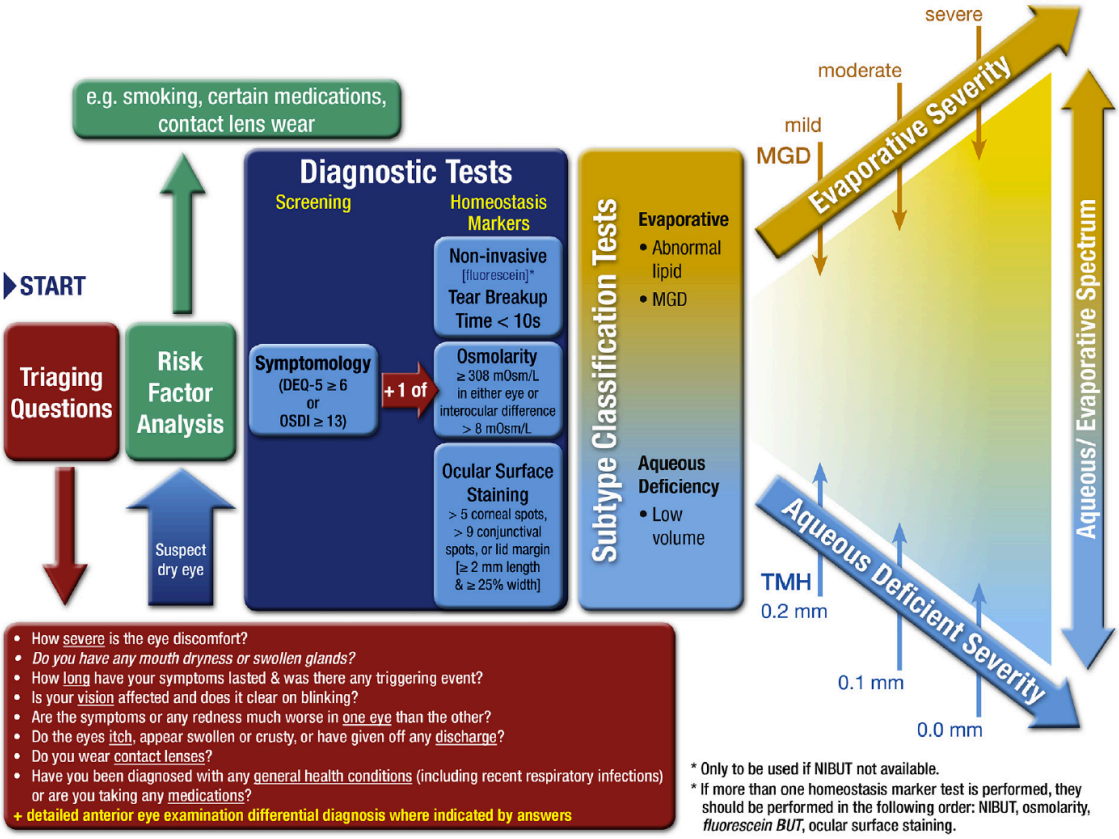

Figure 1. DED diagnostic test battery. Retrieved from TFOS DEWS II Diagnostic Methodology report. The ocular surface, 15(3), 539-574. doi:10.1016/j.jtos.2017.05.001, by Wolffsohn, J. S., Arita, R., Chalmers, R., Djalilian, A., Dogru, M., Dumbleton, K., . . . Craig, J. P. (2017).

According to the new diagnostic recommendations in DEWS II (Wolffsohn et al., 2017), the symptom screening with DEQ-5 or the OSDI, indicates that the patient may have DED, and a procedure of clinical diagnostic testing can start. The questionnaires are also important in monitoring DED treatment or progression of the disease. OSDI is a 12-item questionnaire developed to measure ocular irritation and its effect on vision-related function (Allergan). It provides a fast assessment and grading of the severity of symptoms associated with dry eye. It has been used in several dry eye studies, and is validated (Schiffman, Christianson, Jacobsen, Hirsch, & Reis, 2000). DED is diagnosed by dry eye symptoms (OSDI ≥ 13) and a positive test result for one of the three clinical diagnostic tests (NIKBUT, osmolarity or staining). If there are symptoms of DED but no clinical signs or vice versa, DED is not the diagnosis (Wolffsohn et al., 2017).

1.4.2 Differential diagnosis

Other ocular surface diseases must be ruled out. One must also be aware of possible co-morbidity and the complexity of interactions between different ocular surface conditions and secondary dry eye (Jennifer P. Craig et al., 2017). Examples of conditions that can mimic the signs and symptoms of DED are: allergic conjunctivitis, giant papillary conjunctivitis (GPC), atopic keratoconjunctivitis, vernal keratoconjunctivitis, viral keratoconjunctivitis, bacterial conjunctivitis, anterior blepharitis, demodex, parasitic infections, corneal and conjunctival abnormalities, filamentary and other keratitis and keratopathies, rheumatological conditions, lid related disease, visual asthenopia, graft versus host disease, contact lenses, psychological factors and neuropathic pain (symptoms without signs) (Wolffsohn et al., 2017).

1.5 Risk factors

The tear film is influenced by lifestyle, environmental exposures, and conditions like connective tissue disease, metabolic diseases, and ocular diseases. The list of modifiable and non-modifiable risk factors is extensive, but we have to keep in mind that the exact understanding of the different factors is limited due to different methodologies and different diagnostic criteria used in different studies (Stapleton et al., 2017). Knowing the risk factors of DED can help us provide targeted and effective prevention and treatment of the disease. The following risk factors are listed in the TFOS DEWS II report: age, sex, race, meibomian gland dysfunction (MGD), allergy, alcohol intake, smoking, caffeine intake, computer use, diet, nutritional factors, uncorrected refractive errors, certain groups of systemic and topical medications (antihistamines, diuretics, antidepressants, antipsychotics, anxiolytics, oral beta blockers, cholinergic drugs, oral diuretics, preservatives and oral contraceptive use), environmental exposures, lifestyle factors, socioeconomic status, hematopoietic stem cell transplantation, hormone replacement therapy, pregnancy, menopause and ovarian dysfunction/menstrual irregularity, Sjögren syndrome, radiotherapy, chemotherapy, pseudoexfoliation, pterygium, eye makeup, contact lens wear, ocular surgery including cataract surgery, refractive surgery, keratoplasty, botulinum toxin use, Demodex infestation, diabetes, autoimmune disease, cardiovascular disease, hepatitis B and C infection, Herpes Simplex virus infection, human immunodeficiency virus infection, human T-cell

lymphotropic virus infection, Epstein-Barr virus infection, rosacea, gout, sarcoidosis, thyroid disease, anxiety, psychiatric disease, chronic pain, migraine, post-traumatic stress disorder, depression, and sleep disorder (Stapleton et al., 2017).

1.6 Classification and etiopathogenesis

DED is divided into two subtypes: evaporative dry eye (EDE), and aqueous deficient dry eye (ADDE). The specific subtype of DED is found based on assessment of the meibomian glands and the lipid layer, and measurement of the tear-volume, in addition to the specific diagnostic tests (NIKBUT, osmolarity or staining). Figure 1 and 2 shows the classification of DED.

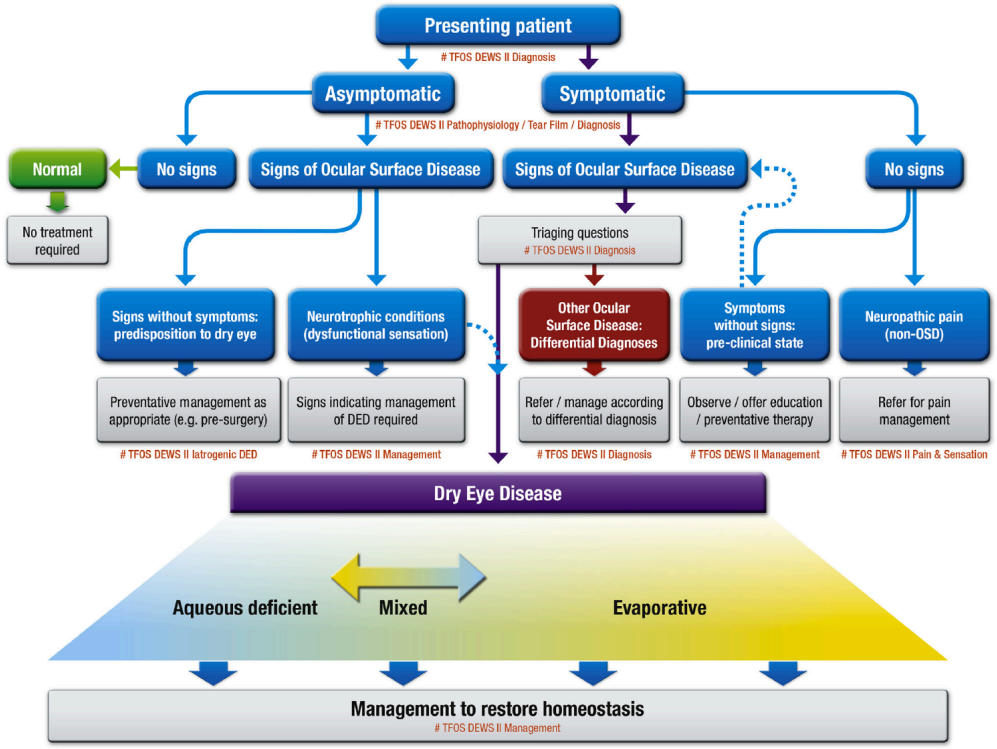

Figure 2 Classification of dry eye disease (DED). Retrieved from TFOS DEWS II Diagnostic Methodology report. The ocular surface, 15(3), 539-574. doi:10.1016/j.jtos.2017.05.001, by Wolffsohn, J. S., Arita, R., Chalmers, R., Djalilian, A., Dogru, M., Dumbleton, K., . . . Craig, J. P. (2017).

The TFOS DEWS II report recommends that the term EDE and ADDE are used to describe the initiating basis of a dry eye but emphasises that with progression any form of DED may take on additional evaporative features (Bron et al., 2017). The two types are not mutually exclusive, and they both result in disturbance of homeostasis and hyperosmolarity (Stapleton et al., 2017). MGD is known to be the leading cause of EDE

(Blackie et al., 2010), and EDE is the most common form of DED (Lemp, Crews, Bron, Foulks, & Sullivan, 2012). Subtyping of DED should be considered to guide treatment of DED (Wolffsohn et al., 2017). ADDE is divided into two subgroups: Sjögren syndrome-dry eye (SSDE), and non-Sjögren syndrome dry eye (NSSDE). TFOS DEWS II also acknowledges the possibility of having signs without symptoms and vice versa, by including neurosensory abnormalities. Figure 1 shows the DEWS II guide for diagnosis and treatment of DED based on presenting features.

1.6.1 Evaporative Dry Eye

EDE is a subtype of DED predominantly caused by excessive evaporation of the tear film, which leads to hyperosmolarity and loss of homeostasis of the tear film. The lacrimal function is normal in EDE (Bron et al., 2017). The main cause of EDE is lid-related, e.g. MGD and incomplete blinking, but it can also be mucin and contact lens related (Jennifer P. Craig et al., 2017). It all leads to a dysfunctional lipid layer. EDE is three times more likely to cause DED than ADDE (Lemp et al., 2012) and it is therefore suggested that DED is mainly evaporative in nature.

1.6.2 Aqueous-Deficient Dry Eye

ADDE is a subtype of DED where the tear evaporation is normal, but the lacrimal function is reduced with resulting hyperosmolarity (Bron et al., 2017). Moreover, the reduced thickness of the tear film may disturb the spreading of lipid and cause a secondary functional EDE. ADDE is subdivided into SSDE and NSSDE. Sjögren syndrome is a chronic, autoimmune disorder characterized by lymphocytic infiltration and dysregulation of the immune system that causes a self-destruction of the exocrine glands including the lacrimal gland. SSDE includes both acquired and congenital forms. NSSDE is mostly age-related or caused by inflammation or obstruction of the lacrimal gland. It can also be due to blockages in the afferent or efferent nervous tear reflex, or caused by other disorders such as pseudoexfoliation and diabetes mellitus (Bron et al., 2017). Acquired tear reflex abnormality might be secondary to lid surgery, refractive surgery or chemical injuries.

1.6.3 The vicious Circle of Dry Eye

The term "vicious circle" can be used to describe the complex pathogenesis of DED (Baudouin et al., 2016), where a multitude of factors interacts and leads to a loss of homeostasis of the tear film accompanied by ocular symptoms. Blink- and eyelid abnormalities as well as defects of the ocular surface, or deficiencies in the tear composition, and volume of tears can initiate the circle. The water loss causes hyperosmolarity, and tissue damage. These changes leads to a damaging cascade of inflammation, reduced ocular surface wettability and lowered tear film break-up time that further accelerates the level of hyperosmolarity (Bron et al., 2017). Water loss is the key feature of any type of DED, and any unfavorable external condition like airflow, ambient humidity, temperature, blink interval, globe prominence or lid aperture may enhance or trigger DED.

1.7 Norwegian eye health care and dry eye disease

The Norwegian eye care system consists of ~ 1500 optometrists, ~ 350 ophthalmologists and ~ 40 othoptists (Lundmark & Luraas, 2017). The KONUS (Kartlegging og Oftalmologisk Nasjonal Utredning av Framtidig Status [Ophthalmological National Assessment of Future Status]) report from 2012 finds Norwegian ophthalmology to be unsustainable (Skau & Norsk oftalmologisk, 2012). The report surveyed the status of Norwegian ophthalmology, its capacity, production, future demographic challenges and the Norwegian eye-healthcare in special, and found the capacity of Norwegian ophthalmologists to be under great pressure. Based on predicted, future, demographic changes with an aging population and increasing demand for primary eye care, the KONUS report expects a 76 % increase in consultations by ophthalmologists by 2030 (Skau & Norsk oftalmologisk, 2012). Norwegian optometrists, scattered around in almost every Norwegian municipality, are the major providers of primary eye healthcare services in Norway (Lundmark & Luraas, 2017). The lack of capacity in the Norwegian specialist eye-care services implicates an enhanced role of Norwegian optometrists. Pre-clinical, and less severe forms of DED, not in demand of prescription based medications, can be diagnosed, treated and followed up by optometrists. DED should be considered an issue of sheared-care between optometrists and ophthalmologists.

Age is one of the major risk factor for DED (Stapleton et al., 2017), and the Norwegian population is ageing (Lundmark & Luraas, 2017), we can therefore assume that the prevalence of DED in Norway is rising. Among the goals of the Coordination Reform (2010), patients in Norway, among them patients suffering from DED, should get treatment as fast as possible, as close to their local community as possible, from qualified health personal. The health care service should target sustainability, coordination between the health professions and promote prevention of disease. It is therefore interesting to investigate the role of the optometrists in dry eye and question if the optometrists are qualified and able to contribute in the prevention, diagnosing and treatment of DED. If optometrists, to a greater extent, could help the predicted increasing amount of Norwegian DED patients, it would free resources among ophthalmologists.

1.8 Aims and objectives

The aim of this study is to explore the VQoL of patients attending a dry eye examination in a Norwegian optometric practice and the association between DED, MGD and VQoL with respect to general vision and ocular pain. Moreover, the study will estimate the number of patients with dry eye symptoms examined in optometric practice that needs DED or MGD treatment and the number of DED patients that needs referral to ophthalmologist.

The study is relevant due to socio-economic matters. Increased competence about dry eye among optometrists can reduce the number of referrals to ophthalmologists. Our study investigates the positive potential in sheared-care between optometrists and ophthalmologists in DED. If more patients could get targeted help by optometrists in the primary health care system, this could free resources among Norwegian ophthalmologists in the specialist healthcare services.

2 Methods

2.1 Study design

The study had an observational prospective, cross-sectional design. A cross-sectional design provides a snapshot for comparison of population groups at a single point in time, providing information on frequency of symptoms of dry eye, DED and MGD. Moreover, the design allows comparison of many different variables at the same time, such as between VQoL and DED, MGD, age and gender. However, the design does not provide definite information about cause-and-effect. The study was carried out through questionnaires and different clinical tests.

2.2 Study subjects

2.2.1 Study population

The study population was all adult men and women attending a Norwegian optometric practice for an eye examination.

2.2.2 Study sample

The study sample included all men and woman between 18 and 70 years having a standard eye examination at Erøy Optikk in the period from 01 April 2018 to 05 July 2018, and persons who made contact with Erøy Optikk after seeing the invitation on Facebook or Instagram.

2.2.3 Recruitment

All men and woman between 18 and 70 years having a standard eye examination at Erøy Optikk got information about the study, and were orally invited to participate in the study (n = 37). Persons both with and without dry eye symptoms and/or ocular discomfort were eligible to participate. Participants were also recruited through a campaign on Facebook and Instagram (n = 13). A Facebook advertisement with information about the study and invitation to join was promoted to inhabitants in Vest Agder County. A specific appointment was made for the dry eye examination. One participant recruited through Facebook and Instagram was excluded according to

lacking abilities to read and understand the questionnaires. In all 49 subjects participated in the study, 37 recruited among persons having an eye examination and 12 through social medias. The size of the sample met the requirement for detecting a difference in mean VQoL score between patients with and without DED.

2.2.4 Size of sample

The sample size, n = 40 was calculated with a sample size calculator (Glaziou, 2005) to be able to detect a difference in mean score general vision on the NEI VFQ-25 questionnaire (Mangione et al., 2001) between patients with dry eye symptoms (69 ± 12) (Le et al., 2012) and patients without dry eye symptoms (83 ± 12) (Mangione et al., 2001) with a precision (alpha) of 5 % and power of 90 %.

2.3 Data collection

All data was collected between 08 June and 05 July 2018. At the day of the data collection, patients with known dry eye symptoms, already undergoing treatment was instructed not no use any eye-drops, contact lens wearers was instructed not to wear their lenses, and no make-up should be worn. Patients were instructed to meet five minutes before the appointment and to bring prescription glasses and a list of their medicines. Initially all patients got a written information form (appendix 1) and an informed consent form (appendix 2), and had the opportunity to ask questions. Then they filled in two questionnaires: 1) NEI VFQ-25 (Mangione et al., 2001), (appendix 3) and 2) OSDI (Schiffman et al., 2000), (appendix 4). Patients were prompted to read the instructions and mark out the answers most appropriate for them.

2.3.1 National Eye Institute Visual Function Questionnaire-25

NEI VFQ-25 is a generic, non-disease specific, vision related QoL questionnaire. It was developed to measure the self-reported vision-related health status most important for persons with chronic eye diseases, and measures how certain visual symptoms and visual disabilities affects different visual domains (Mangione, 2000). The NEI VFQ-25 questionnaire has been used in several clinical studies across a number of chronic ocular conditions, and is validated (Mangione et al., 2001). NEI VFQ-25 has been translated to Norwegian, distributed by Mapi research trust (MAPI, 2019), (appendix 3).

The Norwegian translation is to my knowledge not yet validated (Schippert, Jelin, Moe, Heiberg, & Grov, 2018). The form consists of 26 questions; 25 items directly vision-targeted and one single item about general health. The questionnaire is divided into three parts concerning 1) general health and vision, 2) difficulties with activities and 3) responses to vision problems. Part 1 consists of 4 questions, with answers scored on a 5 - point scale, except question two, which is scored on a 6 - point scale. Part 2 has 13 questions scored on a 6 - point scale except question 15 (c) which is scored on a 4 - point scale. Part 3 consists of nine questions, each scored on a 5 - point scale. The scales describe how VQoL are affected by vision. The three parts are further divided into 11 vision targeted sub-scales concerning global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and colour vision, and ocular pain. Patients are asked to mark out the answer most likely to describe their situation. If the patient uses glasses or contact lenses, he/she is supposed to answer as if they used their prescription (Mangione et al., 2001).

2.3.2 Ocular Surface Disease Index

OSDI is a 12-item questionnaire developed to measure ocular irritation and its effect on vision-related function (Allergan). It provides a fast assessment and grading of the severity of symptoms associated with dry eye. It has been used in several dry eye studies, and is validated (Schiffman et al., 2000). The Norwegian translation is being validated (Sundling, personal communication), (appendix 4). The 12 questions are divided into three subgroups concerning ocular symptoms, visual function and environmental factors. Patients are asked to rate how often a specific symptom or difficulty has occurred the last week on a 5 - point -scale from 0 – 4, where 0 is never and 4 is all the time.

2.3.3 Sequence of tests

The clinical diagnostic tests was performed in the following order: 1) tear osmolarity, 2) best corrected visual acuity (BCVA), 3) tear meniscus height (TMH), 4) non-invasive keratograph break-up time (NIKBUT), 5) bulbar redness, limbal redness, 6) slit-lamp

examination of the external eye, 7) fluorescein break-up time (FBUT), 8) ocular surface fluorescein staining, 9) ocular surface lissamine green staining, 10) lid-wiper epitheliopathy (LWE), 11) phenol red-thread (PRT), 12) meibum expressibility, 13) meibum quality and 14) meibography of the superior lid. The sequence of tests was chosen according to the National Centre for Optics, Vision and Eye care protocol for dry eye assessment (USN, 2017), and based on the recommendations given in the TFOS DEWS II report (Wolffsohn et al., 2017).

2.3.4 Test procedure and technique

2.3.4.1 Osmolarity

Tear osmolarity was measured with I-PEN (I-MED Pharma Inc.). The device is new on the market and has been validated only in minor studies (Chan, Borovik, Hofman, Gulliver, & Rocha, 2018). The I-PEN measures the tear film osmolarity quantitatively, directly from the tear volume on the surface of the inferior, lateral conjunctiva. The test pen is loaded with a single-use sensor, one for each eye. The test was performed with the patient sitting in the test chair. The right eye was measured first by gently pulling down the lower eyelid, instructing the patient to look up and left. While holding the device at a 45-degree angle, the tip of the I-PEN was gently placed on to the lower conjunctiva, slightly depressing the surface. The same procedure was repeated for the left eye with the patient looking in the opposite direction. An audible beep was heard when the measurement was completed. Osmolarity ≥ 308 mOsm/L or an intraocular difference > 8 mOsm/L was defined as a positive diagnostic finding of dry eye. The value is a validated and widely used criteria for dry eye (Wolffsohn et al., 2017).

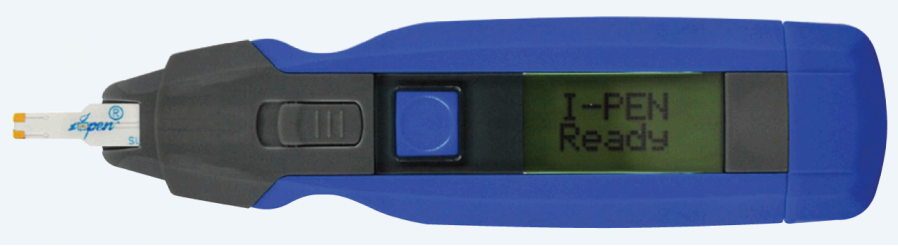

Figure 2 I-PEN, retrieved from https://imedpharma.com/diagnostic-tools/tear-osmolarity/, access date 24.02.19

2.3.4.2 Visual Acuity

BCVA, logarithm of the minimum angle of resolution (logMar), was measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart on a Topcon CC 100 XP digital LED, LCD screen, registered with one decimal on a continuous scale. Viewing distance was 3.80 meters and the size of the letters was calibrated according to the manufacturers instructions. The room was lit up with two Glamox C90-R, 60 cm X 60 cm ceiling mounted LED fixtures, colour temperature 4000 Kelvin, colour-rendering (Ra) > 80. Visual acuity was noted based on the logMar formula: logMar = Baseline acuity + (0.02 * the number of missed letters or letters not read). Baseline acuity was defined as the lowest line where the test person was able to read at least one letter correctly (Bailey & Lovie-Kitchin, 2013). The BCVA was measured both in the right eye, the left eye, and binocular.

2.3.4.3 Tear meniscus height

TMH was measured with a Keratograph® 5M (Oculus, Optikgeräte, GmbH, Wetzlar, Germany), infrared illumination module, 1.0 magnification, low aperture. The patient was seated in front of the device with the chin in the chinrest, focusing on the light in the centre of the device. One measurement was made perpendicular to the centre of the cornea. A TMH < 0.1 mm was considered a positive finding of dry eye(Mainstone, Bruce, & Golding, 1996). The TMH was used to guide sub-classification of DED. Lower values indicates a more predominantly aqueous deficient type of DED (Wolffsohn et al., 2017).

2.3.4.4 Non-invasive Keratograph break-up time

NIKBUT was measured with the Keratograph® 5M, infrared illumination. The patient was seated in front of the device with the chin in the chinrest, focusing on the light in the centre of the device. Thereafter the patient was instructed to blink gently twice according to the devices built-in instructions, and then to keep the eye open as long as possible. The Keratograph® 5M measures the time from the last blink until the first tear film break-up, and calculates the average break-up time of all break-up incidents. The "break-up average " time was noted, not the "break-up first" time. The procedure was repeated three times, and the sum of the measurements was averaged. If the patient

did not blink or the tear film did not break during 23 seconds (maximum test duration), 23 seconds was noted as break-up time. If the patient blinked before the first break-up appeared, the time between the last and the first blink was noted. NIKBUT ≤ 10 seconds was considered indicative of DED (Wolffsohn et al., 2017).

2.3.4.5 Observation of the external eye

The external eye was observed through a Keeler Symphony® (Keeler Ophthalmic Instruments, Windsor, UK) slit-lamp with respect to morphological changes. Any pathology in upper and lower eyelids observed was noted and commented with respect to positive or negative findings of: ectropion, entropion, trichiasis, eyelid tumor, and anterior blepharitis. Findings of blepharitis were graded from 0 – 4 with the Efron grading scale (Efron, Morgan, & Katsara, 2001). Zero indicating pale lid margins, clean lashes and visible meibomian glad orifices, and four indicating severe telangiectasis, yellow crusting, lashes stuck together and skin irritations. The nasal and temporal conjunctival and limbal redness was assessed and graded with the Keratograph® 5M´s internal software, bulbar redness module. The redness was graded on a 5-point scale from 0 – 4, zero indicating no findings and four indicating severe, diffuse injections (Sickenberger, 2010).

2.3.4.6 Fluorescein break-up time

FBUT was observed with 10 X magnification through the slit-lamp using cobalt blue light and yellow filter. Fluorescein from a saline moistened pre-impregnated fluorescein strips (Fluo GP, Pro Cornea) was installed into the inferior, lateral fornix with the patient sitting behind the slit-lamp. One single drop of saline was used to release the dye and any excess fluid was gently shaken off; the same strip was used for both eyes. FBUT was measured 30 seconds after instillation of fluorescein. The patient was instructed to blink three times, and then cease blinking for as long as possible or instructed otherwise. The time from the last blink until the first dry spot occurred was measured in seconds using an iPhone. The FBUT was measured three times for each eye and the mean score was calculated (Johnson & Murphy, 2007). A value ≤ 10 seconds was considered a positive finding of dry eye disease (Wolffsohn et al., 2017). Forty-five seconds were noted if the patient had no visible break-up and did not blink within 45

seconds. If the patient blinked before the first break-up appeared, the time between the last and the first blink was noted.

2.3.4.7 Ocular surface damage

The ocular surface damage was assessed according to the recommendations in DEWS II; corneal damage with fluorescein, and conjunctival damage and lid wiper epitheliopathy with lissamine green (Wolffsohn et al., 2017). The corneal fluorescein staining was assessed directly after FBUT measurements, observed through the slit-lamp using cobalt blue light and yellow filter, 16 X magnification. The nasal and temporal conjunctival lissamine green staining was observed through the slit-lamp using white light, no filter, and 16 X magnification. Saline moistened pre-impregnated lissamine green strips (Green Glo, AMWO), was installed into the inferior, lateral fornix with the patient sitting behind the slit-lamp. One drop of saline was used to release the dye; the same strip was used for both eyes. The lissamine green staining was assessed tree minutes after instillation. LWE was observed directly after the conjunctival lissamine green staining through the slit-lamp, the right eye first. The upper eyelids were everted and a positive score for dry eye disease was given with LWE of ≥ 2 mm in length and/or ≥ 25 % sagittal width excluding the line of Marx (Korb et al., 2005). Both fluorescein and lissamine green staining was graded according to the Oxford grading scheme (Bron AJ, 2003). It is a picture based grading system where the visible part of the anterior eye is divided into three zones: temporal conjunctiva, cornea and nasal conjunctiva. Each zone is graded according to a 6 - point scale from 0 – 5, zero represents absence of staining, and five represents severe staining. The sum of the three panels is added and gives a possible total score ranging from 0 – 15. DEWS II does not utilize the Oxford grading system, but considers more than five corneal spots of fluorescein staining and/or more than nine conjunctival spots of lissamine green as a positive diagnostic finding (Wolffsohn et al., 2017). The transition between these two systems was made by considering an Oxford staining score ≥ grade 1 to be corresponding with the DEWS II diagnostic numbers of staining spots. An overall positive diagnostic staining score for dry eye disease was given if there was positive results in one or more of the three described ocular surface damage markers (Wolffsohn et al., 2017).

2.3.4.8 Tear volume

The volume of tears was assessed with the PRT-test (PRT-test, AMWO). The folded end of the thread was hooked within the temporal one-third of the eyelid margin for 20 seconds. The test was performed with eyes closed (Doughty, Whyte, & Li, 2007). The red, moistened part of the thread, without the folded end, was measured in mm, and values < 10 mm was considered a positive finding of dry eye disease (H. Pult, Purslow, & Murphy, 2011).

2.3.4.9 Meibomian gland expressibility

The expressibility of the five most central meibomian glands on the lower eyelid was assessed by applying firm pressure with a Q-tip, and evaluation of the expression through the slit-lamp using 16 X magnification. The number of glands with expressed meibum was registered and scored on a scale from 0 – 3. The grade was defined as: grade 0 for 5 glands expressible, grade 1 for 3 – 4 glands expressible, grade 2 for 1 – 2 glands expressible and grade 3 when 0 glands were expressible (Tomlinson et al., 2011).

2.3.4.10 Meibomian gland quality

At the same time as the expressibility was evaluated, the quality of the expressed meibum from each of the central eight glands on the lower eyelid was assessed and scored on a scale from 0 – 3, according to the grading scheme for meibum quality (Tomlinson et al., 2011). The grade was defined as grade 0 for clear fluid, grade 1 for cloudy fluid, grade 2 for cloudy, particulate fluid and grade 3 when the fluid was like toothpaste. The score from each of the central eight glands was summarized (0 – 24), and gave a possible maximum expressibility score of 24.

2.3.4.11 Meibomian gland dropout

The level of meibomian gland dropout in upper eyelid was assessed and quantified using Keratograph® 5M, "meibo-scan" module. The patient was seated in front of the device with the chin in the chinrest and the upper eyelid was everted. A single meibography picture was taken. The Keratograph® 5M make use of infrared illumination to perform the meibography. The area of loss was compared to and graded according to images on the meiboscale which ranges from 0 – 4, where zero indicates no loss and four indicates more than 75 % loss (H. H. Pult, Riede-Pult, & Nichols, 2012).

2.4 Data registration

Test results were consecutively noted by hand on a registration form (appendix 5). The project manager manually entered raw data from the registration forms and the questionnaires into separate Excel 2016 (Microsoft Office) spreadsheets. All data were controlled by visual inspection as regards to biases, to ensure optimal quality of the material. Unrealistic values were checked by looking at outliers and treated as missing if still considered unrealistic. Punching errors were not counted, but consecutively corrected. Missing values in the Excel 2016 (Microsoft Office) spreadsheet was automatically detected and coded "NA" by algorithms in Excel.

2.5 Statistical analysis

Total OSDI score was calculated in Excel 2016 (Microsoft Office), according to the OSDI manual (Schiffman et al., 2000) (appendix 6). A score for each of the three subgroups was calculated by adding the sum of scores for the questions answered. The subtotal score for the subgroups was added and multiplied by 25, then divided by the number of questions answered. The total score ranged from 0 - 100, with a higher number indicating more severe symptoms. NEI VFQ-25 score was calculated in Excel 2016 (Microsoft Office) in a two-step process according to the NEI VFQ-25 manual (appendix 7). Numeric values from the questionnaire was re-coded and the items was further converted to a 0 - 100 scale according to given scoring rules in the manual, a higher score representing better function. Then 12 sub-scale scores were calculated by averaging together the specific items for the particular scale. The subscales are: general health, general vision, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and colour vision, and ocular pain. This study only applied the general vision and the ocular pain sub-score in the analyses. MGD was defined according to the recommendations of the MGD workshop (2011) (Kelly K. Nichols et al., 2011). A positive diagnose of MGD was given with at least MGD stage 2 symptoms and clinical signs. MGD stage 2 is described as mildly altered secretions grade, (≥ 4 - < 8) and expressibility grade 1. An OSDI score ≥ 13 and at least one positive diagnostic finding of dry eye disease (NIKBUT, osmolarity or staining) was defined as

diagnostic criteria for DED (Wolffsohn et al., 2017). Figure 2 describes the diagnostic procedure for DED. Patients with DED and MGD, without reduced TMH (TMH < 0.2mm), were sub-classified as EDE. Patients with DED and TMH < 0.2mm without MGD, was sub-classified as ADDE (Wolffsohn et al., 2017). Patients with DED without MGD or reduced TMH (TMH < 0.2mm), was defined as unclassifiable. The pattern of the lipid layer can be used for further guidance of the sub classification of DED. Assessment of the lipid layer was not applied in this study.

All statistical analyses except the sample size calculation were performed using standard parametric or non-parametric tests in "R" commander version 3.4.3 (2017-11-30). The level of significance was set at 5 %. The distribution of the variables was tested with the Shapiro-Wilk normality test; p-values < 0.05 indicating that the variable was not normally distributed. The Welch two-sample t-test was used to check for difference in mean between two groups, if the variable was normally distributed. The two-sample Wilcoxon test was used to check for difference in median if the variable was not normally distributed. The Spearman rank-order test was used to check for association between two, numeric, continuous, variables where one or both were not normally distributed The Chi-squared test was used to check for group differences for categorical variables with expected counts > 5 in each contingency cell. The Fischer´s exact test was used to check for group differences for categorical variables in small samples with expected counts < 5 in each contingency cell. The size of a correlation coefficient was interpreted according to the following rule of thumb: correlation coefficient ≥ 0.7 = strong, correlation coefficient ≥ 0.5 but < 0.7 = moderate, correlation coefficient ≥ 0.3 but < 0.5 = low, correlation < 0.3 = very low (negligible) (Witz, Hinkle, Wiersma, & Jurs, 1990).

2.6 Ethical considerations

The research was carried out in accordance with the principles embodied in the Declaration of Helsinki (Code of Ethics of the World Medical Association) and the study was performed after approval by the Regional Committee for Medical Research Ethics for the Southern Norway Regional Health Authority (REK) (Reference: 2017/2542/REK sør-øst) (appendix 8).

All the participants signed the informed consent form (appendix 2) before joining the study. The consent included information about the study and the procedures to be carried out. The patients were encouraged to ask questions before and after the testing. All the procedures applied in this study were non-invasive and did not cause any severe discomfort or pain. There was no risk or danger associated with the tests. The procedures carried out were all standard procedures in optometric practice. If the tests revealed a need for further follow up, the patients were offered basic dry eye treatment. If necessary the patients were referred to a specialist or assigned to a new appointment at Erøy Optikk. The tests carried out gave the patients a free dry-eye examination and in cases where the patients wanted, they were offered a free optical refraction.

Participation was voluntary and the participants were free to withdraw their consent and leave the study at any time without giving any reason and without consequences for further follow-up and management by Erøy Optikk AS. All personal information was handled confidentially to secure the privacy of the research objects. A manual record containing the data registration form, the informed consent form and the two questionnaires was created and stored in the location of Erøy Optikk AS. Only the project manager and one assistant had access to the premises which were securely locked every day. All the forms were thereafter scanned into a file on a computer, and attached to each patients profile in the practice patient data system (Serve IT 4.0). Secure online backup was provided two times per day. A personal identification number was assigned to each patient. An identification key associating the identification numbers with the participants was created and stored separately, away from personal information. The identification key was deleted shortly after it had served its original purpose, and the data used for analysis did not contain any sensitive information.

3 Results

3.1 Demography

Among all patients in the sample population, having a standard eye examination in the data collection period, 49 (84 %) participated in the study. The majority of the participants were female (59 %). The mean age of the patients was 48 (± 13) years (range 20 - 68); there was no significant difference in age between females and males. Twenty participants (41 %) reported some sort of allergy, nine (18 %) were contact lens users, seven (14 %) smoked daily, and five (10 %) patients had undergone eyelid surgery. Table 1 shows an overview of the clinical findings. All were using computer screens, and the mean reported screen time per day was 4.8 (± 2.6) hours.

Table 1: All findings - overview

Findings	All (n=49)	DED positive (n=32)	DED negative (n=17)
Risk factors:			
Allergy	20 (41)	13 (41)	7 (41)
Contact lens wear	9 (18)	6 (19)	3 (18)
Smoking[a]	7 (14)	6 (19)	1 (6)
Screen time (mean, SD)	4.8 (± 2.6)	5.0 (± 2.8)	4.5 (± 2.1)
Eyelid surgery	5 (10)	4 (13)	1 (6)
Symptoms:			
OSDI score	24.9 (± 20)	34.7 (± 18.7)**	6.4 (± 4.0) **
Clinical diagnostic signs[b]:			
Staining n (%)	41 (84)	27 (84)	14 (82)
Osmolarity n (%)	32 (65)	22 (69)	10 (59)
NIKBUT n (%)	16 (33)	10 (31)	6 (35)
Clinical sub-diagnostic signs:			
TMH[c]	21 (43)	15 (47)	6 (35)
MGD[d]	35 (71)	24 (75)	11 (65)

DED; dry eye disease, OSDI; ocular surface disease index, NIKBUT; non-invasive Keratograph break-up time, TMH; tear meniscus height, MGD; meibomian gland dysfunction, LWE; lid wiper epitheliopathy,
[a] One or more cigarettes in a normal week
[b] Osmolarity ≥ 308 mOsm/L, and/or NIKBUT ≤ 10 seconds, and/or staining (LWE of ≥2 mm in length and/or ≥ 25 % sagittal and/or more than 5 corneal spots of fluorescein staining and/or more than 9 conjunctival spots of lissamine green)
[c] TMH <0.2 mm
[d] MGD (secretions grade ≥ 4, and expressibility ≥ grade 1)
** Statistically significant difference in median OSDI score between patients with and without DED (Wilcoxon's rank sum test, p= < 0.001)

Thirty-two patients (65 %) had dry eye. Table 2 describes the dry eye characteristics of the patients in the study. The mean age in the dry eye group was 49 (± 12) years. There was no significant difference in the frequency of DED between females and males, and the mean age was not different between patients with and without DED.

Twenty-four patients needed some sort of DED treatment; all of them were advised to use artificial tears and/or eye lubricants, among them, seven patients were started on basic MGD treatment (heat, massage, eyelid-hygiene). Two participants needed referral to ophthalmologist after basic DED treatment. One patient, with a medical history of stroke, was referred for further dry eye treatment with prescription medication in order to reduce ocular inflammation. The medical report agreed on the diagnosis of DED, no further treatment was initiated. The other patient had previously tried different dry eye treatments without any effect and specifically requested a referral to ophthalmologist. The medical report agreed on the diagnosis of DED, and basic dry eye treatment was initiated again. The patient was advised to stop smoking, and in case of no symptom relief after three months, treatment with Softacort should be initiated.

Table 2: Dry eye characteristics of participants, n (%)

Characteristics	All patients (n=49)	Female (n=29)	Male (n=20)
Any clinical diagnostic signs[a]	46 (94)	28 (97)	18 (90)
Symptoms[b]	33 (67)	22 (76)	11 (55)
Dry eye disease (DED)	32 (65)	22 (76)	10 (50)

NIKBUT; Non-invasive Keratograph break-up time, LWE; Lid wiper epitheliopathy, OSDI; Ocular surface disease index
[a] Osmolarity ≥ 308 mOsm/L, and/or NIKBUT ≤ 10 seconds, and/or staining (LWE of ≥ 2 mm in length and/or ≥ 25 % sagittal and/or more than 5 corneal spots of fluorescein staining and/or more than 9 conjunctival spots of lissamine green)

[b] (OSDI ≥ 13)

3.2 Symptoms

Table 3 describes the severity of dry eye symptoms by gender. The mean OSDI score of the participants were 25 (± 20), and 27 (± 18) and 21 (± 22) for females and males, respectively. There was no significant difference in the mean OSDI score between females and males, and no association between OSDI score and age. The mean OSDI score among DED patients was 35 (± 18). There was a significant difference in median OSDI score between patients with and without DED (Wilcoxon's rank sum test, p= < 0.001). The severity of dry eye symptoms was not significantly different between females and males. There was no difference in mean OSDI score between contact lens wearers and non-contact lens wearers, between smokers and non-smokers, between patients with and without MGD, and between participants with and without allergy. There was no association between time spent using computer screens and OSDI score.

Table 3: Severity of dry eye symptoms by gender n (%)

OSDI score[a]	Total (n=49)	Female (n=29)	Male (n=20)
None	16 (33)	7 (24)	9 (45)
Mild (13-22)	14 (28.5)	8 (28)	6 (30)
Moderate (23-32)	5 (10)	4 (14)	1 (5)
Severe (≥33)	14 (28.5)	10 (34)	4 (20)

OSDI; Ocular surface disease index
[a] 0-100

3.3 Clinical diagnostic signs

Table 4 describes the clinical diagnostic signs in patients with and without dry eye symptoms. The majority of the participants (94 %) had one or more clinical diagnostic signs. There was no significant difference in the prevalence of clinical diagnostic signs (NIKBUT, osmolarity or staining) between females and males. The prevalence of positive clinical diagnostic signs (NIKBUT, osmolarity or staining) was not significantly different between participants with and without positive OSDI score for dry eye symptoms (OSDI ≥ 13). One of the participants had dry eye symptoms without signs of dry eye, and 14

participants had dry eye signs without dry eye symptoms. The most frequent clinical diagnostic sign was ocular surface staining, found in 84 % of all the participants. There was no significant difference in age between participants with and without positive clinical diagnostic ocular surface staining.

Table 4: Clinical diagnostic signs not mutually exclusive in patients with and without DED symptoms, n (%)

Finding	All (n=49)	OSDI ≥ 13 (n=33)	OSDI < 13 (n=16)
Any clinical diagnostic signs[a]	46 (94)	32 (97)	14 (88)
Staining (positive)	41 (84)	27 (82)	14 (88)
Osmolarity (positive)	32 (65)	22 (67)	10 (63)
NIKBUT (positive)	16 (33)	10 (30)	6 (38)

NIKBUT; Non-invasive Keratograph break-up time, LWE; Lid wiper epitheliopathy, OSDI; Ocular surface disease index
[a] Osmolarity ≥ 308 mOsm/L, and/or NIKBUT ≤ 10 seconds, and/or staining (LWE of ≥2 mm in length and/or ≥ 25 % sagittal and/or more than 5 corneal spots of fluorescein staining and/or more than 9 conjunctival spots of lissamine green).

3.4 DED subgroups

Table 5 describes the dry eye disease sub-categories. There was no difference in the prevalence of EDE, ADDE or mixed dry eye between females and males.

Table 5: Distribution of dry eye disease sub-categories, n (%)

	All (n=32)	Female (n=22)	Male (n=10)
EDE[a]	13 (41)	8 (36)	5 (50)
Mixed[b]	11 (34)	9 (41)	2 (20)
ADDE[c]	4 (12.5)	3 (14)	1 (10)
Unclassifiable[d]	4 (12.5)	2 (9)	2 (20)

EDE; evaporative dry eye, ADDE; aqueous deficient dry eye, MGD; meibomian gland dysfunction
[a] Patients with DED and MGD (secretions grade ≥ 4, and expressibility ≥ grade 1), without reduced TMH (TMH < 0.2 mm)

[b] Patients with DED and both MGD (secretions grade ≥ 4, and expressibility ≥ grade 1), and TMH < 0.20 mm
[c] Patients with DED and TMH < 0.2mm without MGD
[d] Patients with DED without MGD or reduced TMH (TMH < 0.2mm)

3.5 General vision

The mean general vision score was 78 (± 15.9). Table 6 describes ocular pain score and general vision score, in patients with and without DED. There was a significant difference in median general vision score between patients with and without DED (Wilcoxon's rank sum test, p = 0.002). Patients with DED reported poorer general vision than patients without DED. There was moderate correlation between general vision score and OSDI score (Spearman's rank correlation = - 0.5, p < 0.001). Patients with higher OSDI score (more severe symptoms) reported poorer general vision. There was a significant difference in median general vision score between females (74 ± 15) and males (84 ± 15), (Wilcoxon's rank sum test, p = 0.02). Females rated their quality of general vision lower than males. The association between general vision and age was very low (Spearman's rank correlation r = - 0.23, p = 0.13).

There was no significant difference in median general vision score between patients with or without positive signs of NIKBUT, osmolarity or staining. There was no significant difference in median general vision score between patients with or without allergy, between contact lens wearers and non-contact lens wearers, and between smokers and non-smokers. The association between general vision score and screen time was very low (Spearman's rank correlation r = 0.07, p = 0.6).

3.6 Ocular pain

The mean ocular pain score was 71 (± 20.6). There was a significant difference in ocular pain score between patients with and without DED (Wilcoxon's rank sum test, p < 0.001). Patients with DED reported to have more ocular pain than patients without DED. Table 6 describes ocular pain score and general vision score, in patients with and without DED. There was a weak, negative, correlation between ocular pain and age (Spearman's rank correlation r = - 0.3, p = 0.04). Older patients reported more ocular pain. There was no significant difference in ocular pain score between females (68 ± 19), and males 76 ± 22). There was no significant difference in median ocular pain score

between patients with or without positive signs of NIKBUT, osmolarity or staining, between patients with and without allergy, or between contact lens wearers and non-contact lens wearers. However, there was a significant difference in median ocular pain between smokers and non-smokers (Wilcoxon's rank sum test, p = 0.014). Smokers reported higher levels of ocular pain than non-smokers. The association between ocular pain score and screen time was very low (Spearman's rank correlation r = 0.03, p = 0.8).

Table 6: Dry eye disease and mean VQoL subscores for general vision and ocular pain, score 0-100 (SD)

	NEI VFQ General Vision*	NEI VFQ Ocular Pain **
Participants with DED	73 (±13)	63,9 (±19)
Participants without DED	87 (±17)	86 (±15)
All participants	78 (±16)	71 (±21)

VQoL; visual quality of life, NEI VFQ; National Eye Institute Visual Function Questionnaire, DED; dry eye disease
*Statistically significant difference between participants with and without dry eye disease, Wilcoxon's rank sum test, p=0.002
** Statistically significant difference between participants with and without dry eye disease, Wilcoxon's rank sum test, p<0.001

Table 7 describes the mean general vision and ocular pain score in the different dry eye disease subgroups.

Table 7: Dry eye disease, subgroups and mean VQoL, score 0-100 (SD)

	NEI VFQ General Vision*	NEI VFQ Ocular Pain**
Non dry eyes	87 (±17)	86 (±15)
EDE[a]	79(±10)	66 (±20)
Mixed[b]	72(±10)	67 (±17)
ADDE[c]	70 (±20)	66 (±19)
Unclassifiable[d]	60 (±16)	47 (±21)

VQoL; visual quality of life, NEI VFQ; National Eye Institute Visual Function Questionnaire; EDE; evaporative dry eye, ADDE; aqueous deficient dry eye, DED; dry eye disease, MGD; meibomian gland dysfunction
[a] Patients with DED and MGD (secretions grade ≥ 4, and expressibility ≥ grade 1) without reduced TMH (TMH <0.20mm),
[b] Patients with DED and both MGD (secretions grade ≥ 4, and expressibility ≥ grade 1) and TMH <0.20mm,

[c] Patients with DED and TMH <0.20mm without MGD,
[d] Patients with DED without MGD or reduced TMH.
* Wilcoxon's rank sum test, p=0.03
** Wilcoxon's rank sum test, p=0.03.

Mild, moderate or severe MGD was found in 71 % of the participants and 43 % of the participants had positive signs of reduced tear volume (TMH). There was a significant difference in mean age between patients with MGD (50 ± 12), and without MGD (41 ± 14) (Welch two sample t-test, p = 0.04). There was no significant difference in the prevalence of MGD between females and males, between patients with or without DED or between patients with or without positive diagnostic signs of NIKBUT, osmolarity or staining, between contact lens wearers and non-contact lens wearers, smokers and non-smokers, or between allergy sufferers and non-allergy sufferers.

4 Discussion

The prevalence of DED in our study was 65 %. In the general population, the prevalence of dry eye disease ranges from five to 50 % according to the operational definition applied and the specific population surveyed (Stapleton et al., 2017). To our knowledge there has not been done any larger prevalence studies in this field from comparable populations based on the new diagnosis criterion stated in DEWS II. One study, based on both symptoms and signs, found a prevalence of 11 % in the general population (Viso, Rodriguez-Ares, & Gude, 2009). However, it is based on different DED definitions and diagnostic methods. A recent master thesis by Ingeborg Sand (Sand, 2016) reported a prevalence of 28 % among patients in Norwegian optometric practice, based on the old diagnostic criterion for dry eye disease. In the study by Sand (2016), a higher OSDI cut-off value was used (OSDI ≥ 23), which might have caused an under-estimation of the DED prevalence. The prevalence of DED in our study is expected to be higher than in the general population, and in Norwegian optometric practice in general. This expectation is based on a predicted skewedness in our sample. Participants, suspecting they have DED, have joined the study after seeing the invitation to take part in a study specifically investigating their problems, and people attending an eye-examination do have eye problems, which might be dry eye related. However, the incidence of DED may in general be under-reported because people do not recognise the signs, under-estimate the severity of their symptoms and therefore do not seek treatment. In our study 46 patients had one or more clinical diagnostic signs (NIKBUT, osmolarity or staining), among them; 14 participants did not report OSDI symptoms within the diagnostic range (OSDI ≥ 13). These patients might have under-estimated their symptoms. In addition, DED is often under-diagnosed in clinical practice because clinical signs under-estimates the severity of the condition, and have a tendency not to correlate with patient symptoms (Guillemin, Begley, Chalmers, Baudouin, & Arnould, 2012). In our study, 97 % of the participants with OSDI symptoms within the diagnostic range (OSDI ≥ 13) had one or more clinical diagnostic signs (NIKBUT, osmolarity or staining), which indicates that this is not the case in our study.

In our study, symptoms of dry eye were correlated with reduced quality of general vision and DED was correlated with increased ocular pain. To our knowledge, no previous studies have evaluated how DED, as defined by the DEWS II guidelines affects visual quality of life in a Norwegian population. The findings in our study is similar to a study by Li et al (2012) which was based on data from NEI VFQ-25 and OSDI questionnaires from 87 DED patients and a control group of 71 healthy volunteers (Li et al., 2012). They found that DED patients had lower (worse) general vision score and more ocular pain than patients without DED (Li et al., 2012). However, the clinical diagnose of DED in this study was based on FBUT and Schirmer test. The validity of these two instruments are debated and not included in the new guidelines in DEWS II (Wolffsohn et al., 2017).

There was a strong correlation between DED and ocular pain in our study. This correlation is expected as ocular pain is one of the hallmarks of DED (Belmonte et al., 2017). There was no significant difference in the level of ocular pain or dry eye symptoms between females and males. Neither were females more likely to have DED than males. This is not in accordance with the literature. DEWS II found it evident that females are more likely to have DED than males, and that female gender is a major risk factor for DED (D. A. Sullivan et al., 2017). In general females are six years younger than males at the time they get the DED diagnose (D. A. Schaumberg et al., 2013), and females are known to live longer than males. Age is a risk factor for DED (Stapleton et al., 2017), which implies more females than males with DED. However, there was no significant difference in age between females and males in our study, which can partly explain the lacking difference. One major study suggests that sex differences in DED might lessen with increased age (Schein, Muñoz, Tielsch, Bandeen-Roche, & West, 1997), however, the mean age in our study is considered low. This lack of agreement between our study and the literature might also be caused by a small sample size, or that females and males report different on the self-administered questionnaires.

In our study, patients with DED rated their general vision lower than patients without DED, and patients with higher (worse) OSDI score reported poorer general vision. A

study by Li et al (2012), based on other diagnosis criterions, confirms these findings (Li et al., 2012). Our study has not in particular investigated the associations between visual acuity and DED, but our findings indicates that optometrists should consider the possibilities that DED might cause their patients to see poorly. Moreover, our findings of reduced general vision in DED correlates with the findings of Miljanović et al. (2007), who found that DED negatively affected peoples ability to carry out tasks with requirements to sustained visual attention like to read, carry out professional work, use a computer, watch television, and drive both in the day and night (Miljanović et al., 2007). Our study has not specifically investigated these abilities, which corresponds to the NEI VFQ-25 subscales: difficulty with near vision activities, difficulty with distance vision activities, role limitations due to vision, and driving difficulties. The study by Miljanović et al. (2007) was based on their own classification of DED and self-administered questionnaires - diagnosis criterions different from the recommendations given in DEWS II. Based on our findings of reported reduction in general vision among DED patients, optometrists should consider consequently to screen their patients for dry eye symptoms with an OSDI questionnaire, before the eye examination. This information can enable them to decide if further DED testing is needed, and can, in addition to standard optometric tests, contribute to explain why some patients does not see as good as they wish, even with their best corrected prescription. This theory is supported by studies who has found visual acuity to be significantly deteriorated in subjects with ocular surface disease, improving temporarily with instillation of artificial tear drops (Wolffsohn et al., 2017). Females in our study reported lower on quality of general vision than males. These findings are in agreement with former studies and expected gender-related differences (D. A. Sullivan et al., 2017). However, there was no significant difference in dry eye symptoms (OSDI score) between females and males in our study. Such a difference would be expected from the literature. In a study from 2018 females was found to have significantly higher OSDI score than males (Vehof, Jansonius, Snieder, & Hammond, 2018), unlike the findings in our study. The lack of difference between genders in OSDI score might be caused by the size of the sample, our sample might have been to small to capture a statistically significant difference. Our study was not designed to reveal such a difference. Studies have also found that differences in OSDI score are most prevalent in the more severe cases of DED. This

study has not investigated possible differences in OSDI score between different levels of DED severity.

General differences between how females and males reports symptoms have been reported, and one study found females to report significantly worse (greater problems) on the different OSDI subscales questions than males (D. A. Schaumberg et al., 2013). The stereotypical, socially accepted role of gender is that females are more willing to report pain, and that the masculine role is associated with reluctance to report pain or admit physical weakness (stoicism) (D. A. Sullivan et al., 2017). Males might therefore be under-estimating or under-reporting symptoms, or females might in general report more. DED has been found generally to be experienced as more severe among woman, and to have a greater effect on their self-assessed well-being than among males (D. A. Schaumberg et al., 2013). These tendencies might have contributed to a lower finding of general vision among females than males in our study. Regarding sensitivity and tolerance for pain in general; studies have suggested that women are more likely to experience a variety of chronic pain syndromes than males (D. A. Sullivan et al., 2017), and therefore also might be suspected to experience more ocular pain than males. This does not seem evident from our study. However, the research on the relationship between pain in DED and sex has been reviewed in DEWS II and was found to be inconsistent and confounded by several variables, among others inconsistent use of the terms sex and gender in previous studies (D. A. Sullivan et al., 2017)

In this study the correlation between increasing age and ocular pain score was weak; older patients in our study experienced more ocular pain than younger. Our findings are supported by the literature which describes more severe symptoms (higher OSDI score) with increasing age (Stapleton et al., 2017). The opposite was found in a large study in the Netherlands based on 79866 participants (Vehof et al., 2018); younger participants reported higher levels of symptoms. Older patients in our study might in general have a higher threshold for pain and discomfort, or actually experience higher levels of ocular pain. The corneal sensitivity has been found to be reduced in DED patients due to damage to the sensory nerve endings (Belmonte et al., 2017). In dry eye research there is general consensus that age is a risk factor for DED (Stapleton et al., 2017). It is also

known that the corneal sensitivity to mechanical stimulus is reduced in DED patients and might wary due to disease severity and subtypes (Belmonte et al., 2017), this might influence how the patients subjectively report their DED symptoms an contribute to the lack of signs and symptoms.

Pain in general is common (D. A. Sullivan et al., 2017), and untreated pain has a deteriorating effect on quality of life at any age, regardless of the source of the pain (Katz, 2002). Our findings are comparable with the findings of Isabel Espelid (2018), who found symptoms of DED (OSDI) to be correlated with reduced QoL (Espelid, 2018). Mean OSDI score was 30.5 ± 19.1 in the study by Espelid (2018) versus 24.9 ± 20 in our study. However, that study was based on the old diagnosis criterions and cohort of patients from a dry eye clinic with expected more severe DED than the patients in our study. The severity of symptoms would be expected to impact the reduction of QoL. Pain is found to have negative consequences both to the patients and their families. It negatively effects their social and professional life and should be prevented or treated to minimalize or avoid burdens both to themselves, their social network and the health-care system (Duenas, Ojeda, Salazar, Mico, & Failde, 2016), (Fine, 2011). As compared to how other medical conditions deteriorates quality of life; severe DED have been found to be comparable with moderate and more severe angina pectoris (Schiffman et al., 2003). Our study has not investigated the association between reduced QoL in DED patients and reduced QoL in other conditions. Li et al (2012) found VQoL scores to be reduced in DED, and correlated with anxiety, depression and lower quality of life. This implicates that avoiding or identifying and treating DED is important and contributes to maintain patients QoL. Norwegian optometrists, as the major contributor of primary eye care services in Norway (Lundmark & Luraas, 2017), are positioned and should be considered to contribute in this matter.

Among the 32 patients diagnosed with DED in this study, 24 patients were started on some sort of treatment; only two needed referral to ophthalmologist. Without being able to say something about the end-result of the treatment, the number of referrals is low. This supports the argument that optometrists can take part in DED eye care, and thereby contribute to reduce the number of DED related referrals to ophthalmologists.

In cases of more severe DED that needs treatment in the specialist health care service, optometrists should refer the patient. Preliminary results from one study, assessing the general degree of diagnostic agreement between referrals from optometrists and medical-reports from ophthalmologists (Lundmark & Luraas, 2017), supports our argument that optometrists are competent to decide when a referral should be made. That study found the general level of diagnostic agreement to be high between these two eye care providers in Norway, but did not investigate DED related referrals in particular. However, Norwegian optometrists are bound by the Health Personnel Act (Helsepersonelloven, 1999), and required to provide competent and qualified health care. Optometrist's handling DED has to consider his or her own competence and refer to a general practioner, ophthalmologist or colleague when necessary.

Our study finds poor correlation between clinical signs and symptoms. Patients with positive clinical diagnostic findings of NIKBUT, osmolarity or staining did not have statistically significant different OSDI score than patients without these findings. The lack of correlation between clinical signs and symptoms is confirmed and as expected from the literature (Wolffsohn et al., 2017), (Espelid, 2018). This discrepancy has been a challenge in DED research. It has especially been a challenge to get approval on new drugs for the treatment of DED where an effect on both signs and symptoms is required in the same trial (Novack et al., 2017). Some of the reason for the lack of correlation is that DED patients experiences significant variation and fluctuation of symptoms over time, and seasonal variations might influence the severity of symptoms (Wolffsohn et al., 2017). As mentioned in the introduction; the term "vicious circle" is used to describe the complex pathogenesis of DED; one example of this is the possible finding of increased tear film osmolarity, which may both, be the initializing factor and the endpoint of DED. The variability in osmolarity is in itself an indication of DED (Wolffsohn et al., 2017).

Another suspected reason could be that the tool assessing the symptoms is not accurate. Ninety-four % of the participants in our study had signs of DED; only 67 % had positive diagnostic symptom (OSDI ≥ 13) score. Is the OSDI questionnaire accurate to measure ocular symptoms related to DED? Thirteen patients met the diagnostic

symptoms requirements as defined in DEWS II without having DED. These patients might be suspected to have allergic conjunctivitis, ocular infections, contact lens induced discomfort or other comorbidities that mimic the symptoms of DED (Wolffsohn et al., 2017). Our study has not looked into this possible causation. Another reason that can explain the high number of OSDI positive patients might be that the diagnostic OSDI criterion is set to low. Raising the diagnostic OSDI criterion would improve the sensitivity in cases of more severe DED; however, patients with less severe DED, at risk of DED, or with pre-clinical DED could be overlooked. According to DEWS II, a diagnosis of neuropathic pain (neuralgia) due to nerve disease or damage should be considered in cases of symptoms of DED without signs of DED. The condition might still warrant prophylactic treatment (Wolffsohn et al., 2017). The prevalence of moderate to severe neuropathic pain in adult Europeans is 19 % (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). From that study we could expect nine participants in our study to have ocular symptoms without signs. In our study, 14 patients (28.5 %) had dry eye signs without dry eye symptoms, which is higher than the expectation. A system or questionnaire to distinguish neuropathic pain from DED related ocular pain has not yet been made (Belmonte et al., 2017).

Another possible reason why the signs in our study do not correlate with the symptoms might be that the sensitivity of the clinical diagnostic tests are too low. In that case, we would miss patients with DED because of under-estimation of clinical diagnostic signs. These patients are still likely to report symptoms, and would falsely be classified as patients with symptoms without signs. In our study, only one patient had symptoms without signs, which does not indicate that the sensitivity of clinical diagnostic tests is too low. However, another pitfall is that the specificity of the clinical diagnostic tests is too low. In that case, clinical diagnostic signs would be discovered in patients without DED. These patients might still report symptoms, and would falsely be diagnosed with DED. In cases where patients without symptoms falsely are assigned clinical diagnostic signs, they would be categorized as patients with signs, without symptoms. In all 14 patients in our study fell into this category which arguments that the specificity of the diagnostic tests are to low. These 14 patients might also falsely have been classified with symptoms, which can happen if the diagnostic criterion of the OSDI questionnaire

is too low. This leads us to another possible cause of discrepancy between signs and symbols in DED, the sensitivity and specificity of the questionnaire assessing the symptoms.

An interesting group of patients that can highlight shortcomings and sources of error in the diagnostic process are the four subjects found in the DED, unclassifiable, subgroup. Among them, three patients had allergy, two were smokers, and the mean OSDI score among them was 66. This is clearly higher than the mean OSDI score of 35 in the DED group. The fourth patient had an OSDI score of 17, was not a smoker, did not use contact lenses and had not been diagnosed with allergy. However, this patient reported an average screen time of eight hours and had a history of watery eyes. For the group of unclassifiable DED patients it seems that the OSDI questionnaire is not specific enough and that the diagnostic OSDI criterion of 13 might be to low. This highlights the importance of specific questions in the diagnostic process aimed to rule out common comorbidities like allergy.

The prevalence of MGD in our study was 71 %. This coincides with a study investigating the prevalence of MGD in an Austrian dry eye population. Based on the same diagnostic criterions for MGD as our study (Tomlinson et al., 2011), it was found to be 70.3 % (Rabensteiner, Aminfar, Boldin, Schwantzer, & Horwath-Winter, 2018). The reported prevalence of MGD among Caucasians in the general population varies between 3.5 % and 20 % according to different definitions of the disease (D. Schaumberg et al., 2011). The prevalence of MGD in our study is expected to be higher than in the general population. In our study, there was a significant difference in mean age between patients with and without MGD, patients with MGD was older than patients without MGD. Age has been suspected to be a risk factor for MGD, but the literature does not conclude on this matter, and states that further research is needed (D. Schaumberg et al., 2011). MGD is suspected to be the most common cause of DED, and appears to be a prevalent problem (Kelly K. Nichols et al., 2011). Our study did not reveal any statistically different prevalence of MGD between females and male. The literature is inconclusive on gender differences, but studies have shown a higher prevalence of MGD among males than females (Alghamdi et al., 2016). Patients in our study with MGD did

not have significantly different OSDI than patients without MGD, and they did not have significantly different ocular pain score than patients without MGD. This is in agreement with the literature. Studies have found most MGD patients to be asymptomatic (Chhadva, Goldhardt, & Galor, 2017). The TFOS International workshop on MGD dysfunction (2011) raised the question if MGD was a risk factor or cause of DED, or if DED was a risk factor or cause of MGD (D. Schaumberg et al., 2011). DEWS II finds the diagnostic value of meibomian gland expressibility and duct appearance not to have been established in DED (Wolffsohn et al., 2017). This study has not investigated the diagnostic value of MGD in DED.

The tests used, and the sequence of testing in this study, are chosen according to the recommendations in DEWS II. There are many possible pitfalls in the diagnostic process of DED, and the fact that there are several tests involved will make it possible for the tests to interact and interfere the result of the next test to be performed. It also increases the probability of operator errors. The sequence of testing can affect the results (Wolffsohn et al., 2017). A rule of thumb has been to perform the least invasive tests first (Foulks, 2003). FBUT should be performed only if NIKBUT is not available. Some of the test involves bright light and the use of fluorescein, which might destabilise the tear film, alter the natural sequence of blinking and trigger reflex tearing. The constitution of proteins differs in reflex tears and open-eye tears (basal tears) (Willcox et al., 2017). These differences are suspected to change the corneal wettability, the thickness of the lipid layer, and the osmolarity (Craig et al., 2013). Alternations in the natural blinking sequence can change the tear film thickness and tear film spreading which among other tests can affect NIKBUT readings. Prolonged eye closure can cause hyperosmolarity (Willcox et al., 2017). The reliability and validity of the test-results in this study is strong because only one operator has been involved. This excludes the possibility of inter-operator errors and ensures that the tests were carried out in the exact same way.

The IPEN measures the osmolarity directly from the lower bulbar conjunctiva and does not remove any tears, as opposed to the Tearlab device, which extrapolates a sample of tears from the inferior, lateral conjunctiva. Tear osmolarity has been demonstrated as

the single clinical DED test to have the highest correlation to disease severity (Wolffsohn et al., 2017). However, there is no evidence that osmolarity measured in the inferior, lateral conjunctiva represent the overall osmolarity of the pre-corneal tear film, and the osmolarity measurement might differ as to where the sample is taken from (Willcox et al., 2017). The osmolarity measurements performed in this study are considered valid. The Keratograph® 5M measures the time until the tear-film breaks up anywhere on the cornea. The patients were thoroughly instructed to blink normal twice, then cease blinking for as long as possible. To avoid the risk for the patients to under-perform by not paying attention, the measurements were made three times and the results were averaged. A study assessing the NIKBUT in 100 eyes from 100 patients found the Keratograph® 5M to report significantly shorter break-up time than Tearscope, and that other instruments correlated better with patient symptoms (Best, Drury, & Wolffsohn, 2012). This might have caused our study to over-estimate the number of positive clinical diagnostic NIKBUT patients, and complicates comparison of NIKBUT measurements in studies applying different instruments. An over-estimation of positive clinical diagnostic NIKBUT patients will contribute to reduced correlation between clinical signs and symptoms. Another study found the NIKBUT measurements performed with the Keratograph® 5M to be a simple, non-invasive screening test for DED with acceptable sensitivity, specificity and repeatability (Hong et al., 2013). Ocular surface staining is considered to be an important aspect in the clinical analysis of DED, however more reliable as a marker of disease severity in the more severe cases of DED (Wolffsohn et al., 2017). The TFOS DEWS II recommends the use of two different dyes to assess the ocular surface staining: fluorescein for the cornea and lissamine green for the conjunctiva. Among other ocular surface staining grading schemes, the Oxford grading scheme (Bron AJ, 2003) was chosen due to its ability to grade the severity of the ocular surface staining more than just consider the staining to be positive or negative. TFOS DEWS II does not recommend the use the Oxford grading system directly. They have simplified it and considers a finding of > five corneal spots of fluorescein staining, or > nine conjunctival spots of lissamine green or staining, or LWE of ≥ 2 mm in length or ≥ 25 % sagittal with in either eye, a positive finding (Wolffsohn et al., 2017). The transition between these two grading systems was made by considering an Oxford staining score **≥** grade 1 to be corresponding with the DEWS II diagnostic numbers of

staining spots. The number of nasal or temporal conjunctival staining spots appearing on the Oxford grading scale, grade 1 picture, is 10 (Bron AJ, 2003), which corresponds with the DEWS II diagnostic number. However, the number of corneal staining spots appearing on the Oxford grading scale, grade 1, picture is 10 which might have caused an under-estimation of the corneal fluorescein staining in our study, especially in the cases of less severe corneal staining, and might have contributed to the lack of correlation between signs and symptoms in our study. The volume of saline used to release the dye from the pre-impregnated strips influences the evaluation of staining, and to standardize the volume of instilled saline, it could be beneficial to use a micropipette. A maximum fluorescence effect is obtained with a concentration of 0.08 g/l. If a larger volume is instilled, the fluorescent effect might decrease (Speedwell & Phillips, 2007), and cause an under-estimation of ocular staining. Both fluorescein and lissamine green are exposed to photobleaching and looses 70 % of its fluorescent effect within 60 seconds (Efron, 2013). This emphasises the importance of timing when staining is observed to avoid miscalculation and further discrepancy between signs and symbols in DED.

Strengths of this study are that the same operator collected all data. This eliminates the risk of intra-observer errors. Two different types of questionnaires are used in this study: one generic, and one disease specific. This is a strength because they provide a slightly different viewing angle to the disorder, and in cases where findings from these two utilities correlate, we can be more certain its not a coincidence (Vitale, Goodman, Reed, & Smith, 2004). In our study, both OSDI score and ocular pain was found to be associated with DED. Two different measures of ocular discomfort, providing strength to our finding that DED is painful and causes discomfort.

Weaknesses of the study: The measurements are made in the allergy season. DED might vary according to time of the year, and patients with ocular allergy might fall into this category of DED patients. The osmolarity measurement was performed first, which could have effected the NIKBUT measurements. This choice was made, based on the assumption that the IPen used to perform the measurement was less invasive than the TFOS DEWS II recommended Tearlab device and the fact that the IPEN does not

physically extract tears from the eye. Osmolarity measurements should, according to TFOS DEWS II, be performed with a temperature stabilised, calibration checked device (Wolffsohn et al., 2017). The IPEN is not temperature stabilised, has not been widely used in clinical studies, and has not been validated in larger studies. Regarding the NIKBUT measurements; the time from the last blink until the first break-up was not used. Instead, the time from the last blink until the average break-up of all broken segments was averaged and used. This might have given a longer break-up time than in comparable studies. When measuring osmolarity with the IPEN, the lower eyelid was pulled down and away from the eye which is not recommended (Wolffsohn et al., 2017). The same strip of fluorescein and lissamine green dye was used for both eyes and the fluorescein staining was assessed after the FBUT measurements without re-installation. This might cause uneven distribution of dye between the eyes, and under-estimation of the corneal staining. The number of punching errors should have been counted to enhance the credibility of the study. The NEI VFQ-25 questionnaire was originally designed and validated in America, for American culture and language (Mangione et al., 2001), and the Norwegian version has not yet been validated. The OSDI questionnaire exists both in a self-guided and in an interview version. A self-administered version was chosen in this study because it is more time- and cost efficient. In a study from 2016, no clinically significant difference was found between the self guided and the interview version (Ngo, Srinivasan, Keech, Keir, & Jones, 2017). A key point in the use of questionnaires in medical research is validation (Laake, 2007). In this case, both the original and the translated version is validated and widely used (Schiffman et al., 2000), (Sundling, personal communication). In the use of questionnaires in medical research, it is possible for patients to misunderstand questions and to under- or over estimate the severity of their symptoms. Are patients that report to have more severe dry eye in worse general health? Comorbidities will possibly make a patient with cancer and severe DED rate his or hers symptoms different than a person with allergy and mild DED (Buchholz et al., 2006). Patients might also refuse to ask for assistance in cases of insecurity regarding specific questions or formulations. This can cause loss of -and biased data in self-administered questionnaires. The use of questionnaires requires honesty. The new recommendations for Patient-reported Outcome (PRO) questionnaires from the Food and Drug

Administration (FDA) is setting a new standard in the development process and the psychometric properties of questionnaires used to evaluate patients health-related quality of life (HRQoL). They are emphasising the importance of standardisation regarding terms of purpose, length, target population, mode of administration and content. The new PRO guidelines might even out the gap between clinical signs and symptoms in DED (Guillemin et al., 2012). A study assessing the performance and repeatability of the self-administered NEI-VFQ-25 questionnaire found it to indicate more ocular pain than the published normative values (K. K. Nichols, Mitchell, & Zadnik, 2002). Both questionnaires in this study were made before the new guidelines and the present correlation between OSDI and NEI VFQ-25 scores in this study suggests that patient's assessments of their health are valid. Patients might be prone to colour the experience of their self-reported problems in the questionnaires according to socially expected tolerance to pain and discomfort. This can lead to an under-estimation of reported symptoms, and that more severe forms of DED are treated ass less severe. Our study has not investigated or taken into account the influence of all possible risk factors, like medicine and seasonal variations, affects DED. The size of our sample was calculated to be able to detect a difference in mean general vision score between patients with and without dry eye symptom, it should also have been calculated to be able to detect a difference in mean ocular pain score.

Recommendations for further research: In a larger study it would be interesting to investigate the group of DED unclassifiable patients and look for common features. Studies of the prevalence of DED in the general population in Norway, according to the new diagnosis criterions in DEWS II, would be beneficial and helpful to apply the results found in our study to our understanding of general health. The possibility of bias in the test results due to test interactions, points in the direction that the diagnostic process of DED still are too complicated, and that further research aimed to simplify the diagnostic process is necessary. There is not yet any gold-standard diagnostic instrument available, and the clinical assessment of signs needs to be based on a battery of tests (Wolffsohn et al., 2017), and there are still several measurements and sub-categorizations to be made before a treatment plan can be made. A new, all in one, gold standard instrument would be of great value to the clinician.

5 Conclusion

In this study, patients' VQoL was reduced by DED. Patients with DED experienced more ocular pain and poorer general vision than non-DED patients. These findings suggest that DED and its adverse, negative, effects on VQoL is a public health issue in Norway. We propose that preventing or treating DED is beneficial because it can reduce ocular pain and poor vision, which can be a burden for both the patient and the society, and that DED, should be a subject of sheared-care between optometrists and ophthalmologists. Further studies should explore the prevalence of dry eye in the general population in Norway and the effect of systematic dry eye assessment and treatment in Norwegian optometric practice according to the new diagnostic guidelines given in DEWS II.

List of figures, tables and charts

Appendixes

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FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

Tørre øyne, meibomsk kjerteldysfunksjon og synsrelatert livskvalitet blant voksne pasienter i en norsk optometrisk praksis

Dette er et spørsmål til deg om å delta i ett forskningsprosjekt hvor formålet er å undersøke tilstandene tørre øyne og meibomsk kjerteldysfunksjon, og hvordan disse påvirker synsrelatert livskvalitet blant pasienter med og uten symptomer på tørre øyne. Du forespørres om å delta fordi du har hatt synsundersøkelse hos Erøy Optikk AS. Forskningsprosjektet gjennomføres som del av en masteroppgave ved Institutt for optometri, radiografi og lysdesign, Fakultet for helse og sosialvitenskap, Høgskolen i Sørøst-Norge.

HVA INNEBÆRER PROSJEKTET?

Ved deltakelse i prosjektet vil du bli bedt om å fylle ut to spørreskjema knyttet til tørre øyne symptomer og livskvalitet. Alle deltakere får utført en tørreøyneundersøkelse hvor din tårekvalitet og tåremengde blir målt, øyelokk og øyets overflate blir undersøkt med hensyn til forandringer knyttet til tørre øyne. Undersøkelsen vil ta ca. 30 minutter.

I prosjektet vil vi innhente og registrere opplysninger om deg. Dette er opplysninger som kjønn, alder og resultater fra spørreskjemaer og kliniske tester. Dine opplysninger og resultater vil under prosjektperioden være knyttet til en navneliste gjennom en kode. Kodenøkkelen slettes når datainnsamlingen er avsluttet. Opplysningene som lagres vil i etterkant ikke kunne knyttes til din person.

MULIGE FORDELER OG ULEMPER

Som deltaker i prosjektet får du gjennomført en komplett tørre øyne undersøkelse. Undersøkelsen inkluderer måling av tårenes saltinnhold (osmolaritet), spaltelampeundersøkelse av det ytre øye, vurdering av tårefilmens stabilitet, vurdering av øyets overflate, tårevolumberegning med Phenol rød tråd, vurdering av de meibomske kjertlene og meibografi. Du vil få oppdaterte råd, veiledning og tilbud om behandling som kan lindre dine plager dersom det er behov for dette. Det er ikke knyttet risiko, betydelig ubehag eller bivirkninger til noen av de kliniske testene. Det vil bli brukt lys som av noen kan oppfattes som generende og i to av testene vil det bli påført ett lett trykk mot nedre øyelokk. Tørre øyne undersøkelsen er gratis.

Tørre øyne, meibomsk kjerteldysfunksjon og synsrelatert livskvalitet blant voksne pasienter i en norsk optometrisk praksis

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling ved Erøy Optikk AS. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte optiker og masterstudent Åsmund A. Erøy på tlf: 99097733 eller epost: aasmund@eroyoptikk.no.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Prosjektleder, førsteamanuensis Vibeke Sundling, Fakultet for Helsevitenskap, Institutt for Optometri og Synsvitenskap ved Nasjonalt Senter for optikk syn og øyehelse har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt. Prosjektleder kan kontaktes på tlf: 924 24 360 eller vibeke.sundling@usn.no .

FORSIKRING

Pasientskadeloven.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, 2017/2542/REK sør-øst (16.02.18).

Tørre øyne, meibomsk kjerteldysfunksjon og synsrelatert livskvalitet blant voksne pasienter i en norsk optometrisk praksis

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato

Signatur

Masterstudent

PB/SA

National Eye Institute
Spørreskjema om synsfunksjon - 25
(VFQ-25)

(FOR EGENUTFYLLING)

Februar 1997

Dette er et spørreskjema med utsagn om problemer du har med synet ditt, eller følelser du har omkring dette. Etter hvert spørsmål ber vi deg velge det svaret som best beskriver din egen situasjon.

Vennligst svar på alle spørsmålene som om du hadde på deg dine briller eller kontaktlinser (hvis du bruker noe av dette).

Vennligst ta den tiden du trenger for å svare på hvert spørsmål. Alle svar behandles konfidensielt. For at denne spørreundersøkelsen skal øke vår kunnskap om synsproblemer og hvorledes disse problemene påvirker din livskvalitet, må svarene være så presise som mulig. Husk at dersom du bruker briller eller kontaktlinser, så vennligst svar på alle spørsmålene som om du hadde dem på deg.

VEILEDNING:

1. I det store og hele vil vi helst at folk forsøker å fylle ut disse skjemaene på egenhånd. Dersom du merker at du trenger hjelp, så vennligst ikke nøl med å henvende deg til prosjektmedarbeiderne, som vil gi deg assistanse.

2. Vennligst svar på alle spørsmålene (unntatt de spørsmålene du blir bedt om å hoppe over, fordi det/de neste spørsmål(ene) ikke angår deg).

3. Svar på spørsmålene ved å sette en ring rundt tallet for det svaret som passer.

4. Hvis du er usikker på hvilket svar du skal velge, vennligst velg det svaret som passer best, og sett en kommentar i venstre marg.

5. Vennligst fyll ut skjemaet før du går herfra og gi det til en av prosjektmedarbeiderne. Ta ikke med skjemaet hjem.

6. Hvis du har noen spørsmål, må du gjerne spørre en av prosjektmedarbeiderne, og de vil med glede hjelpe deg.

KONFIDENSIELLE OPPLYSNINGER:

Alle opplysninger som kunne tillate identifisering av en person som har fylt ut dette skjemaet, skal anses som strengt konfidensielle. Slike opplysninger vil bare bli brukt til denne undersøkelsens formål, og vil ikke være tilgjengelige for innsyn eller bruk til andre formål uten forhåndssamtykke, unntatt dersom loven krever det.

Spørreskjema om synsfunksjon - 25

DEL 1 - HELSE OG SYN GENERELT

1. <u>Stort sett</u>, vil du si at din <u>helse</u> alt i alt er:

(Sett ring rundt ett tall)

Utmerket 1
Meget god 2
God 3
Nokså god 4
Dårlig 5

2. Vil du si at synet ditt på det nåværende tidspunkt, når du bruker begge øynene (med briller eller kontaktlinser hvis du bruker det), er <u>utmerket</u>, <u>godt</u>, <u>nokså godt</u>, <u>dårlig</u> eller <u>meget dårlig</u>, eller er du <u>helt blind</u>?

(Sett ring rundt ett tall)

Utmerket 1
Godt 2
Nokså godt 3
Dårlig 4
Meget dårlig 5
Helt blind 6

3. Hvor ofte bekymrer du deg om synet ditt?

(Sett ring rundt ett tall)

Aldri	**1**
Sjelden	**2**
Iblant	**3**
Ofte	**4**
Alltid	**5**

4. Hvor mye smerte eller ubehag har du hatt i eller rundt øynene (for eksempel at det brenner, klør eller gjør vondt)?

(Sett ring rundt ett tall)

Ingen/ikke noe	**1**
Mild(t)	**2**
Moderat	**3**
Sterk(t)	**4**
Meget sterk(t)	**5**

DEL 2 - VANSKER MED GJØREMÅL

De neste spørsmålene dreier seg om hvor store vansker, om noen, du har med å utføre visse gjøremål når du bruker briller eller kontaktlinser, dersom du bruker briller eller kontaktlinser til slike gjøremål.

5. Hvor store vansker har du med å lese vanlig skrift i en avis?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

6. Hvor store vansker har du med å drive med arbeid eller hobbyer som krever at du må se godt på kort avstand, slik som matlaging, søm, småreparasjoner i hjemmet eller bruk av håndholdt verktøy?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

7. Hvor store vansker har du, på grunn av synet ditt, med å finne noe på en overfylt hylle?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

8. Hvor store vansker har du med å lese veiskilt eller navnet på butikker?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

9. Hvor store vansker har du, på grunn av synet ditt, med å gå ned trinn, trapper eller fortauskanter i svak belysning eller når det er mørkt?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

10. Hvor store vansker har du, på grunn av synet ditt, med å legge merke til gjenstander som er til siden for deg når du er ute og går?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

11. Hvor store vansker har du, på grunn av synet ditt, med å se hvordan folk reagerer på ting du sier?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

12. Hvor store vansker har du, på grunn av synet ditt, med <u>å velge og sette sammen dine egne klær</u>?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

13. Hvor store vansker har du, på grunn av synet ditt, med <u>å være sammen med mennesker hjemme hos folk, i selskaper eller på restauranter</u>?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

14. Hvor store vansker har du, på grunn av synet ditt, med <u>å gå på forestillinger/oppvisninger, i teater eller på sportsbegivenheter</u>?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**

Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette..... 6

15. Kjører du selv bil for tiden, i alle fall en gang iblant?

(Sett ring rundt ett tall)

Ja..... 1 ***Gå til spm. 15c***

Nei 2

15a. HVIS NEI: Har du aldri kjørt bil, eller har du sluttet med å kjøre?

(Sett ring rundt ett tall)

Har aldri kjørt.... 1 ***Gå til del 3, spm. 17***

Har sluttet 2

15b. HVIS DU HAR SLUTTET Å KJØRE: Sluttet du først og fremst på grunn av synet, først og fremst av andre grunner, eller både på grunn av synet og av andre grunner?

(Sett ring rundt ett tall)

Først og fremst synet ..... 1 ***Gå til del 3, spm. 17***

Først og fremst andre grunner .... 2 ***Gå til del 3, spm. 17***

Både synet og andre grunner ..... 3 ***Gå til del 3, spm. 17***

15c. HVIS DU KJØRER SELV FOR TIDEN: Hvor store vansker har du med å kjøre på dagtid på kjente steder?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt 1
Små vansker 2
Moderate vansker 3
Svært store vansker 4

16. Hvor store vansker har du med å kjøre når det er mørkt?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

16a. Hvor store vansker har du med å kjøre under vanskelige forhold, slik som i rushtiden, på motorveien, i bytrafikk eller i dårlig vær?

(Sett ring rundt ett tall)

Ingen vansker i det hele tatt	**1**
Små vansker	**2**
Moderate vansker	**3**
Svært store vansker	**4**
Har sluttet å gjøre dette pga. synet	**5**
Har sluttet å gjøre dette av andre grunner, eller er ikke interessert i å gjøre dette	**6**

DEL 3 - KONSEKVENSER AV SYNSPROBLEMER

De neste spørsmålene dreier seg om hvorledes ting som du gjør kan bli påvirket av synet ditt. For hvert spørsmål ber vi deg sette en ring rundt det tallet som viser om utsagnet stemmer for deg alltid, ofte, iblant, sjelden eller aldri.

	(Sett ring rundt ett tall på hver linje)				
	Alltid	**Ofte**	**Iblant**	**Sjelden**	**Aldri**
17. Får du utrettet mindre enn det du kunne ønske på grunn av synet?	**1**	**2**	**3**	**4**	**5**
18. Er det begrenset hvor lenge du kan arbeide eller drive med andre gjøremål på grunn av synet?	**1**	**2**	**3**	**4**	**5**
19. Hvor mye hindrer smerte eller ubehag i eller rundt øynene (for eksempel at det brenner, klør eller gjør vondt) deg i å drive med det du har lyst til å drive med?	**1**	**2**	**3**	**4**	**5**

For hvert av de følgende utsagnene ber vi deg sette en ring rundt det tallet som viser om utsagnet gjelder for deg i meget stor grad, i stor grad, i liten grad eller overhodet ikke, eller om du er usikker.

(Sett ring rundt ett tall på hver linje)

	I meget stor grad	I stor grad	Usikker	I liten grad	Over-hodet ikke
20. På grunn av synet holder jeg meg hjemme mesteparten av tiden	**1**	**2**	**3**	**4**	**5**
21. På grunn av synet føler jeg meg oppgitt og frustrert mye av tiden	**1**	**2**	**3**	**4**	**5**
22. På grunn av synet har jeg mye mindre kontroll over det jeg gjør	**1**	**2**	**3**	**4**	**5**
23. På grunn av synet må jeg stole alt for mye på det andre folk forteller meg.....	**1**	**2**	**3**	**4**	**5**
24. På grunn av synet trenger jeg mye hjelp fra andre.....	**1**	**2**	**3**	**4**	**5**
25. På grunn av synet bekymrer jeg meg for å gjøre ting som vil være pinlig for meg selv eller andre.....	**1**	**2**	**3**	**4**	**5**

Ocular surface disease index (OSDI©)[2]

Be pasienten svare på følgende 12 spørsmål ved å sette en sirkel rundt tallet i den boksen som passer best for hvert svar. Kryss deretter av i rubrikkene A, B, C, D og E etter gitt instruksjon ved siden av rubrikken.

Har du opplevd noen av de følgende symptomene *i løpet av forrige uke?*	**Hele tiden**	**Det meste av tiden**	**Halv-parten av tiden**	**Noe av tiden**	**Ikke noe av tiden**
1. Øyne som er sensitive for lys?	4	3	2	1	0
2. Sandfølelse i øynene?	4	3	2	1	0
3. Smertefulle eller såre øyne?	4	3	2	1	0
4. Tåkesyn?	4	3	2	1	0
5. Dårlig syn?	4	3	2	1	0

Delsum for svarene 1 til 5 **(A)**

Har øyeproblemene dine begrenset deg i å utføre noe av det følgende *i løpet av forrige uke?*	**Hele tiden**	**Det meste av tiden**	**Halv-parten av tiden**	**Noe av tiden**	**Ikke noe av tiden**	**IA Ikke aktuelt**
6. Lesing?	4	3	2	1	0	IA
7. Kjøring om kvelden?	4	3	2	1	0	IA
8. Skjermarbeid?	4	3	2	1	0	IA
9. Se på TV?	4	3	2	1	0	IA

Delsum for svarene 6 til 9 **(B)**

Har du følt ubehag i øynene dine i noen av følgende situasjoner *i løpet av forrige uke?*	**Hele tiden**	**Det meste av tiden**	**Halv-parten av tiden**	**Noe av tiden**	**Ikke noe av tiden**	**IA Ikke aktuelt**
10. I vind	4	3	2	1	0	IA
11. På steder eller områder med lav luftfuktighet (veldig tørt)	4	3	2	1	0	IA
12. På steder hvor klimaanlegg er i bruk	4	3	2	1	0	IA

Delsum for svarene 10 til 12 **(C)**

Legg sammen delsummene A, B og C for å få D
(D = summen av alle besvarte spørsmål) **(D)**

Antall besvarte spørsmål
(Ikke regn med spørsmål besvart med IA) **(E)**

Vennligst snu spørreskjemaet for å beregne pasientens endelige OSDI© poengsum.

Checklist for the DED VQoL-study:

Examinations and Results

Date of examination: **Study Id. nr.:**
Name of patient:
Date of birth:
Name of patients` GP:

Any adverse events during the examination:

No: **Yes:**
……

Relevant History and symptoms
……
……
……

Allergy

No: **Yes:**

Smoking (def: one or more cigarettes pr. day in a normal week)

No: **Yes:**

CL wear (Nr of daily use in a normal week)

No: **Yes:**

Medicine:

……

Screen time

……

Other relevant information:
……

Questionnaires	Score
1.a.: OSDI Questionnaire Normal = 0-12, mild = 13-22, moderate = 23-32 and severe = 33-100)	
1.b.: NEI-VFQ-25	

OD / RIGHT EYE					**OS / LEFT EYE**			
mOsm/L				**2. TEAR OSMOLARITY** Cut-off value ≥ 316 mOsm/L (i-Pen)	mOsm/L			
				3. BEST CORRECTED VISUAL ACUITY (LogMar)				
……. mm				**4.a. TEAR MENISCUS HEIGHT (TMH)** (Keratograph)	…… mm			
Sec.	Sec.	Sec.	Sec. (avg.)	**4.b. Non-invasive Keratograph Break-up Time (NIKBUT)** (Keratograph)	Sec.	Sec.	Sec.	Sec. (avg.)
Temporal:		Nasal:		**4.c. BULBAR REDNESS** (Keratograph)	Nasal:		Temporal:	
Temporal:		Nasal:		**4.d. LIMBAL REDNESS** (Keratograph)	Nasal:		Temporal:	
Type: Normal: Reduced:				**4.e. Lipid Layer Thickness** (Image types: 1-4 by Remeseiro) Type 1: ~13-15 nm, 2: ~ 30-50 nm,3: ~50-80 nm, 4: ~ 90-14 nm (Keratograph)	Type: Normal: Reduced:			

				5.a. EYE LIDS Ectropion / entropion / trichiasis, eye lid tumor, (Slit-lamp)				
Blepharitis, anterior, upper and lower, grade 0-4 (Efron):				**5.b. Anterior blepharitis** (Slit-lamp)	Blepharitis anterior, upper and lower, grade 0-4 (Efron):			
Grade 0-3 temp.		Grade 0-3 nas.	Sum	**5.c LIPCOF** (Slit-lamp)	Grade 0-3 temp		Grade 0-3 nas.	Sum
Sec.	Sec.	Sec.	Avg. Sec.	**6. FBUT** (Slit-lamp)	Sec.	Sec.	Sec.	Ang. Sec.
Grade Temp.	Grade Corneal	Grade Nasal	Total	**7.a OCULAR SURFACE STAINING and GRADING Fluorescein** (Oxford grading)	Grade Temporal	Grade Corneal	Grade Nasal	Total

<table>
<tr><td>Grade Temp.</td><td>Grade Corneal</td><td>Grade Nasal</td><td>Total</td><td>7.b. OCULAR SURFACE STAINING and GRADING Lissamine Green (Oxford grading)</td><td>Grade Temporal</td><td>Grade Corneal</td><td>Grade Nasal</td><td>Total</td></tr>
<tr><td colspan="4">Positive/negative</td><td>8. LWE</td><td colspan="4">Positive/negative</td></tr>
<tr><td colspan="4">…… mm /20 sek.</td><td>9. PRT TEST</td><td colspan="4">…… mm/20 sek.</td></tr>
<tr><td colspan="2">Nr. of expressible glands OD

……..</td><td colspan="2">Grade

……..</td><td>10.a. MEIBUM EXPRESSIBILITY
(Central 5 glands)
Grade 0= All 5 glands expressible,
Grade 1= 3 - 4 glands expressible,
Grade 2= 1 - 2 glands expressible,
Grade 3= 0 gland expressible</td><td colspan="2">Nr. of expressible glands OS

……..</td><td colspan="2">Grade

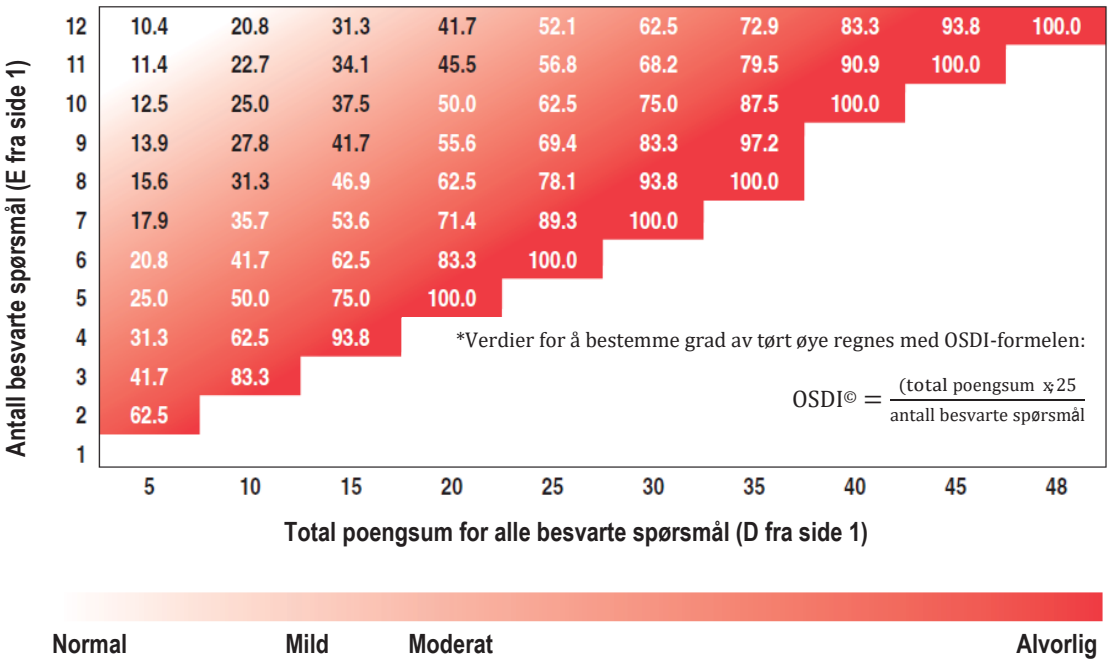
……..</td></tr>
<tr><td colspan="2">Nr. of glands X grade for the quality = score
…. glands x 0 =
…. glands x 1 =
…. glands x 2 =
…. glands x 3 =</td><td colspan="2">Total score</td><td>10.b. MEIBUM QUALITY (central 8 glands evaluated for the quality of expressed meibum).
Clear fluid= 0, cloudy fluid= 1, cloudy particulate fluid = 2 , Like toothpaste = 3</td><td colspan="2">Nr. of glands X grade for the quality = score
…. glands x 0 =
…. glands x 1 =
…. glands x 2 =
…. glands x 3 =</td><td colspan="2">Total score</td></tr>
<tr><td colspan="4">Upper lid:</td><td>11. MEIBOGRAPHY
Grading of meibomian gland drop-out level
Upper lid according to “Meiboscale”</td><td colspan="4">Upper lid:</td></tr>
</table>

EVALUERING AV OSDI©[1]

OSDI© vurderes på en skala fra 0 til 100. Høyere poengsum representerer alvorligere grad av tørt øye. Indeksen viser sensitivitet og spesifisitet i å skille mellom normale personer og personer med tørre øyne. OSDI© er et sterkt og pålitelig verktøy for å måle tørt øye (normal, mild til moderat og alvorlig) og effekten på synsfunksjonen.

VURDERING AV PASIENTENS TØRRE ØYNE [1, 2]

Bruk svarene D og E fra side 1 for å sammenligne poengsummene fra alle besvarte spørsmål (D) og antall besvarte spørsmål (E) med diagrammet nedenfor*. Finn ut hvor din pasients poengsum ligger. Sammenlign rødheten med skalaen nedenfor for å bestemme om din pasients poengsum indikerer normale, milde, moderate eller alvorlig tørre øyne.



Pasientens navn:_____Dato:_____

Hvor lenge har pasienten opplevd symptomer på tørre øyne? _____

Øyehelsepersonellets kommentarer:

_____

_____

_____

_____

1. Lagrede data, Allergan Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Disease Index. Arch Ophthalmol. 2000; 118:615-621

Oversatt av Ann Elisabeth Ystenæs, Vibeke Sundling, Jan Richard Bruenech
07-07-2017

Version 2000

The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25)

Version 2000

This final version of the VFQ-25 differs from the previous version in that it includes an extra driving item from the appendix of supplementary questions as part of the base set of items. Also, the revised scoring algorithm excludes the single-item general health rating question from the calculation of the vision-targeted composite score. Because of these 2 changes, the base set of items actually includes 26 questions, however, only 25 are vision-targeted and included in the composite score. Please see the "Frequently Asked Questions" or FAQ section for additional clarifications of these changes.

Background

The National Eye Institute (NEI) sponsored the development of the VFQ-25 with the goal of creating a survey that would measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases. Because of this goal, the survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. Questions included in the VFQ-25 represent the content identified during a series of condition-specific focus groups with patients who had age-related cataracts, glaucoma, age-related macular degeneration, diabetic retinopathy, or CMV retinitis.[1]

The VFQ-25 is the product of an item-reduction analysis of the longer field test version of the survey called the 51-item National Eye Institute Vision Function Questionnaire (NEI-VFQ).[2] The longer version contains 51 questions which represent 13 different sub-scales. The NEI-VFQ Field Test Study collected the data needed to examine the reliability and validity of the survey across all of the above-mentioned ocular diseases. Also, reliability and validity was assessed in a heterogeneous group of patients with low vision from any cause and a group of age-matched persons with normal vision. A published report describes the psychometric properties of the longer field test version of the survey.[3] Additional a number of clinical studies have used either the 51 or the 25-item version of the NEI-VFQ across a number of chronic ocular conditions.[4-8] Despite the success of the longer field test version and its continued use, to enhance feasibility a short-form version was planned since the earliest developmental phase.

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 also includes an appendix of additional items from the 51-item version that researchers can use to expand the scales up to 39 total items. All items in the VFQ-25 are from the 51-item field test version; no new items were developed for use in the VFQ-25. Unless otherwise specified, the remainder of this document will use the term VFQ-25 to refer to the base set of items.

The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. There is also a self-administered version of the survey, however, psychometric testing of the self-administered version has not been done. The VFQ-25 generates the following vision-targeted sub-scales: global vision rating (1), difficulty with near vision activities (3), difficulty with distance vision activities (3), limitations in social functioning due to vision (2), role limitations due to vision (2), dependency on others due to vision (3), mental health symptoms due to vision (4), driving difficulties (3), limitations with peripheral (1) and color vision (1), and ocular pain (2). Additionally,

the VFQ-25 contains the single general health rating question which has been shown to be a robust predictor of future health and mortality in population-based studies. Please see the FAQ section for more information about the general health rating question.

Development of the NEI VFQ-25

The guiding principles for the selection of the short-form items included: 1) low item-level missing data rates; 2) normal distribution of response choices; and 3) retention of items that explained the greatest proportion of variance in the 51-item sub-scales. The items retained in the VFQ-25 and the optional items (provided in the appendix to the survey) are listed on Table 1. A report describing the performance of the VFQ-25 relative to the Field Test version is currently under review. [2] The reliability and validity of the VFQ-25 is similar to that observed for the 51-item version of the survey. On average, each VFQ-25 sub-scale predicts 92% of the variance in the corresponding 51-item sub-scale score.

Optional Items

Appendix 1 consists of additional questions that users may add to a specific sub-scale. Inclusion of these may be helpful if a particular sub-scale represents the primary domain of vision-targeted HRQOL that is felt to be most important for the condition under study. For example, if a user is testing a new treatment for macular degeneration, by adding near vision questions A3, A4, and A5 to VFQ-25 questions 5, 6, and 7, the investigator would have a six-item near vision scale rather than a three-item scale. The addition of these items would enhance the reliability of the near vision sub-scale and is likely to improve the responsiveness of the sub-scale to the intervention over time (Table 6). If items from the appendix are used, the VFQ-25 developers would encourage users to incorporate all optional items for a given sub-scale. This strategy will enhance the comparability of results across studies.

Scoring

Scoring VFQ-25 with or without optional items is a two-step process:

- First, original numeric values from the survey are re-coded following the scoring rules outlined in Table 2. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

- In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores. Table 3 indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the sub-scale that the respondent answered.

Composite Score Calculation

To calculate an overall composite score for the VFQ-25, simply average the vision-targeted sub-scale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each sub-scale, whereas averaging the items would give more weight to scales with more items.

Table 1. Item Number Translation from the 51-Item Field Test Version to the VFQ 25

S = retained in the VFQ-25, A = retained in the appendix should be used for the VFQ-39,

--- = deleted from the VFQ-25 & VFQ-39

Field Test Version Ques.#	Sub-scale	Status	VFQ-25 Ques. #	Field Test Version Ques.#	Sub-scale	Status	VFQ-25 Ques. #
1	general health	S	**1**	**29**	social fx	---	---
2	general health	A	**A1**	**30**	social fx	A	**A9**
3	general vision	S	**2**	**31**	social fx	S	**13**
4	expectations	---	---	**32**	distance vision	A	**A8**
5	well-being/ distress	S	**3**	**33**	distance vision	A	**A7**
6	well-being/ distress	---	---	**34**	distance vision	S	**14**
7	ocular pain	S	**19**	**35**	driving (filter item)	S	**15**
8	expectations	---	---	**35a**	driving (filter item)	S	**15a**
9	expectations	---	---	**35b**	driving (filter item)	S	**15b**
10	expectations	---	---	**35c**	driving	S	**15c**
11	well-being/ distress	S	**25**	**36**	driving	---	---
12	ocular pain	S	**4**	**37**	driving	S	**16**
13	well-being/ distress	---	---	**38**	driving	S	**16a ***
14	general vision	A	**A2**	**39a**	role limitations	S	**17**
15	near vision	S	**5**	**39b**	role limitations	A	**A11a**
16	near vision	A	**A3**	**39c**	well-being/ distress	---	---
17	near vision	S	**6**	**39d**	role limitations	---	---
18	near vision	---	---	**39e**	role limitations	A	**A11b**
19	near vision	S	**7**	**39f**	role limitations	S	**18**
20	distance vision	S	**8**	**40**	well-being/ distress	A	**A12**
21	distance vision	---	---	**41**	dependency	S	**20**
22	distance vision	S	**9**	**42**	well-being/ distress	S	**21**
23	peripheral vision	S	**10**	**43**	well-being/ distress	S	**22**
24	distance vision	A	**A6**	**44**	dependency	---	---
25	social fx	S	**11**	**45**	dependency	A	**A13**
26	near vision	A	**A4**	**46**	dependency	S	**23**
27	color vision	S	**12**	**47**	dependency	S	**24**
28	near vision	A	**A5**				

* VFQ-25 item 16a was listed in previous versions as part of the appendix of supplemental items (#A10).

Table 2. Scoring Key: Recoding of Items

Item Numbers	Change original response category [a]	To recoded value of:
1,3,4,15c[b]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a A3,A4,A5,A6,A7,A8,A9[c]	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25, A11a,A11b,A12,A13	1	0
	2	25
	3	50
	4	75
	5	100
A1,A2	0	0
	to	to
	10	100

[a] Precoded response choices as printed in the questionnaire.

[b] Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.

[c] "A" before the item number indicates that this item is an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use <u>all</u> items for a given sub-scale. This will greatly enhance the comparability of sub-scale scores across studies.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Table 3. Step 2: Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Table 4. Step 2: Averaging of Items to Generate VFQ-39 Sub-Scales (VFQ-25 + Optional Items)

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	2	1, A1
General Vision	2	2, A2
Ocular Pain	2	4, 19
Near Activities	6	5, 6, 7, A3, A4, A5
Distance Activities	6	8, 9, 14, A6, A7, A8
Vision Specific:		
Social Functioning	3	11, 13, A9
Mental Health	5	3, 21, 22, 25, A12
Role Difficulties	4	17, 18, A11a, A11b
Dependency	4	20, 23, 24, A13
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Figure 1. Example of VFQ-25 Scoring Algorithm for Near Activities Sub-Scale

5. How much difficulty do you have <u>reading ordinary print in newspapers</u>? Would you say you have:

No difficulty at all..... 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty **.....(4)**
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not
interested in doing this..... 6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing . . . ? Would you say you have:

No difficulty at all**.....(1)**
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not
interested in doing this..... 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf? Would you say you have:

No difficulty at all..... 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty **.....(4)**
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not
interested in doing this..... 6

Scoring example - Figure 1

Items 5, 6, and 7 are used to generate the near activities sub-scale score (Table 3). Each of the items has 6 response choices. Response choice 6 indicates that the respondent does not perform the activity because of reasons that are unrelated to vision. If a respondent selects this choice, the answer is treated as missing and an average of the remaining items is calculated. Response choice 5 indicates that an activity is so difficult that the participant no longer performs the activity. This extremely poor near vision response choice is recoded to "0" points before taking an average of all three items. To score all items in the same direction, Table 2 shows that responses 1 through 5 for items 5, 6, and 7 should be recoded to values of 100, 75, 50, 25, and 0 respectively. If the respondent is missing one of the items, the person's score will be equal to the average of the two non-missing items.

Formula:

$$\text{Mean} = \frac{\text{(Score for each item with a non-missing answer)}}{\text{Total number of items with non-missing answers}}$$

Example:

$$\text{With responses converted: } = \frac{(25 + 100 + 25)}{3} = 50$$

Note: 100 = Best, 0 = Worst possible score.

Psychometric properties of VFQ-25 sub-scales

Psychometric data for VFQ-25 reported in the earlier pre-publication version of the scoring manual have been updated and submitted for peer-reviewed publication.[2] The values reported in this document are identical to those reported in the future publication and should be used when citing the performance characteristics of the VFQ-25.

Statistical Power Calculations

Tables 8, 9, and 10 are provided to estimate statistical power when using the VFQ-25 and VFQ-39. These tables estimate the number of subjects needed per group to attain 80% power (alpha = 0.05, two-tailed) depending on the anticipated difference in scores between groups. Table 8 contains power calculations for changes over time between two experimental (i.e. randomized) groups using a repeated-measures design. For example, if one were interested in being able to detect a 5-point difference for the VFQ-25 General Vision sub-scale, one would need 271 subjects per group. Table 9 shows power calculations for two experimental groups using a single, post-intervention measurement design. Such a design is not as precise as a design that uses a baseline and post-intervention measurement points (i.e., more subjects are needed per group to detect the same difference). Table 10 provides corresponding sample size information for a non-experimental (i.e. non-randomized) repeated-measures design where subjects self-select into the two groups. One sees that the number of subjects needed per group is more than that needed for a randomized experiment (Table 8) and less than the number needed for a randomized, post-intervention-only measurement design (Table 9).

Table 8. Sample sizes needed per group to detect differences in *change over time* between two experimental groups for the VFQ-25, repeated measures design

		Number of Points Difference			
Scale Name	SD	2	5	10	20
VFQ-25:					
General Health	26.00	1696	271	68	17
General Vision	21.00	1106	177	44	11
Ocular Pain	17.00	725	116	29	7
Near Activities	29.00	2110	338	84	21
Distance Activities	29.00	2110	338	84	21
Social Functioning	27.00	1829	293	73	18
Mental Health	27.00	1829	293	73	18
Role Difficulties	29.00	2110	338	84	21
Dependency	28.00	1967	315	79	20
Driving	35.00	3073	492	123	31
Color Vision	23.00	1327	212	53	13
Peripheral Vision	27.00	1829	293	73	18
VFQ-25 Composite	20.00	1004	161	40	10
VFQ-39:					
General Health	21.00	1106	177	44	11
General Vision	19.00	906	145	36	9
Ocular Pain	17.00	725	116	29	7
Near Activities	28.00	1967	315	79	20
Distance Activities	26.00	1696	271	68	17
Social Functioning	25.00	1568	251	63	16
Mental Health	26.00	1696	271	68	17
Role Difficulties	28.00	1967	315	79	20
Dependency	27.00	1829	293	73	18
Driving	35.00	3073	492	123	31
Color Vision	23.00	1327	212	53	13
Peripheral Vision	27.00	1829	293	73	18
VFQ-39 Composite	21.00	1106	177	44	11

Note: Scales are all scored on 0-100 possible range. Estimates assume alpha = 0.05, two-tailed t-test, power = 80%, and an inter-temporal correlation between scores of 0.60.

Table 9. Sample sizes needed per group to detect differences between two experimental groups for the VFQ-25, *post-intervention measures only*.

		Number of Points Difference			
Scale Name	SD	2	5	10	20
VFQ-25:					
General Health	26.00	2650	424	106	26
General Vision	21.00	1729	277	69	17
Ocular Pain	17.00	1133	181	45	11
Near Activities	29.00	3297	527	132	33
Distance Activities	29.00	3297	527	132	33
Social Functioning	27.00	2858	457	114	29
Mental Health	27.00	2858	457	114	29
Role Difficulties	29.00	3297	527	132	33
Dependency	28.00	3073	492	123	31
Driving	35.00	4802	768	192	48
Color Vision	23.00	2074	332	83	21
Peripheral Vision	27.00	2858	457	114	29
VFQ-25 Composite	20.00	1568	251	63	16
VFQ-39:					
General Health	21.00	1729	277	69	17
General Vision	19.00	1415	226	57	14
Ocular Pain	17.00	1133	181	45	11
Near Activities	28.00	3073	492	123	31
Distance Activities	26.00	2650	424	106	26
Social Functioning	25.00	2450	392	98	25
Mental Health	26.00	2650	424	106	26
Role Difficulties	28.00	3073	492	123	31
Dependency	27.00	2858	457	114	29
Driving	35.00	4802	768	192	48
Color Vision	23.00	2074	332	83	21
Peripheral Vision	27.00	2858	457	114	29
VFQ-39 Composite	21.00	1729	277	69	17

Note: Scales are all scored on 0-100 possible range. Estimates assume alpha = 0.05, two-tailed t-test, and power = 80%.

Table 10. Sample sizes needed per group to detect differences between two *self-selected groups* for the VFQ-25, repeated measures design

		Number of Points Difference			
Scale Name	SD	2	5	10	20
VFQ-25:					
General Health	26.00	2120	339	85	21
General Vision	21.00	1383	221	55	14
Ocular Pain	17.00	906	145	36	9
Near Activities	29.00	2637	422	105	26
Distance Activities	29.00	2637	422	105	26
Social Functioning	27.00	2286	366	91	23
Mental Health	27.00	2286	366	91	23
Role Difficulties	29.00	2637	422	105	26
Dependency	28.00	2459	393	98	25
Driving	35.00	3842	615	154	38
Color Vision	23.00	1659	265	66	17
Peripheral Vision	27.00	2286	366	91	23
VFQ-25 Composite	20.00	1254	201	50	13
VFQ-39:					
General Health	21.00	1383	221	55	14
General Vision	19.00	1132	181	45	11
Ocular Pain	17.00	906	145	36	9
Near Activities	28.00	2459	393	98	25
Distance Activities	26.00	2120	339	85	21
Social Functioning	25.00	1960	314	78	20
Mental Health	26.00	2120	339	85	21
Role Difficulties	28.00	2459	393	98	25
Dependency	27.00	2286	366	91	23
Driving	35.00	3842	615	154	38
Color Vision	23.00	1659	265	66	17
Peripheral	27.00	2286	366	91	23
VFQ-39 Composite	21.00	1383	221	55	14

Note: Scales are all scored on 0-100 possible range.Estimates assume alpha = 0.05, two-tailed t-test, power = 80%, and an inter-temporal correlation between scores of 0.60.

Frequently Asked Questions (FAQ)

Q. *What kind of permissions are required to use the VFQ-25 in a research study?*

The VFQ-25 is a public document available without charge for all researchers to use provided they identify the measure as such in all publications and cite the appropriate developmental papers. Users do not need to notify the developers or the NEI that they intend to use the measure. However, there are some specific permissions for using the VFQ-25 that are detailed on the cover page of the questionnaire itself. These include acknowledging in all publications that the VFQ-25 was developed by RAND and funded by the NEI, and that any changes made to the measure for your particular study will be identified as such.

Q. *Can I change the format of the VFQ-25 to suit my study?*

Any change to the wording or order of the items would constitute a change to the measure and should be specified as such in any published papers. Other than this, it is expected that researchers may need to change the format or appearance of items to suit their purposes.

As of August 2000, to our knowledge no studies have reported on the effect of item order on responses to VFQ-25 or other similar vision-targeted surveys. That is, whether responses change depending where particular items appear in the questionnaire. However, to ensure the comparability of scores across studies, it is our position that the order of items should not be changed.

Q. Has the VFQ-25 been translated into any other languages?

As of August 2000, the developers are aware of translation into approximately 9 languages. For the cost of distribution, a Spanish language version for Mexican-American populations is available from the UCLA and RAND based developers. The developers will provide researchers with the names of other persons to contact for other language translations. Should researchers wish to translate the VFQ-25, the same permissions apply, with the additional requirement that all publications specify responsibility for the translation along with instructions for obtaining a copy of the translated version.

Q. Do you have any additional normative information for specific populations?

The developers currently are not conducting studies for the express purpose of further investigating the psychometric properties of the VFQ-25 or producing normative data. However, many researchers are currently using the VFQ-25 as an endpoint or outcome in a number of health services and clinical studies. It is likely that as these studies are completed, results that are relevant to better understanding the performance of the VFQ-25 will accompany the main results of each study. The developers and staff at the NEI are aware of other researchers who are collecting condition-specific normative data on population-based samples with the VFQ-25 and when possible will provide contact information for these investigators to new users.

Q. How relevant is the normative data provided in the scoring manual to my sample?

The means, standard deviations, and statistical power values shown in this document were estimated using cross-sectional data from the Field Test Study. Participants recruited for the Field Test were not randomly sampled, but rather were identified for enrollment based on clinical criteria biased towards persons with moderate to severe forms of each target disease. Further, because it was our desire to enroll a broad spectrum of patients based on disease severity, we did not take into consideration treatment status. Please see references #3 for a full

description of the NEI-VFQ field test study sample.

Q. Why is a single-item general health item included in the VFQ-25?

During the developmental phase of the NEI-VFQ, vision-targeted health-related quality of life (HRQOL) was a relatively new concept. For this reason, we included this question to insure that researchers had a minimal amount of information about a person's general health status to use as a benchmark against other published samples or cohorts.

This general health rating question has been widely used in studies and is a robust predictor of future health and mortality. However, to fully measure generic HRQOL, many quality of life measurement experts recommend including a separate generic measure of HRQOL such as the SF-36 or SF-12.[9] In such a situation the single-item VFQ-25 general health rating question is not needed because the identical question is asked as part of these surveys.[10, 11]

Q. Should we be looking at the sub-scales or the composite score?

The VFQ-25 sub-scales are grouped by theme or domain. So, for example, items having to do with near vision are differentiated from items having to do with other vision activities like distance vision or ocular pain. This does not mean that the items are not highly correlated or that they are psychometrically distinct. What it does mean is that researchers should beforehand carefully consider which vision-specific domains are most likely to be influenced by a particular disease and/or treatment and then focus on the results from those sub-scales to support their findings.

The composite score is best used in situations where an overall measure of vision-targeted health related quality of life is desired. For example, in studies where it is not clear what the specific impact of ocular disease or a new treatment might be. Also, in situations where differences can be hypothesized between groups beforehand across multiple sub-scales but the overall sample size of the study is relatively small, because it is likely that the error term for the composite score is likely to be smaller than for any given sub-scale, it may be more efficient to represent these differences as a single score.

Q. What benefit is there to using the VFQ-25 over a measure more specific to a particular disease, like the Activity of Daily Vision Scale (ADVS)[10] for persons with age-related cataracts?

The VFQ-25 contains items that are very similar to items found in other vision-targeted measure like the ADVS that are more task oriented. However, whereas the ADVS was designed specifically to assess a set of activities most relevant to patients undergoing cataract surgery, the VFQ-25 expands the range of activities to measure the impact of ocular disease on broader domains of health such as social and emotional well-being. Serious ocular diseases that lead to irreversible loss of vision are likely to impact dimensions of a person's life beyond simple tasks such as driving or reading the newspaper, and similarly, by preserving vision, many successful interventions also will impact persons' lives at this more global level. Especially in these situations, use of the VFQ-25 should be considered.

Q. Why does the response to item 15b, "stopped driving due to vision <u>and</u> other reasons", generate a missing score for the subsequent driving items?

Driving items 15, 15a, and 15b are filter questions designed to specify whether a person has ever driven a car, and if so, whether they are currently driving or if they have stopped. If people have never driven a car, then, of course, their answers should be set to missing for all driving items. Similarly, this also applies to people who have stopped driving for other reasons not due to vision. However, in the course of pilot testing the field test participants wanted this additional mixed response option. It was our decision that although persons did indeed report

not driving due to vision, it was not clear how much of a role the "other" reason also played in this decision. Therefore, we set the scoring criteria for this response to be missing for all subsequent driving items to be absolutely sure that all driving responses reflected only problems with vision. Should researchers wish to change this response option to allow persons to answer subsequent driving items (currently there is a skip to item #17), this change should be noted in subsequent publications.

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Attachments include:

NEI VFQ-25 (IA = Interviewer-Administered format)
(SA = Self-Administered format)

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Anne S. Kavli	22845512	16.02.2018	2017/2542/REK sør-øst A
			Deres dato:	**Deres referanse:**
			05.12.2017	

Vår referanse må oppgis ved alle henvendelser

Vibeke Sundling
Høgskolen i Sørøst-Norge

2017/2542 Syn og livskvalitet hos pasienter med tørre øyne symptomer

Forskningsansvarlig: Høgskolen i Sørøst-Norge
Prosjektleder: Vibeke Sundling

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 18.01.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektbeskrivelse (revidert av REK)

Formålet med prosjektet er å undersøke synsrelatert livskvalitet hos pasienter som gjennomgår en tørre øyne-undersøkelse hos optiker. Man ønsker også å undersøke sammenhengen mellom tørre øyne, meibomsk kjerteldysfunksjon og livskvalitet, hvor mange av pasientene som undersøkes som trenger behandling for tørre øyne eller henvisning til øyelege samt forskjeller i livskvalitet hos pasienter som har symptomer på tørre øyne og de som ikke har dette.

Tørre øyne kan gi redusert livskvalitet og nedsatt arbeidskapasitet da dette påvirker folks evne til å for eksempel arbeide med datamaskin og kjøre bil. Dersom den generelle kunnskapen om tørre øyne og meibomsk kjerteldysfunksjon blant optikere øker, vil man kunne avdekke tilstandene tidlig og håndtere disse på en målrettet og effektiv måte.

Det planlegges å rekruttere deltakere ved at alle kvinner og menn mellom 18 og 70 år som gjennomfører en vanlig synsundersøkelse ved Erøy Optikk i perioden 1. februar 2018 til 1. november 2018 forespørres om å delta. Det vil også bli sendt brev til øyeleger i området med opplysninger om prosjektet og anmodning om deltakelse. Prosjektet vil bli kunngjort gjennom avisannonse og i sosiale medier.

Deltakerne vil fylle ut to spørreskjemaer, National Eye Institute Spørreskjema om synsfunksjon - 25 (VFQ-25) og Ocular surface disease index (OSDI©) 2. De vil også få en tørreøyneundersøkelse som omfatter måling av synsstyrke, tåreosmolaritet, tårevolum med keratograf, non-invasive keratograf tear break-up time (NIKBUT), evaluering av ytre øye med spaltelampe og keratograf, måling av kvaliteten på lipidlaget i tårefilmen med keratograf, vurdering av tårefilmens stabilitet, øyets overflateegenskaper, tårevolum/tåremenisk med keratograf, tårevolum med phenol rød tråd, fluorescein tear break-up time og meibomsk kjertelfunksjon. Det vil også registreres bakgrunnsinformasjon som kjønn og alder.

Vurdering

Bedre hjelp for pasienter med tørre øyne hos optiker vil være nyttig både for pasientene og samfunnet. Belastningen for deltakerne er liten, og komiteen anser prosjektet som forsvarlig å gjennomføre.

I følge informasjonsskrivet vil det ikke bli utført videre undersøkelser dersom spørreskjemaene avdekker at deltakeren ikke har tørre øynesymptomer. I følge protokoll og søknadsskjema vil alle deltakere få tørre øyne-undersøkelsen. Prosjektleder har bekreftet at alle deltakere skal ha undersøkelsen fordi tørreøynesymptomer, funnet ved bruk av spørreskjema, og kliniske funn, ikke alltid står i forhold til hverandre.

Komiteen stiller derfor følgende vilkår for godkjenning: at informasjonsskrivet revideres så det kommer frem at alle prosjektdeltakere skal få denne undersøkelsen.

Vedtak

Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33 under forutsetning av at ovennevnte vilkår oppfylles.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Det bes om at revidert informasjonsskriv innsendes til vårt arkiv.

Godkjenningen gjelder til 30.06.2019.

Komiteen avgjørelse var enstemmig.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, jf. helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK, jf. helseforskningsloven § 11.

Klageadgang

REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst A. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst A, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anne S. Kavli
Seniorkonsulent

Kopi til:heidi.kapstad@usn.no; Høgskolen i Sørøst-Norge ved øverste administrative ledelse: postmottak@usn.no

Universitetet i Sørøst-Norge

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(nedenfor kalt forfatteren)

er det inngått avtale om å tilgjengeliggjøre forfatterens verk,

tittel: Dry Eye Disease and Visual Quality of Life among Adult Patients seen in a Norwegian Optometric Practice

på de vilkår som er angitt nedenfor.

Fylles ut for studentoppgaver ☒ Masteroppgave ☐ Bacheloroppgave År: 2019

Tilgjengelighet: ☐ Åpen ☒ Klausulert til (dd/mm/åååå): 31.12.2022 ☐ Klausulert permanent/ingen publisering

Fakultet/studium: Fakultet for helse og sosialfag / Master i optometri og synsvitenskap

Privat e-postadresse: aasmund@eroyoptikk.no

Kristiansand, 02.05.2019

Sted, dato

Åsmund A. Erøy

Underskrift forfatter

Vibeke Sundling

Underskrift USN

Underskrift forfatter

Underskrift forfatter

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3.5 Dersom USN skulle bli gjort erstatningsansvarlig overfor tredjepart på grunn av at forfatteren ikke oppfyller sine plikter etter denne avtalen, skal forfatteren holde USN skadesløs.

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4.1 USN kan bare overføre sine rettigheter og/eller plikter i henhold til denne avtale til tredjepart såfremt forfatterens interesser etter avtalen blir ivaretatt i overføringsavtalen.

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Dry Eye Disease, Meibomian Gland Dysfunction and Visual Quality of Life among adult patients seen in a Norwegian optometric practice

07.06.18

Åsmund A. Erøy

Introduction

"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" (Craig et al.). DED is divided into two subtypes; Evaporative Dry Eye (EDE), where excessive evaporation of the tear film causes hyperosmolarity in the presence of normal lacrimal function, and Aqueous-Deficient Dry Eye (ADDE), were the lacrimal function is reduced and tear evaporation is normal with present hyperosmolarity (Lemp et al., 2007). The TFOS DEWS 2 report recommends that the term EDE and ADDE are used to describe the initiating basis of a dry eye but emphasises that with progression any form of DED may take on additional evaporative features (Bron et al.).

Meibomian Gland Dysfunction (MGD) plays an important role in the etiology of DED and is the leading cause of DED (Baudouin et al., 2016). "MGD is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease" (Nichols et al., 2011).

An unhealthy tear film, poor tear quality and ocular surface damages causes eyestrain, ocular discomfort, reduced vision and will untreated in the end lead to reduced quality of life and work capacity by lowering peoples ability to read, drive, work on computers and watch TV (Miljanović, Dana, Sullivan, & Schaumberg, 2007). A recent master's thesis by Ingeborg Sand at University College of Southeast Norway (2015) concluded that dry eye is an under diagnosed condition that can effect the quality of life and vision among patients, and that better knowledge and diagnose techniques among Norwegian optometrists can raise the quality of treatment to these patients (Sand, 2015). Optometrists in general need to know more about DED and MGD, its relevance in Visual Quality of life (VQoL) and its cause and effect, to be able to take care of patients in a professional and effective way. Because there is not yet any gold standard instrument or clear method to classify and diagnose MGD, it is in many cases overlooked and stays undiagnosed (Sullivan, 2014).

Prevalence studies on DED and MGD has been limited because of lack of consensus regarding a clear definition and standardized clinical assessment tools. The Report of the Meibomian Gland Workshop published in 2011, states that population-based studies are needed to better assess prevalence of dry eye disease and that further research to possibly find a gold standard diagnostic test is necessary (Novack et al.). The report also remarks that trials that specifically evaluates the association between MGD and dry eye would be beneficial (Nichols et al., 2011).

The capacity of Norwegian ophthalmologists is under great pressure because they are outnumbered (Skau, 2012). The average waiting time for patients is five months, and rising. The KONUS report expects a 76% increase in consultations by ophthalmologists by 2030. In 2009, about 9 % of the diagnoses made by ophthalmologists was ocular surface conditions, and the number is rising (Skau, 2012). A study by Sundling et al. 2007 found that 6 % of the patients in a general Norwegian optometric practice (n = 4052) was referred to ophthalmologist or general

practioner (Sundling et al., 2007). Whereas in a study by Lundmark et al. 2017, 3,6 % of all eye examinations (n = 49510) resulted in a referral (n = 1779) (Lundmark & Luraas, 2017a). Norwegian optometrists perform approximately 1,8 million eye examinations per year (Lundmark & Luraas, 2017b), (personal communication Per Kristian Knutsen, Synsinformasjon [Optical Information Council Norway]). DED patients that do not require prescription drugs can be diagnosed and managed by optometrists and should be a subject to shared care between optometrists and ophthalmologists. This will reduce the number of referrals to eye specialists. Research and improved competence on this field is therefore relevant due to socioeconomically matters.

Research objectives and significance

The results of the study will provide further knowledge about how MGD and DED affects VQoL among patients attending an optometric practice for a DED examination, and investigate the difference in VQoL between patients with and without DED symptoms and thereby increase the general knowledge about DED and MGD in optometric practice. This can help optometrists to provide targeted examination, diagnosis and treatment, and may improve visual quality of life in patients, and reduce the number of referrals to ophthalmologists.

Primary objectives: To explore the VQoL of patients attending a dry eye examination in a Norwegian optometric practice.

Secondary objectives:
- To understand the association between DED, MGD and VQoL.
- To reveal the number of patients examined in optometric practice for dry eye symptoms that needs DED or MGD treatment.
- To understand the difference in VQoL in patients with and without DED symptoms.
- To investigate the number of DED patients that needs referral to ophthalmologist.

Study design

The study will have a prospective, cross-sectional design. Data collection will be carried out between 01 February 2018 and 01 December 2018.

Study sample

Target population: All adult men and women with or without signs and/or symptoms of dry eye and/or ocular discomfort.

Study population: All men and women between 18 and 70 years with or without dry eye symptoms and/or ocular discomfort who wants to have either a standard eye examination, or a dry eye examination at Erøy Optikk AS in the period between 01 February 2018 and 01 December 2018, will be invited to participate in the study.

The study will aim for a sample of at least (n=40) subjects, 20 patients with dry eye and 20 patients without dry eye.

Sample size, n=40 is calculated with a sample size calculator (http://sampsize.sourceforge.net/) to be able to detect a difference in mean score general vision on the NEI-VFQ 25 questionnaire (Mangione et al., 2001) between

patients with dry eye symptoms (69 ±12) (Le et al., 2012) and patients without dry eye symptoms (83 ±12) (Mangione et al., 2001) with a precision (alpha) of 5% and power of 90%.

Exclusion criteria

Patients unable to give informed consent and patients with superficial eye infections, ocular traumas that complicates the procedures or known hypersensitivity to fluorescein and/or lissamine green will be excluded from the study.

Variables

Outcome variables

DED: The score from the Ocular Surface Disease Index questionnaire is recorded on an ordinal scale from 0 to 100. Positive diagnose is given with OSDI score $\geq$ 13 and at least one positive result of the following homeostasis marker: Non-invasive keratograph brake up time (NIKBUT) $<$ 10 seconds, osmolarity $\geq$ 308 mOsm/L in either eye or intraocular difference $>$ 8 mOsm/L, lissamine green staining $>$ 9 conjunctival spots, fluorescein staining $>$ 5 corneal spots or lid wiper epitheliopathy of $\geq$ 2mm length and/or $\geq$ 25% width (Wolffsohn et al., 2017).

MGD: Positive diagnose is given with MGD stage 2 (minimal to mild symptoms of ocular discomfort, itching or photophobia, minimal to mild MGD clinical signs, scattered lid margin features, mildly altered secretions: grade >4- <8, expressibility: 1, none to limited ocular surface staining [DEWS grade 0-7; Oxford grade 0-3]), (figure 1.), based on the "MGD staging used to guide treatment" from the MGD workshop 2011 (Nichols et al., 2011).

VQoL: The score from the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) is registered on an ordinal scale from 0 to 100 (Mangione et al., 2001).

Osmolarity: Measured with i-Pen on a continuous scale (Wolffsohn et al., 2017).

Eyelid and external eye examination with respect to morphological changes related to MGD. Any pathology observed will be commented. “Normal” is noted when no pathology is observed

Blepharitis: Graded by the Efron scale. Registered on an ordinal scale from 0 to 4 in 0,5 steps (Efron, Morgan, & Katsara, 2001).

Bulbar redness: Assessed by Oculus Keratograph M5, graded by internal software

Tear meniscus height (TMH): Measured in millimetres (mm) with the Oculus Keratograph M5, registered on a continuous scale with two decimals (Wolffsohn et al., 2017).

Lid parallel conjunctival folds (LIPCOF): Graded by the LIPCOF scale, registered on an ordinal scale from 0 to 3 (Hoh, Schirra, Kienecker, & Ruprecht, 1995).

Phenol Red Thread: The moistened part of the thread will be measured in millimetres (mm), registered on a continuous scale with one decimal (Wolffsohn et al., 2017).

NIKBUT: Measured in seconds (s) with Oculus Keratograph M5, registered on a continuous scale with one decimal (Lei, Jing-Hao, Xiao-Yu, & Xu-Guang, 2016).

Corneal and conjunctival fluorescein staining: Score is calculated based on the Oxford Grading Scheme, registered on an ordinal scale from 0 to 15 (Bron AJ, 2003).

Meibomian gland expressibility: Registered on an ordinal scale from 0 to 3 (Tomlinson et al., 2011).

Meibum quality: Registered on an ordinal scale from 0 to 24 (Tomlinson et al., 2011).

Meibography: quantified by the Oculus Keratograph M5, graded by internal software

Predictor variables

Gender: dichotomous registration were males =1, and females =0.

Age: will be known from the patient history, and recorded in years on a continuous numerical scale.

Contact lens wear: user or non-user, number of daily use the last week.

Medicine: name and user program will be known from the patient history.

Smoking (daily): dichotomous registration were yes =1, and no =2.

Mean hours of smartphone, computer and tab use per day: recorded in hours on a continuous numerical scale.

Other variables

Best corrected VA measured with Snellen chart, registered on a logarithmic scale with 1 decimal.

Refraction: measured with standard optometric instruments and registered in dioptries in 0,25 step on a continuous scale.

Methods

Recruitment

Recruitment of patients will take place in the optometric practice of Erøy Optikk AS in Kristiansand, Norway, in the period from 01 May 2018 to 01 July 2018. Patients having a standard optometric examination at Erøy Optikk will continuously during the project orally be invited to participate in the study. There will also be advertisements in the local newspaper and social medias to join the project. At the end of the standard eye exam and before the dry eye examination the patients will get the

written information form and the informed consent form, and will have the opportunity to ask questions. The patients are free to leave the study at any time without providing any reason.

Measurements

The sequence of tests to be performed is chosen according to the National Centre for Optics, Vision and Eye care protocol for dry eye assessment (USN, 2017), and the recommendations given in the TFOS DEWS 2 report (Wolffsohn et al., 2017).

1) a. Quality of life: Assessed with the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). Patients are asked to mark out the answers most correct on the questionnaire. The total score will be calculated according to the NEI VFQ-25 manual. The NEI VFQ-25 has been used in several clinical studies across a number of chronic ocular conditions, and is validated (Mangione et al., 2001). Translation into Norwegian is validated (Mangione, 2017).

1) b. Symptoms: Assessed with the "Ocular Surface Disease Index" (OSDI) questionnaire form. Patients are asked to mark out the answers most correct on the questionnaire. Ocular Surface Disease Index has been used in several dry eye studies, and is validated (Schiffman, Christianson, Jacobsen, Hirsch, & Reis, 2000). Translation into Norwegian is validated (Sundling, personal communication).

2) Osmolarity: Measured with i-Pen (I-MED Pharma Inc.). The i-Pen measures the tear film osmolarity directly from the tear volume on the inside of the inferior, lateral conjunctiva. The test pen has an osmolarity test chip on its tip, and uses one for each eye. The cut-off value for hyperosmolarity is $\geq$ 316 mOsm/L. The value is validated and widely used (Wolffsohn et al., 2017).

3) Visual acuity: (if not previously registered in the eye examination). Best corrected LogMar VA is used for visual acuity assessment. Measured with standard optometric instruments, registered with one decimal on a continuous scale.

LogMar formula: LogMar = Baseline + (0,02 * the number of missed letters or letters not read)

“Baseline” = The lowest line where the test person is able to read at least one letter correctly

4) a. Tear meniscus height (TMH), using a Keratograph® 5M (Oculus, Optikgeräte, GmbH, Wetzlar, Germany). The patient is seated in front of the device with the chin in the chinrest, focusing on the light
⇒ Keratograph ⇒ examination ⇒ Tear meniscus height. One measurement is made perpendicular to the center of the cornea
b. Non-invasive keratograph break-up time (NIKBUT)
⇒ Keratograph ⇒ examination ⇒ NIKBUT (IR) ⇒ optimal focus ⇒ automatic measure three times. "Break-up (average)" is noted ⇒ the sum is divided by three. The patient is asked to blink twice according to the software advice, and the keep the eye open as long as possible. If the patient manages not to blink in more than 23 seconds without any break-up, 23 is noted.

c. Bulbar redness (Keratograph)
⇒ Keratograph ⇒ examination ⇒ Bulbar redness (IR) ⇒ picture manually taken. Special attention needs to be taken regarding focus. Redness is graded with the Keratograph internal software and noted N/T OU
d. Limbal redness (Keratograph)
Assesed from the "bulbar redness pictures), graded by Keratograph internal software. Special attention needs to be taken regarding focus.
e. Quality of lipid layer (Keratograph)
⇒ Keratograph ⇒ examination ⇒ lipid layer. The picture is evaluated. Normal (type 2) is noted when the patterns "amorphus", "closed meshwork", "wave" or normal colours appear. Amorphus refers to the most stable type of lipid layer o f about 80 micron thickness. Any "open meshwork pattern", globular or abnormal colours will be noted "not normal" (type 1) (Guillon, 1998)

5) Observation of the external eye through a slit-lamp with respect to morphological changes and signs of MGD. Any pathology observed will be commented. “Normal” is noted when no pathology is observed.

a. Eyelids: ectropion/entropion, trichiasis, eyelid tumor,
b. Anterior blepharitis (upper and lower lid), EFRON grading scale, assessed with Serve IT internal grading morph
c. LIPCOF (Lid parallel conjunctival folds): Observed on the bulbar conjunctiva in the areas perpendicular to the temporal and nasal limbus above the lower lid, with the slit-lamp and magnification 25X. (Hoh et al., 1995).

6) Fluorescein Break-up Time (FBUT): Observed through the slit-lamp using cobalt blue light and yellow filter, 10X magnification. Fluorescein from a saline moistened pre-impregnated fluorescein strips, is installed into the inferior, lateral fornix with the patient sitting behind the slit-lamp. One single drop of saline is used to release the dye, any excess fluid is gently shaken off. 30 seconds after instillation the procedure is carried out. The patient is instructed to blink three times, and then cease blinking until instructed. The time from the last blink until the first dry spot occurs is measured in seconds using an iPhone. FBUT is measured three times for each eye and the mean in calculated (Johnson & Murphy, 2007). A value ≤ 10 seconds is considered a positive finding (Wolffsohn et al., 2017). 45 is noted if the patient manages not to blink in 45 seconds with no visible break-up.

7) Ocular surface staining: (directly after FBUT)
a. Fluorescein staining: observed through the slit-lamp using cobalt blue light and yellow filter, 16X magnification. Saline moistened pre-impregnated fluorescein strips (Fluo GP, Pro Cornea), is installed into the inferior, lateral fornix with the patient sitting behind the slit-lamp if there is to little visible fluorescein after the FBUT. The staining is graded according to the Oxford grading scheme on a scale from 0 to 5 and the sum of the three panels (temp/mid/nas) is added (Bron AJ, 2003).
b. Lissamine green staining: observed through the slit-lamp using white light, no filter,16X magnification. Saline moistened pre-impregnated Lissamine green strips (Green Glo, AMWO), is installed into the inferior, lateral fornix with the patient sitting behind the slit-lamp. One drop of saline is used to release the dye, any excess fluid is gently shaken off. The staining is graded tree minutes after instillation according to the Oxford grading scheme on a

scale from 0 to 5 and the sum of the three panels (temp/mid/nas) is added (Bron AJ, 2003).

8) Lid wiper epitheliopathy (LWE): Observed through the slit-lamp stained with lissamine green dye, 3 minutes after instillation. One separate pre-impregnated strip is used for each eye, wet with 2 saline drops. Positive is LWE of ≥2 mm in length and/or ≥ 25% sagittal with excluding the line of Marx (Korb et al., 2005).

9) Phenol Red Thread: The folded end of the thread is hooked within the temporal one-third of the eyelid margin for 20 seconds. Eyes closed. The moistened part of the thread has now turned red, and is measured in mm. The test is performed with eyes open and normal blinking rate (Doughty, Whyte, & Li, 2007). The red part of the thread is measured without the folded end (REF = AMWO). <10mm is considered a positive finding (Pult, Purslow, & Murphy, 2011).

10) Assessment of meibomian glands function:

a. Number of expressible meibomian glands: The expressibility is assessed on the five most central glands on the lower eyelid. Evaluated through the slit-lamp by applying firm pressure with cotton tipped applicator to the five most central glands on the lower eyelid margin. The number of glands expressing is registered on a scale from 0 to 3 according to the grading scheme for expressibility of meibum (Tomlinson et al., 2011).

The grades are as follows:

Grade 0: 5	glands expressible
Grade 1: 3-4	glands expressible
Grade 2: 1-2	glands expressible
Grade 3: 0	glands expressible

b. Meibum quality: At the same time as the expressibility is evaluated, the quality of the expressed meibum from each of the central eight glands on the lower eyelid will be assessed on a scale from 0 to 3, according to the grading scheme for meibum quality (Tomlinson et al., 2011). The score from each of the glands will be summarized and give a possible maximum score of 24.

The grades are as follows:

Grade 0:	clear fluid
Grade 1:	cloudy fluid
Grade 2:	cloudy, particulate fluid
Grade 3:	like toothpaste

11 Meibography: To assess and quantify meibomian gland dropout in upper eyelid using Oculus K5.

Analyses

The OSDI and NEI VFQ-25 forms will be collected and stored in a letter holder in the building before they are scanned into a computer. Data from the dry eye examination will be registered and stored in an iMac using the Serve IT software. Backup is provided two times per day.

A personal identification number will identify the patients. The identification key will be kept separate from patient personal information. The project manager will punch the raw data from the paper forms and Serve IT into an Excel 2013 spread sheet. Entering the data twice will check the quality of the data material.

Empty cells and unrealistic values (missing data), will be searched for by algorithms in Excel (Microsoft Inc.) and empty cells will be coded 9999. Unrealistic data will be checked again and excluded or treated as missing. Statistical analyses will be performed using standard parametric or non-parametric tests in SPSS). Level of significance is set at 5%.

Patients that gets the diagnose MGD or dry eye will get further advice regarding treatment according to the DEWS 2 management and therapy report (Jones et al.).

Figure 1.

Stage	MGD Grade	Symptoms	Corneal Staining
1	+ Minimally altered secretions: Grade >2 - <4 Expressibility: 1	No	No
2	++ Mildly altered secretions: Grade >4- <8 Expressibility: 1	Minimal to mild	None to limited Oxford grade 0-3
3	+++ Moderately altered secretions: Grade >8- < 13 Expressibility: 2	Moderate	Mild to moderate; mainly peripheral Oxford grade 4-10
4	++++ Severely altered secretions: Grade >13 Expressibility: 3	Marked	Marked; central in addition Oxford grade 11-15]
"Plus" disease	Co-existing or accompanying disorders of the ocular surface and/or eyelids		

Clinical Summary of the MGD Staging Used to Guide Treatment, "The International Workshop on Meibomian Gland Dysfunction: "Executive Summary", 2011, Investigative Ophthalmology & Visual Science, 52(4), p. 1926.

Figure 2.

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓meniscus	Filamentary keratitis, mucus	Filamentary keratitis, mucus

			clumping, ↑ tear debris	clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

* Must have signs AND symptoms. TBUT: fluorescein tear break-up time. MGD: Meibomian gland disease

Figure 2, Dry eye severity grading scheme, "The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop", 2007, *The Ocular Surface*, 5(2), p. 88.

Project management and organization

Principal investigator: Vibeke Sundling

Project manager: Åsmund A. Erøy

Resources, equipment and physical facilities

- MacBook pro, iMac, standard equipment for refraction and dry eye examination owned by Erøy Optikk AS
- Software: Microsoft Office Word (student license), Microsoft Office Excel (student license), SPSS (licensed by the university college of Southeast Norway).

The tests will be carried out in the facilities of Erøy Optikk AS, Rona 8, Kristiansand, by optometrist Åsmund A. Erøy.

Project plan

Autumn 2016/spring 2018

Activity/month	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Creating ideas											
Literature study											
Protocol REK											

Autumn 2017/spring 2018

Activity/month	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Literature study											
Protocol REK											
Patients											

Autumn 2018/spring 2019

Activity/month	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Patients											
Data analysis											
Writing											
Presentation											

Dissemination:

There will be poster presentation, and an oral presentation of the master thesis at the University College of Southeast-Norway.

The results from the study will be submitted to international conferences and peer-review journals. Whenever possible, first author of published data will be Åsmund A. Erøy.

Ethical considerations:

The study will be performed after approval from the Regional Ethics Committee (REK). All the procedures applied in this study are non-invasive and will not cause any severe discomfort or pain. The procedures are all standard procedures in optometric practice and will last about thirty minutes. If the tests reveal a need for further follow up, the patient will be offered treatment to relief their symptoms. If necessary they will be referred to a specialist or assigned to a new appointment at Erøy Optikk. The tests carried out will give the patients a free dry-eye examination.

All the participants will have to sign an informed consent before they can join the study. The consent includes information about the study and the procedure. The participants are free to leave the study at any time without giving any reason and without consequences for further follow-up and management by Erøy Optikk AS. The data will be treated according to the project protocol. A personal identification key will link the patients to the information during the study. The key will be deleted shortly after the data collection is done.

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