University of South-Eastern Norway
Faculty of health- and social science

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Master's Thesis

Study programme: Optometry and visual science

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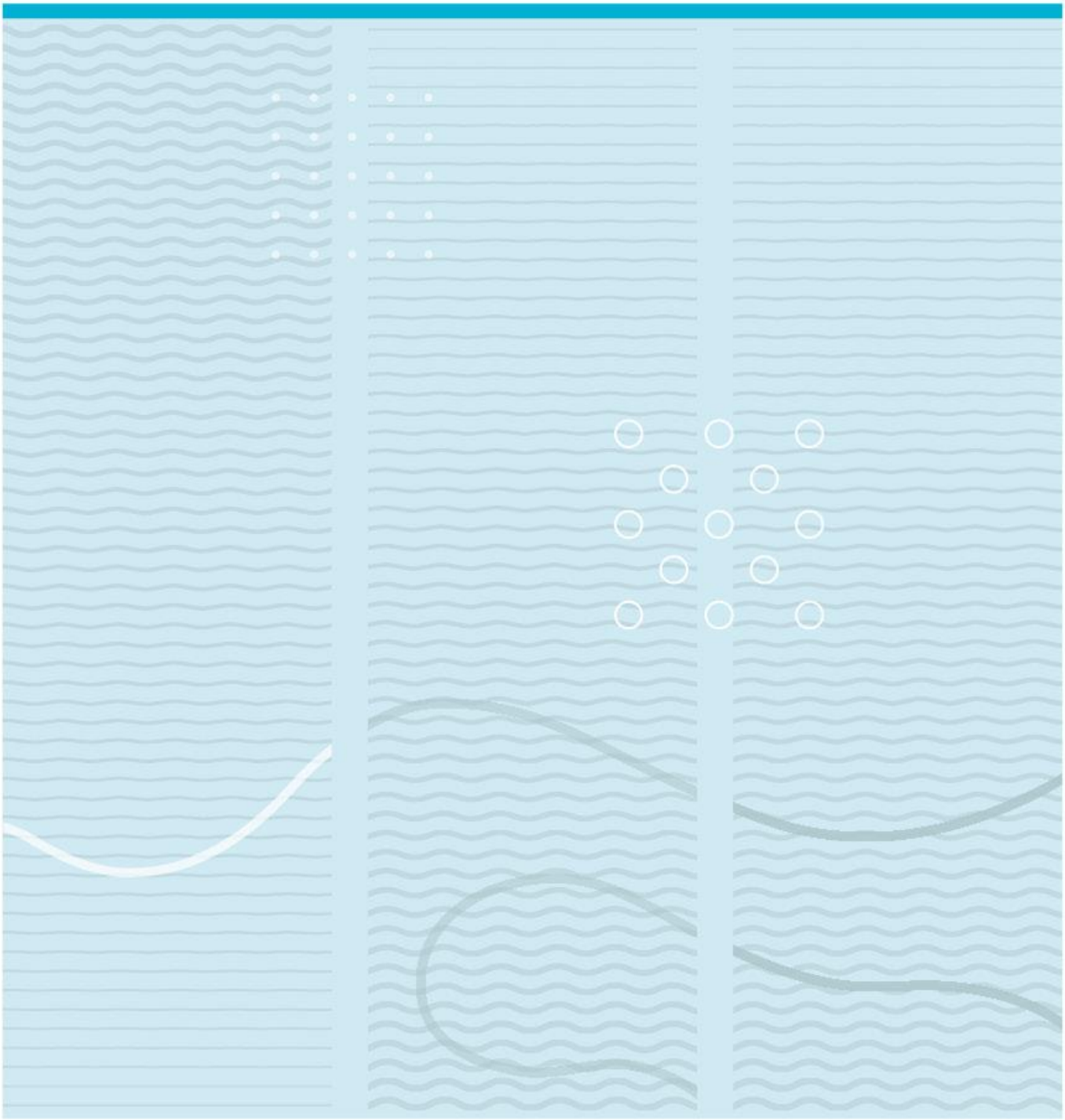
Mapping the structural and functional changes in the macular area in patients with type 2 diabetes



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This thesis is worth 30 study points

Summary

Purpose: Diabetic retinopathy is one of the leading causes to blindness in the working population today. It can be detected, classified and followed up by optometrists through different optometric examinations. The primary purpose of this study is to investigate the clinical findings in patients with diabetes type 2 and mapping the retinal structural- and functional changes using the technique of retinal imaging, optical coherence tomography (OCT), automated perimetry, contrast sensitivity and measuring visual acuity. The secondary purpose is to investigate the effect of cataract on visual function in these patients.

Methods: This is a cross-sectional study with a prospective design. The test subjects were recruited from The Norwegian Diabetes Association in Buskerud, Telemark and Vestfold. Optometric practices in the same counties were contacted and asked if they could inform their patients that had type 2 diabetes about our study and give them our contact information. The recruitment took place from the period of august 2018 to January 2019. Data was collected from patient history and the test subjects underwent the following optometric tests; refraction, best corrected visual acuity, retinal sensitivity and contrast sensitivity, in addition to retinal imaging (photo and optical coherence tomography). Evaluation of sectors of 1° and 10° in diameter of the macular area was conducted as well with retinal imaging using fundus camera, and the central foveal thickness was measured with OCT. The number of retinal findings (microaneurysms, hard exudates, dot & blot hemorrhages and cotton wool spots) were correlated with the retinal sensitivity within the different sectors, and the central foveal thickness were compared with central 1° retinal sensitivity, the contrast sensitivity and with the best corrected visual acuity. Cataract were graded to look for effect on visual function.

Results: Linear regression were used to look for association between retinal findings and retinal sensitivity, and the same for association between central foveal thickness and central 1° retinal sensitivity, the contrast sensitivity and with the best corrected visual acuity. Independent sample t-test were used to look for association between cataract and visual function. The results indicated no statistical significance ($p > 0.05$ in all statistical analysis). The test result showed a tendency that the retinal sensitivity in the

central 1 mm sector was affected by the central foveal thickness, but this was not significant.

Conclusion: Diabetic retinal features does not affect the retinal sensitivity. The central foveal thickness and its effect on visual function like contrast sensitivity or best corrected visual acuity showed no statistical significant relationship. The relationship between central retinal thickness and central retinal sensitivity may suggest that the central visual field might be affected. Presence of cataract has no correlated impact on the visual function in diabetic retinopathy regarding the contrast sensitivity neither the central retinal sensitivity in 1° of the visual field.

Keywords: Diabetic retinopathy, retinal findings, central foveal thickness, visual function.

Word count: 15 565

Sammendrag

Formål: Diabetes retinopati er en av de ledende årsakene til blindhet i den arbeidende populasjonen i dag. Tilstanden kan bli oppdaget, klassifisert og fulgt opp av optometrister gjennom ulike undersøkelser. Primær-formålet med denne studien er å undersøke de kliniske funnene hos pasienter med diabetes type 2 og kartlegge retinale strukturell- og funksjonelle endringer ved bruk av retinal billedtakning, optisk koherens tomografi (OCT), automatisk perimetri, kontrastsensitivitet og måling av synsstyrke. Sekundær-formålet er å undersøke effekten katarakt har på visuell funksjon hos disse pasientene.

Metoder: Dette er en tverrsnittstudie med et retrospektivt design. Test subjektene ble rekruttert fra Diabetesforbundet i Buskerud, Telemark og Vestfold. Optometriske forretninger i de samme fylkene ble kontaktet og spurt om de kunne informere pasientene i de hadde til synsundersøkelse som hadde type 2 diabetes om vår studie og gi dem kontaktinformasjonen vår. Rekruteringen fant sted i perioden fra august 2018 til januar 2019. Dataene ble samlet inn fra pasient historikk og test subjektene gjennomgikk følgende optometriske undersøkelser; refraksjon, beste korrigerte visus, retinal sensitivitet, kontrastsensitivitet i tillegg til retinal billedtakning (foto og optisk koherens tomografi). Evaluering av sektorene som utgjorde 1° og 10° i diameter av macula-området, ble utført, så vel som fundus foto og sentral foveal tykkelse målt med OCT. Antall retinale funn (mikroaneurysmer, harde eksudater, «dot og blot»-blødninger og fibersjiktsinfarkter) ble korrelert med retinal sensitivitet innenfor de ulike sektorene og sentral foveal tykkelse ble sammenliknet med sentrale 1° av retinal sensitivitet, kontrastsensitivitet og beste korrigerte visus. Katarakt ble gradert for å se effekten på visuell funksjon.

Resultater: Lineær regresjon ble brukt til å se på assosiasjon mellom retinale funn og retinal sensitivitet, og det samme for assosiasjonen mellom sentral foveal tykkelse og sentrale 1° av retinal sensitivitet, kontrastsensitivitet og beste korrigerte visus. «Independent sample t-test» ble brukt til å assosiere katarakt med visuell funksjon. Det var ingen statistisk signifikans blant resultatene ($p > 0,05$ i alle statistiske analyser). resultatene viste dog tendens til at retinal sensitivitet i sentrale 1 mm sektor var affisert av sentral foveal tykkelse, men ikke signifikant.

Konklusjon: Diabetes-lignende endringer på netthinnen affiserer ikke retinal sensitivitet. Den sentrale foveale tykkelsen og dens effekt på visuell funksjon som kontrastsensitivitet og beste korrigerte visus, viste ingen statistisk signifikant forhold. Forholdet mellom sentral foveal tykkelse og sentral retinal sensitivitet kan foreslå at sentral retinal tykkelse kan være affisert. Tilstedeværelse av katarakt har ingen korrelert innvirkning på visuell funksjon i diabetes retinopati når det kommer til kontrastsensitivitet og heller ikke sentral retinal sensitivitet 1° av synsfeltet.

Nøkkelord: Diabetes retinopati, retinale funn, sentral foveal tykkelse, visuell funksjon.

Antall ord: 15 565

Contents

Foreword

The optometrists in Norway are slowly but steadily getting more responsibility in regard of patients care ocular health wise. We are getting more recognition in peoples life as the primary instance for visual aid in the society. To be prepared for the future, it is key to comprehend all aspects of optometry and visual science and perform clinical excellence. This master program has been an educational journey, working with other clinicians and facing challenges. Regarding this master's thesis I will first and foremost like to thank my main supervisor associate professor Tove Lise Morisbakk at the Institute for Optometry, Radiology and Lightning Design in Kongsberg. Thank you very much for constructive criticism, flexibility and quick response whenever a question was raised, and thanks to my co-supervisor associate professor Vibeke Sundling for handling the administrative part in the project. I would also like to thank my colleges Hanna Karoline Figenschau, Marina Rønning, Siv Sandvik and Jenna Aro for phenomenal co-operation working with the test subjects trough testing and eye examinations. Thanks to associate professor Per Olof Lundmark for help with the statistical analysis in the project.

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Jonas Christopher Luhr-Pettersen

1 Introduction

1.1 Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most sight threatening systemic diseases and it is implied that it will be the principle reason of new blindness among the working population (Sayin, Kara, & Pekel, 2015). Based on its severity, it reduces the visual acuity and contrast sensitivity (Stavrou & Wood, 2003), and as optometrists, working in an optometric practice we can detect, identify and follow up the pathology by looking at the structures on the retina on fundus photo and with optical coherence tomography (OCT). The retinal findings can give a reduction in the retinal sensitivity measurable with automated perimetry (Raman, Nittala, Gella, Pal, & Sharma, 2015).
Diabetic retinopathy is characterized as a microvascular late complication of diabetes mellitus. It develops gradually, and symptoms does not necessarily occur before advanced stage, as retinopathy does not affect the macula in the initial phase (Sundling & Aamodt, 2017). This study will give an understanding of the relationship between the structural changes we as optometrists see in the diabetic retina, and how these changes can alter the function in the retinal sensitivity, central retinal thickness, contrast sensitivity and visual acuity.

1.2 Previous research

Some previous studies have looked at the structure-function relationship in the macular area in patients with diabetic retinopathy. A Dutch study from 2010 evaluated the possible relationship between structure in the retina, using optical coherence tomography, and function, using central visual field testing with perimetry in patients with diabetes mellitus and no or minimal diabetic retinopathy. They found loss of macular visual function corresponding with thinning of the ganglion cell layer in the pericentral area of the macula in diabetic subjects (van Dijk et al., 2011). A research team from Sweden examined to what extent visual acuity and perimetric sensitivity, as measures of central and paracentral visual function, would be useful for evaluating the presence and severity of diabetic macular edema in patient with diabetic retinopathy. The study concluded that visual acuity did not differ regardless of presence of any macular edema. Retinal sensitivity showed reduction in eyes with edema. (Agardh,

Stjernquist, Heijl, & Bengtsson, 2006). Joltikov et al. observed in 2017 whether quantitative functional tests, like visual acuity and contrast sensitivity, and OCT-defined structure could serve as effective tools to diagnose and monitor early diabetic neuroretinal disease. They demonstrated that their measures of visual acuity and retinal perimetry was not sensitive for functional difference among subjects with diabetes. They also found thinning in the ganglion cell layer in moderate NPDR subjects compare to the controls (Joltikov et al., 2017). In 2011, A research group in Italy, looked at the use of microperimetry in function testing in subjects with diabetic retinopathy, and suggested that microperimetry may contribute to understanding of the pathophysiology of early phases of diabetic retinopathy (Midena & Vujosevic, 2011). Microperimetry is still a fairly new technique in Norway and have not found its way into Norwegian optometric practices yet. There is still a need to compare diabetic retinal findings with retinal function using traditional perimetric methods, like static automated perimetry to get a clue how the central visual field can get altered due to diabetic retinopathy, and the possibility to detect these changes in an early stage.

1.3 Changes in the eye due to diabetic retinopathy

1.3.1 Structures and changes in the macular area and retina

The regions of the macula lutea consists of the foveola (0.35 mm diameter), the fovea centralis (1.5 mm diameter) the parafovea (0.5 mm diameter) and the perifovea (1.5 mm diameter). These structures make up the macula lutea (5.5 mm diameter) (Remington, 2012). These distances can also be seen in the light of degrees of visual field on the retina. 1° in the human retina is 0.35 mm in diameter (Bron, Tripathi, & Tripathi, 1998). Retinal findings are usually the first structural sign that are helping to give the correct diagnosis of diabetic retinopathy (Kauppi et al., 2013). The different findings related to diabetic changes in the retina are:

- Microaneurysms are isolated, spherical, red dots of varying size. They may reflect an abortive attempt to form a new vessel or may simply be a weakness of capillary vessel wall through loss of normal structure integrity (Wong et al., 2018)

- Dot hemorrhages cannot always be differentiated from microaneurysms as they are similar in appearance but with varying size (Wong et al., 2018)
- Blot hemorrhages forms where clusters of capillaries occlude leading to formation of intraretinal blot hemorrhages (Wong et al., 2018)
- Cotton wool spots represent the swollen ends of interrupted axons where build up of axoplasmic flow occurs at the edge of the infarct (Wong et al., 2018)
- Intraretinal microvascular anomalies are dilated capillary remnants following extensive closure of capillary network between arteriole and venule. Associated features include (Wong et al., 2018):
    - Venus beading is foci of venous endothelial cell proliferation that have failed to develop into new vessels (Wong et al., 2018)
    - Venous loops are thought to develop due to small vessel occlusion and opening of alternative circulation (Wong et al., 2018)
    - Retinal pallor and white vessels (Wong et al., 2018)
- Macular changes consist of thickening of the retina that takes place due to accumulation of exudative fluid from damaged outer blood-retina barrier (extracellular damage) or as a result of hypoxia, leading to fluid accumulation within individual retinal cells (intracellular edema). It may be focal or diffuse. Flame hemorrhage and cotton wool spot formation may occur due to arteriolar occlusion, without capillary occlusion, which frequently affects the horizontal nerve fibre layer of the retina (Wong et al., 2018)
- Optic disc changes due to occasionally swollen optic disc (diabetic papillopathy) may be seen in diabetic patients (Wong et al., 2018)
- New vessels at the disk (NVD) are new vessels at the disc usually arise from the venous circulation on the disc or within 1 disc diameter of the disc (Wong et al., 2018)
- New vessels elsewhere (NVE) are new vessels, which usually occur along the border between healthy retina and areas of capillary occlusion (Wong et al., 2018)
- Fibrous proliferation occurs in proliferative retinopathy where new vessels grow on a platform of glial cells (Wong et al., 2018).

1.3.2 Functional changes

Other visual and ocular features that can be affected in patients with diabetic retinopathy are:

- Retinal sensitivity throughout the visual field may be impaired due to diabetic retinopathy. Diffuse retinal neurodegenerative changes can occur prior to retinopathy development, raising the prospect that non-central vision may also be compromised by primary neural damage. Furthermore, diabetic peripheral neuropathy may play an important role in autonomous innervation to both periphery and central visual field (Sampson et al., 2012)
- Contrast sensitivity has been reported to be reduced before visual acuity in those suffering from diabetic changes in their retina. Usually the reduced sensitivity becomes more severe as the disease progresses. Even though the pathways and underlying mechanisms behind impaired contrast sensitivity is poorly understood, the existing literature are leaning towards association with the structural changes of the inner layers of the diabetic retina, that similarly affects the magnocellular and parvocellular pathways. (McAnany & Park, 2018)
- Visual acuity which is the most common measure of visual function in patients with diabetic retinopathy, can be reduced when the vascular abnormalities affects the central macula. In addition to vascular changes, neural and optical abnormalities have also been described, and optical defects include structural changes of the cornea and lens and elevated higher-order optical aberration (McAnany et al., 2014).
- Refraction has been shown to tend to more myopic in patients with diabetic retinopathy because of acute elevations in blood glucose level (Klein, Lee, & Klein, 2011)
- Color vision is associated with diabetic changes in the eye, and most often associated with involvement of blue-yellow color deficiency (Gella et al., 2017)
- Binocular vision problems can be a visual outcome due to oculomotor nerve palsy caused by posterior communicating artery aneurysm in diabetic patients (Dhume & Paul, 2013)

- Pupillary involvement is rarely in association with diabetic changes but has been seldom seen as a result of oculomotor nerve palsy (Dhume & Paul, 2013).

1.4 Classification

There are five clinical stages of diabetic retinopathy according to the "International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scale" ((ICO), 2017). Stage one is called no apparent diabetic retinopathy because there is no diabetic abnormality on fundus. Stage two is called mild non-proliferative diabetic retinopathy and it is characterized by only microaneurysms. In stage three we have moderate non-proliferative diabetic retinopathy and here one can see the presence of microaneurysms and other signs, such as dot and blot haemorrhages, hard exudates and cotton wool spots, but less than in severe non-proliferative diabetes retinopathy. The fourth stage is called severe non-proliferative diabetic retinopathy and is characterized by the signs in the previous stage plus intraretinal haemorrhages (≥ 20 in each quadrant), definite venous beading (in 2 quadrants), intraretinal microvascular abnormalities (IRMA in 1 quadrant, but there will be no signs of proliferative retinopathy. The last stage of the retinopathy is proliferative diabetic retinopathy and is characterized by the same signs in stage four but with one or more sign of neovascularisation and vitreous/preretinal hemorrhages. Diabetic macular edema has a similar classification as the retinopathy. Stage 1 is called no diabetic macular edema and it is characterized by no retinal thickening or hard exudates in the macular area. Next stage is the non-central-involved diabetic macular edema and consists of retinal thickening in the macula that does not involve the central subfield zone that is 1 mm in diameter. The third and last stage is called central-involved diabetic macular edema and is characterized by retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter (Wong et al., 2018).

1.5 Pathophysiology

The development of diabetes retinopathy consists of biochemical mechanisms associated with hyperglycaemia (abnormally high concentration of glucose in the blood) that include oxidative stress, polyol, hexosamine pathway activity, advanced glycation end-product formation and activation of protein kinase C (Heng et al., 2013).

Inflammation is a prominent part of the pathogenesis, and in the retinal vasculature, the inflammatory response results in the formation of new weak vessels and their increased permeability owing to vascular endothelial growth factor (VEGF) which in turn leads to hemorrhages in the retina and the leukostasis. Leukostasis leads to capillary occlusion and non-perfusion. VEGF promotes breakdown of the blood-retina barrier, stimulation of endothelial cell growth and neovascularisation. This increases the vascular permeability in the ischemic retina (Mathebula, 2018).

1.6 Prevalence

Diabetes retinopathy is one of the most sight threatening eye diseases in the world (Nentwich & Ulbig, 2015). Approximately 90 000 – 120 000 Norwegians have known diabetes and among these, it is reported prevalence of diabetic retinopathy range from 11 – 28% (Sundling et al., 2013). Among people with diabetes, 1 – 13% develop sight threatening retinopathy and 0.4 – 1.3% are visually impaired because of the pathology (Sundling et al., 2013).

1.7 Risk factors for developing diabetic retinopathy

- Duration of diabetes mellitus is an unmodifiable risk factor. Studies have shown that patients with diabetic retinopathy had longer duration of diabetes, double than those without retinopathy. Furthermore, it is reported that the retinopathy increased by 1.7 ± 0.2 per year of duration of the disease. In addition, it is found that each year of increased history of diabetes was associated with an 8 % increased risk of having diabetes retinopathy. This association can be explained by a prolonged exposure to the hyperglycaemic state that may increase the risk if vascular injury, leading to diabetic retinopathy and other complication (Wat, Wong, & Wong, 2016).
- Systemic vascular diseases such as hypertension has been consistently demonstrated to have a positive association with the development of diabetes retinopathy. It is reported that patients with high blood pressure have more than double the risk of developing diabetic retinopathy after 10 years compared to diabetic retinopathy patients with normal blood pressure (Wat et al., 2016).

- It has been purposed relationship between high body mass index (BMI) and diabetic retinopathy. A study looked at **obesity** in patients with a BMI > 30 kg/m^2 and patients with diabetes type 1, found that it was a predominant risk factor for diabetic retinopathy (Wat et al., 2016).
- In a study performed in the United States, revealed that the male **gender** over the age of 40 years shows a greater risk in developing diabetes retinopathy than females. The "LALES" study (Varma et al., 2007) along with a multivariate model in the "UKPDS 50" (Stratton et al., 2001) study also showed that men are more in the risk zone to develop the disease than women (Wat et al., 2016).
- There is some disagreement in whether **hyperlipidaemia** is to be considered as a risk factor or not. Some studies report that elevated total serum cholesterol is associated with a higher prevalence of diabetic macular edema and vision-threatening diabetic retinopathy, other studies have been unable to reproduce similar results (Wat et al., 2016).
- Consensus regarding **chronic kidney disease** and its association with development of diabetic retinopathy is quite strong. In diabetic patients, chronic hyperglycaemia causes microvascular changes in both the glomerulus of the kidney and in the retina (Wat et al., 2016).

1.8 Screening for diabetic retinopathy

An Oxford study from 2017 reviewed the evidence that lower risk groups who could safely be screened less frequently for sight-threatening diabetic retinopathy than annually. The result demonstrated that people with no diabetic retinopathy in either eye are at low risk of progression to sight-threatening retinopathy over a 2-year period, irrespectively of whether the screening method is one-field non-mydriatic or two-field mydriatic digital photography (Scanlon, 2017). In 2014 a research team from America evaluated diabetic retinopathy prevalence, risk factors and the effectiveness of non-mydriatic fundus camera as a screening tool for detection of the retinal condition. They concluded that it was an effective and feasible screening tool for early detection of retinopathy in diabetic eyes. They further meant it should be considered in areas with limited access to health care to improve quality of care and potentially reduce vision loss rates (Schwartz et al., 2015). In Norway, according to the current guideline, the

Directorate of health recommends that patients with diabetes mellitus are been followed up by ophthalmologist. In the ophthalmologic practice or in the hospital, retinal photography is taken and graded with purpose of diagnose any retinopathy. Patients with diabetes type 2 are being referred at the time of diagnosis, while patients with diabetes type 1 are being referred five years after time of diagnosis. If there is no sign of retinopathy, it is sufficient with regular controls at the ophthalmologist every second year (Helsedirektoratet, 2017). Furthermore, it is recommended that qualified personnel, that has documented experience in retinal imaging and OCT performs the examinations (Sundling & Morisbakk, 2017). According to the "Konus-report" from 2012 from the Norwegian Ophthalmologic Association, there were 6116 diabetic consultations in 2009. It is estimated that in 2030, the number of diabetes consultations will raise to 7339 (20% increase) (Oftalmologiforeningen, 2012). To prevent this increase and to prevent loss of vision, it is essential to detect diabetic changes at an early point. With knowledge of which structural and functional tests to conduct in examination of patients with diabetes, optometrists can help relieving the specialist health service, and contribute to "shared care" across health professions. Diabetic retinopathy is a well-known retinal condition in the Norwegian health care system, but to pinpoint where the responsibility lies among different health care professionals, can be a hard task. General practitioners, optometrists and ophthalmologists need to find a way to co-operate better to benefit the individual patient with diabetes, over time.

1.9 Research questions and significance

1.9.1 Purpose and research questions

The main research objective in this study is:

1. To investigate the clinical findings in patients with diabetes type 2 and mapping the retinal structural- and functional changes using the technique of retinal imaging, optical coherence tomography (OCT), automated perimetry, contrast sensitivity and measuring visual acuity.
2. To investigate the effect of cataract on visual function in these patients.

The primary objective is based on the following research questions:

1. How strong is the association in clinical macular findings in retinal imaging compared with retinal sensitivity with automated perimetry in patients with diabetes type 2?
2. How strong is the association in central foveal thickness measured with OCT compared with central retinal sensitivity, contrast sensitivity and best corrected visual acuity in patients with diabetes type 2?

These objectives and questions give rise to the following research hypothesis:

1. Among patients with type 2 diabetes, who participates in this study there is a measurable reduction in central retinal sensitivity compared to the central macular findings when documenting the retinopathy with retinal imaging and automated perimetry
2. Among patients with type 2 diabetes, who participates in this study there is a measurable reduction in central retinal sensitivity, contrast sensitivity and best corrected visual acuity when documenting the retinopathy with OCT

Secondary research objective:

1. What is the effect of presence of cataract in the results of the measurements and how does cataract impact on central retinal sensitivity and contrast sensitivity in patients with diabetes type 2?

1.9.2 Significance

Ocular health is crucial to investigate when handling patients with diabetes mellitus in order to diagnose the condition as early as possible. The patient can go for a long time without knowing they have retinal vascular changes in their eyes. The significance with this study was to find out if it was possible to detect any structure-function relationship in early diabetic changes using standard and special optometric procedures that are in use daily by optometrists. Knowledge about this will add information to optometrists what to be aware of when examine patients with diabetes. Diabetic retinopathy is an ocular pathology that optometrists often is the first of any authorised health personnel to discover. Through carefully selected tests and examinations, the condition can be

detected as a sign in the symptoms and medical history, as a function deficit in the initial standard and special optometric measurements or in the evaluation of the retinal sensitivity and retinal thickness, or as a structural change when looking at the retinal vascularity. To be able to fully comprehend all these different techniques, its key to detect, investigate and follow up the systematic condition best as possible.

1.9.3 Study design

This is a cross-sectional study with a prospective design, and a part of a larger study concerning Diabetes, vision and ocular health at Department of Optometry, Radiography and Lightning Design at University of South-Eastern Norway.

2 Methods

2.1 Inclusion criteria

The test subjects included in this scientific study were men and women who had the diagnosis type 2 diabetes mellitus and were over the age of 18 years. They also had to be competent to provide informed consent.

2.2 Exclusion criteria

- Under 18 years of age
- People who were not competent to provide informal consent
- People that were not able to attend the clinic at the National Centre for Optics, Vision and Eye Care at the University of South-Eastern Norway in Kongsberg
- Poor image quality
- Unreliable visual field test result, false positive (FP) and false negative (FN) > 30%
- Macular pathology (e.g. central epiretinal membrane, macular hole, wet AMD and large central drusen).

2.3 The recruitment

This study is part of a larger study concerning Diabetes, vision and ocular health at the Department of Optometry, Radiography and Lightning Design at University of South-Eastern Norway. The study population for this research, consisted of patients seen at the clinic at the National Centre for Optics, Vision and Eye Care at the University of South-Eastern Norway in Kongsberg. They were also recruited from The Norwegian Diabetes Association in Buskerud, Telemark and Vestfold. Optometric practices in the county of Buskerud, Vestfold and Telemark were contacted and asked if they could inform their patients that had type 2 diabetes about our study and give them our contact information. We also send the optometric practices a poster be E-mail that they could hang up in the waiting area. The project supervisors held some lectures in local diabetes associations in Buskerud area, and collected names from people with type 2 diabetes who was interested in participating in the project, on a list. This people were

called by two of the projects operators and booked an appointment. People who were asked and given information about the project out in the optometric practices, did also call us and booked an appointment as well. The booking of the patients was done in a journal system “HEADS” where they were given a default generated ID-number and also they were scheduled a day to have they eye examinations. The plan was to book patients from the period of august 2018 to January 2019.

2.4 Data collection

2.4.1 Preparations and pilot study

This study was a part of a larger study concerning diabetes, vision and ocular health where five experienced optometrists collected the data included. We designed a booklet with a structurally organized overview of all necessary examinations and tests and an informative letter to the test subjects, which they had to sign and give their informed consent in. Two copies of this letter were made for them to sign, one to keep together with the booklet of the patient and the other one for the patient to keep. A pilot study was arranged. The data was collected by five different operators with different level of experience as optometrists. The tests and examinations were done on fellow students and on subjects with diabetes type 2 in order to get familiar with the procedures and to ensure that all of the project operators graded and did the tests the same way. Each subject was given a unique ID-number as a code key and it was assigned to a unique folder containing the booklet of examination results and one signed copy of the information consent. All the folders were kept in a locked fire-proof filing cabinet, and the list with the code keys were kept separated from the folders.

2.4.2 Data acquisition

After signing the informed consent, the eye examinations started. The test subjects underwent a comprehensive examination that lasted for roughly 3 hours, and the following list shows which clinical tests that were essential for the current project:

- The following data from the patient history was collected:
    - Gender
    - Age
    - History of any ocular disease
    - Duration of type 2 diabetes (in years)
    - History of vascular disease
- Subjective refraction was measured in right and left eye with a manual phoropter and noted as spherical equivalent in diopters (D)
- Best corrected visual acuity was measured in right and left eye by recording it on a LogMAR visual acuity chart
- Metamorphosia was measured in right and left eye with an amsler grid pattern, and noted as 0 = normal, 1 = metamorphopsia and 2 = visual field loss
- Contrast sensitivity was measured in right and left eye at 50 cm with a MARS chart measured in a logarithmic scale
- Van Herick technique was used evaluate the chamber depth in right and left eye to see if the patient were suited to be dilated
- Dilation of the pupils with Tropicamide (0,5% Chauvin)
- Cataract was investigated with a Haag Straight slit lamp and graded with the LOCS lll grading scale, looking especially at nuclear and posterior subcapsular cataract
- OCT was performed in both eyes with the Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Germany) using the 'Macular Cube 200x200' test'-scan (6x6 mm) centred on the fovea
- Fundus photography of the macular area was obtained with the KOWA nonmyd Wx 3D (InnZ medical AS, Japan) with the 'Normal – macula' image program
- To measure the central visual function, automated perimetry was measured in right and left eye with the Haag Straight Octopus visual field analyser using the test algorithm '10-2 Standard / White/White / 4000 / III Dynamic'

All the images that were taken of the subjects, were stored locally on the hard drives on all computers involved in the examinations.

After finishing the procedures, we evaluated if there were any need of further management of the subjects based on the results. We re-scheduled them in the

university clinic if we saw the need to have a closer look on their symptoms or ocular health, or due to inaccurate measurements. The examinations were also written as a journal in the university's journal system (HEADS) for future references. If they had any findings or signs on fundus due to development of diabetic retinopathy or any pathology that needed further follow up, we referred them to an ophthalmologist and/or general practitioner if necessary.

2.5 Raw data analysis

An Excel spread-sheet was made in Microsoft Excel version 16.22 for mac to punch in and analyse the results from the eye examinations and tests needed in this study. The data was collected in one row for each test subject, and the anonymized ID-number was used. Data was collected from both eyes in each subject. When analysing the retinal structure versus the function (visual acuity, contrast sensitivity and visual field), only one eye was used. The fundus images were used to determine which eye had the highest number of findings related to diabetic retinopathy i.e. microaneurysms, dot/blot hemorrhages, cotton wool spots and exudates. The eye with the highest number of findings were selected. If there were no findings, or equal appearance in both eyes, a coin toss decided which eye to choose.

2.5.1 Retinal photography analysing

All fundus images were taken with the camera "KOWA nonmyd Wx 3D". The light settings in the room, were roughly 200-250 lux. The KOWA fundus camera was connected to a computer with two screens, a Dell and an Eizo. The Eizo CG277, 27 inches screen was used as the viewing screen with resolution 2560 x 1440 (109 ppi) A dedicated retinal image analysing and viewing software - 'VK-2' were used on the Dell to find the correct fundus images. The image setting "normal – macula" (45° of central posterior pol) were chosen to analyse both fundi of the patient in normal colors and in red-free filter to detect any findings, and the images were quality checked after the following criteria:

Table 2. Grading scale of retinal imaging

GRADE	RETINAL IMAGING			
NO / YES	IMAGE QUALITY	SHARPNESS	EXPOSURE	BRIGHTNESS
NO Poor quality	Several structures in the macular area were not clearly enough to grade	The retinal blood vessels were very blurry in the macular area	Obvious under/over exposure	The foveal avascular zone was so dark that it was impossible to find even with red free filter
YES Good quality	All of the structures in the macular area were clearly enough to grade	The retinal blood vessels were sharp and clear in the macular area	Even brightness in the image	The foveal avascular zone was clearly identifiable either in normal mode or in red free filter

To be included, the image quality had to be graded as "good quality". If the criteria were met, the images were used further in the study, if not, the images were rejected. Every image that were "accepted" after the given criteria, were tracked to its original location on the computers local hard drive and opened in the photo editor program "Photoshop Elements" version 2019 on the Eizo screen with the screen setting adjusted to 300 cd/m^2. The images were all in Tiff raw format, in 4288 x 2848 px and the zoom of every image in Photoshop was set to 100 %. To analyse within defined areas of the fundus (within circles of 1° and 10° in diameter), a new layer was added over the fundus image. This layer was custom made in photoshop as well, and the following procedure was done to centre the image for grading of findings:

1. Images that was captured with the KOWA, were opened in the image processing program Photoshop Elements 2019. The images were inspected to look for landmarks in the retina, like the fovea and the optic nerve head (figure 1a).
2. The distance between centre of the fovea and the centre of the optic nerve head is reported to be 15.5 ± 1.1° [13.0 – 17.9°] (≈ 15°) (Rohrschneider, 2004) and this was used as a measuring reference. A circle touching the centre of the fovea and the centre of the optic nerve head was made, illustrating this distance in degrees (15°). The exact diameter of this circle in pixels (972 px) was

measured using simple tools in photoshop (figure 1b). The distance in degrees (X°) and in pixels (Y px) of the circle, gave a simple calculation: $\frac{Y}{X} = Z\ (\frac{972px}{15^\circ} = 64.8\ px)$ where Z (64.8 px) indicated the relationship between each circle that had to be made in order to have the precise measuring area of interest in the retina.

3. New concentric circles were made, with a diameter of Z – 64.8 px less than the previous one, until the correct number of concentric circles was made (figure 1c) to define circles of 1° diameter and 10° diameter. All unnecessary circles were removed (figure 1d).
4. The 10° circle was divided into 4 sectors (superior, nasal, inferior and temporal) surrounding the inner circle of 1° (centre) (figure 1e).
5. This figure was used as a measuring tool and was positioned as a new layer in each fundus photo and dragged into centre (figure 1f), in order to search for findings, and start the fundus analysis (figure 1g).

The outer circle was only used as reference scale to know the correct distance from fovea to the optic nerve head (15°). The inner circle was placed with its centre either in the spot where the fovea reflex was seen, or in the spot where the estimated foveal avascular zone had its centre. In some cases, the foveal avascular zone was difficult to find, so the red-free filter tool in VK-2 were used to locate the correct area before the fundus image was opened in Photoshop. Before the grading started, the outer circle was aligned so that one tangent was in the centre of the optic nerve head and the other tangent touched the centre of the fovea. The area that was analysed, was inside the middle, and the the inner circle. The sectors were named center-1, superior-2, nasal-3, inferior-4 and temporal-5. The grading was done in each individual sector, by counting the number of findings related to diabetic retinopathy such as microaneurysms, hard exudates, dot and blot haemorrhages and cotton wool spots. The data of the analysis were punched into the excel spread-sheet.

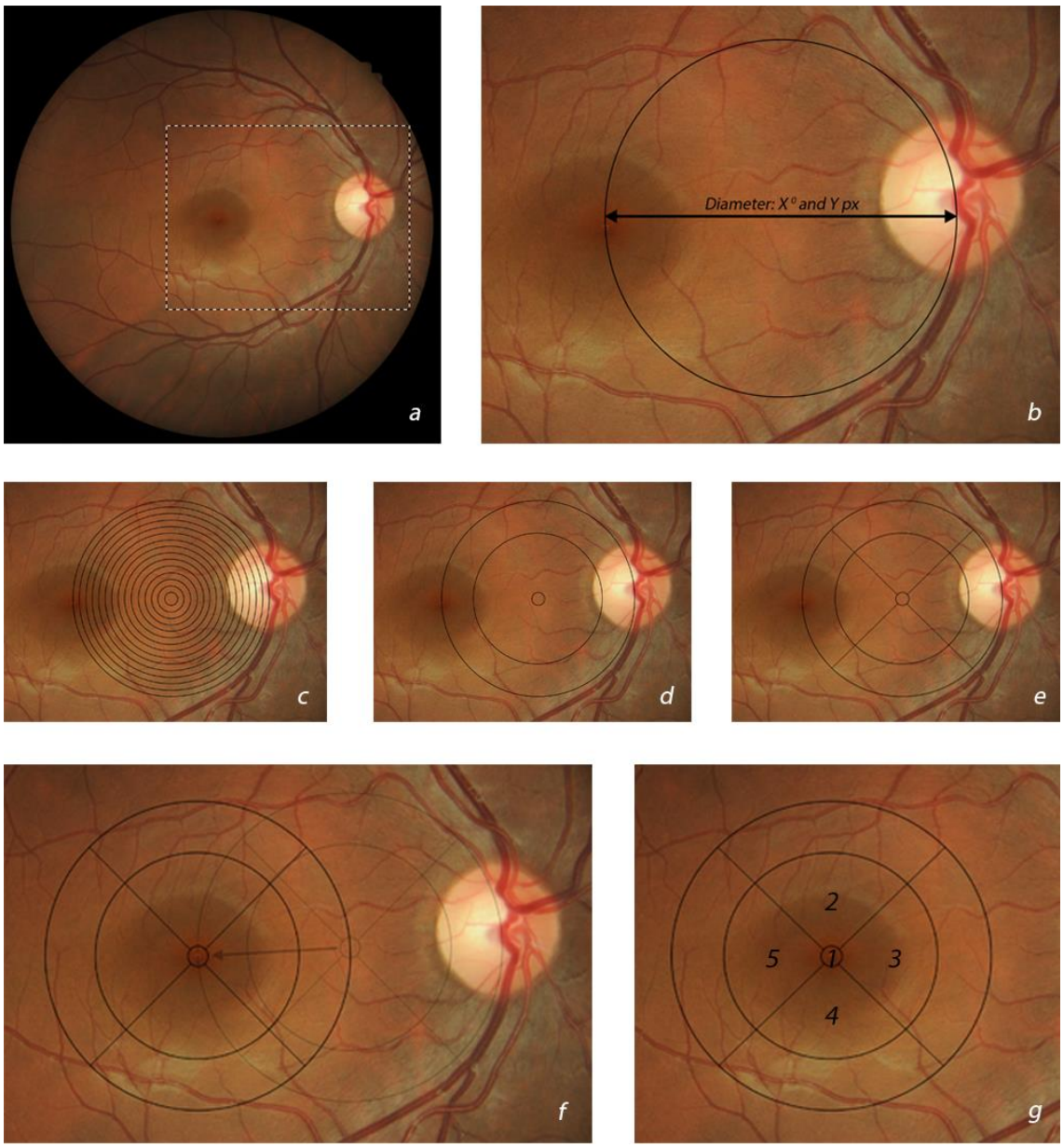

Figure 1. Landmarks in the retina in a 45° fundus photo (a), distance between fovea and the optic nerve head, assumed to be 15° (Rohrschneider, 2004) (b), all the concentric cicles between the structures with distance 1° for each circle (c), only the necessary concentric circles (1°, 10° and 15°) (d), concentric cicles divided in sectors, creating the measuring tool of 5 sectors (e), dragging the measuring tool into the central macular area (f), measuring tool correctly positioned centrally (with sector numbers) and ready to be used for grading fundus (g).

The fundus images were graded first, and the eye with the highest number of findings, were selected as the eye to analyse when looking at the visual field plots and the central retinal thickness measured with OCT.

2.5.2 Interrater- and intrarater reliability

In order to verify the reliability of the fundus analysis, an interrater- and intrarater reliability analysis were performed for 10 selected cases. Five subjects with findings and five subjects without findings were reanalysed both by a second co-worker (interrrater) (T.L.M.), and by the same operator (intrarater) as for the initial analysis. The fundus images were graded again using the same procedure as described above, and it was compared to the first initial grading for the sake of repeatability. Cohens kappa was calculated from this.

2.5.3 Visual field plot analysis

Next, was to look at the visual field (VF) plots. Which eye to analyse was decided from the fundi analysis as described above. The whole 10-2 Standard-plot tests a diameter of 20° of the central visual field and consists of 64 measuring points (figure 2a). The area of interest was the central 5° (diameter 10°) of the visual field (the values within the inner circle in the VF pot, figure 2b). This area corresponded to the area on the fundus analysed earlier. It is important to note that in the 10-2 test program, the space between each test spot (black numbers in the figures) represents 2°. The horizontal test locations are distributed at 1° from the horizontal axis (Yaqub, 2012).
The following procedure was used to collect the data from the VF:

1. The VF-plot from each test subject was printed out, the names was taken away and the anonymized ID-number was written on each
2. The inner circle of the plot (10° diameter) was divided into 5 sectors, as for the fundus images, figure 2b (central 1° sector 1, inferior sector 2, temporal sector 3, superior sector 4 and nasal sector 5).
3. The decibel (db) values for each measuring point in each sector was collected in the excel-sheet and the average sensitivity was calculated for each sector
4. The measuring points that fell on the line between two sectors was counted and averaged for both sectors. As an example for sector 3 OD, the average db-value is: $\frac{28+28+27+28+29+27}{6} = \frac{167}{6} = 27.83$ db

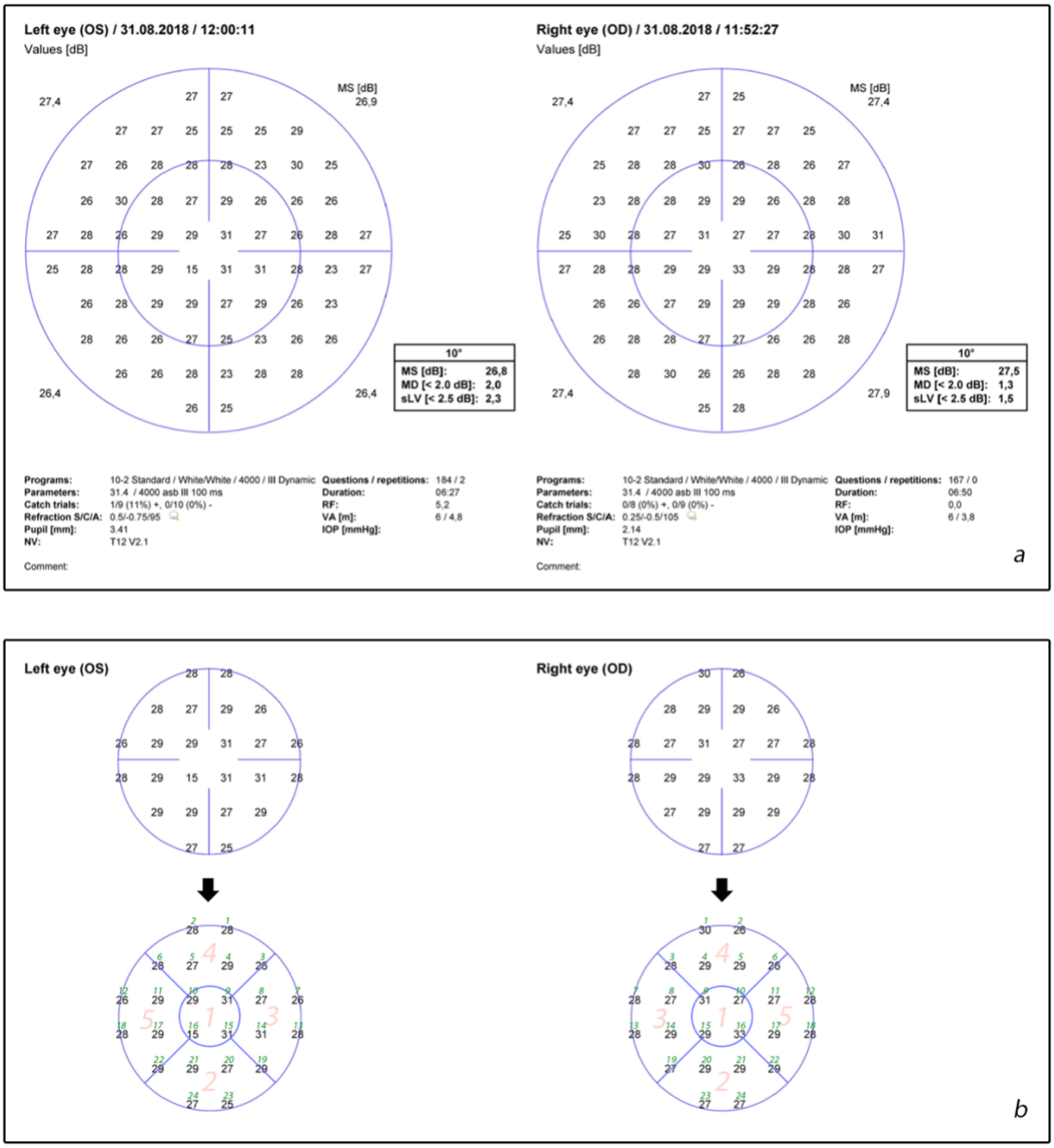

Figure 2. The raw visual field plot with all the test locations (measuring points) for both eyes (a), isolating only the visual field of interest (diameter 10°) and modifying it to correspond to the same sectors for the fundus images (sectors 1-5) (b).

Every visual field plot was evaluated by the reliability indices of the octopus perimeter, represented by the false positives (FP) and the false negatives (FN). If both factors were < 30% the test subject were included. If one of the FP or FN > 30% the test subject was excluded.

Table 2. Grading scale of automated perimetry reliability

GRADE NO / YES	AUTOMATED PERIMETRY RELIABILITY INDICES
NO – Rejected	FP or FN > 30 %
YES – Accepted	FP or FN < 30 %

2.5.4 OCT analysis

The macular scan used with the Cirrus HD-OCT was the 'Macular Cube 200x200'. This generated a visual presentation of the macular thickness (figure 3a) in an ETDRS ("Early Treatment Diabetic Retinopathy Study") sector diagram, were the central foveal thickness within 1 mm was represented in the middle of this figure. In the analysis, the "report" produced by the Cirrus HD-OCT and the ILM-RPE Thickness sector diagram were used, only focusing on the centre (figure 3b). Which eye to choose for each patient from the fundus analysis.

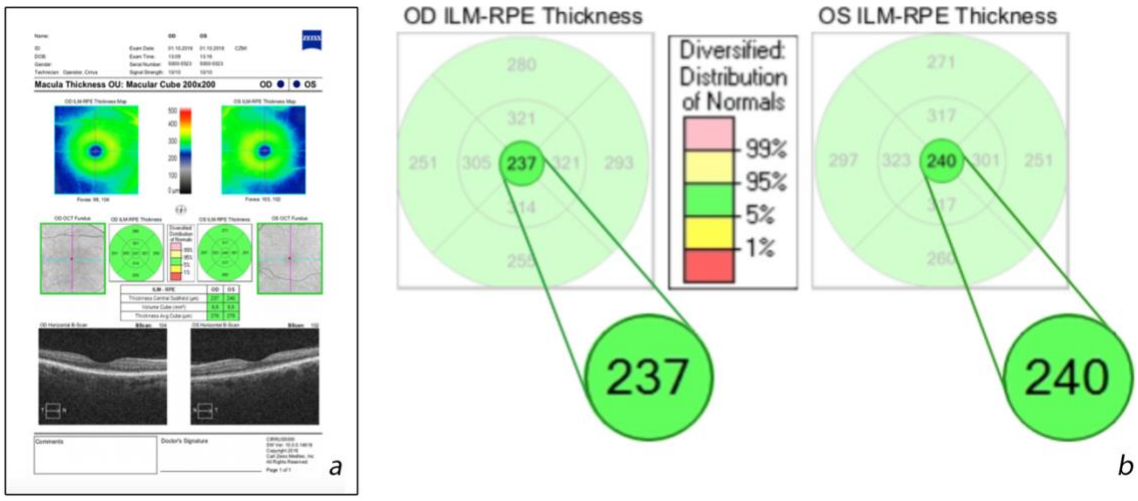

Figure 3. OCT Macular cube 200x200 graphic report (a), central foveal thickness (µm within 1 mm diameter) (b).

To be critically about the quality of the test, it was very important that the IR-image did not have any disturbance in the picture, and the OCT image had to capture all the individual layers of the retina. In some of the images, the build in algorithm failed to

recognize the layer segmentations correctly and this gave an unreliable central foveal thickness. These were excluded from the analysis. A grading scale with the quality criteria for the OCT IR-image and the OCT image was made (table 3).

Table 3. Grading scale of the infrared (IR) image and the OCT image

GRADE	INFRARED (IR) IMAGE		OCT IMAGE	
NO / YES	SHARPNESS	BRIGHTNESS	RESOLUTION	ANALYSIS*
NO Poor quality	Retinal blood vessels and retinal nerve fibre layer (RNFL) unclear and not visible in the macular area	Uneven bright-ness. Obvious under/over exposure	External limiting membrane (ELM)** not visible	Definitions of the individual retinal layer-segmentation failed
YES Good quality	Retinal blood vessels and retinal nerve fibre layer (RNFL) clear and visible in the macular area	Even brightness in the image. No under/over exposure	ELM** clearly visible	Definitions of the individual retinal layer-segmentation correct

*Most important of all grading criteria
**ELM only used as an indicator for image quality, not used for analysis

Every OCT analysis graded to “good quality” was included in the project, if not, they were excluded.

2.5.5 Cataract evaluation

A Haag Streight slit lamp was used to grade the crystalline lens. This happened after they were dilated with tropicamide. The Lens Opacities Classification System lll (LOCS lll, table 4) was used when grading.

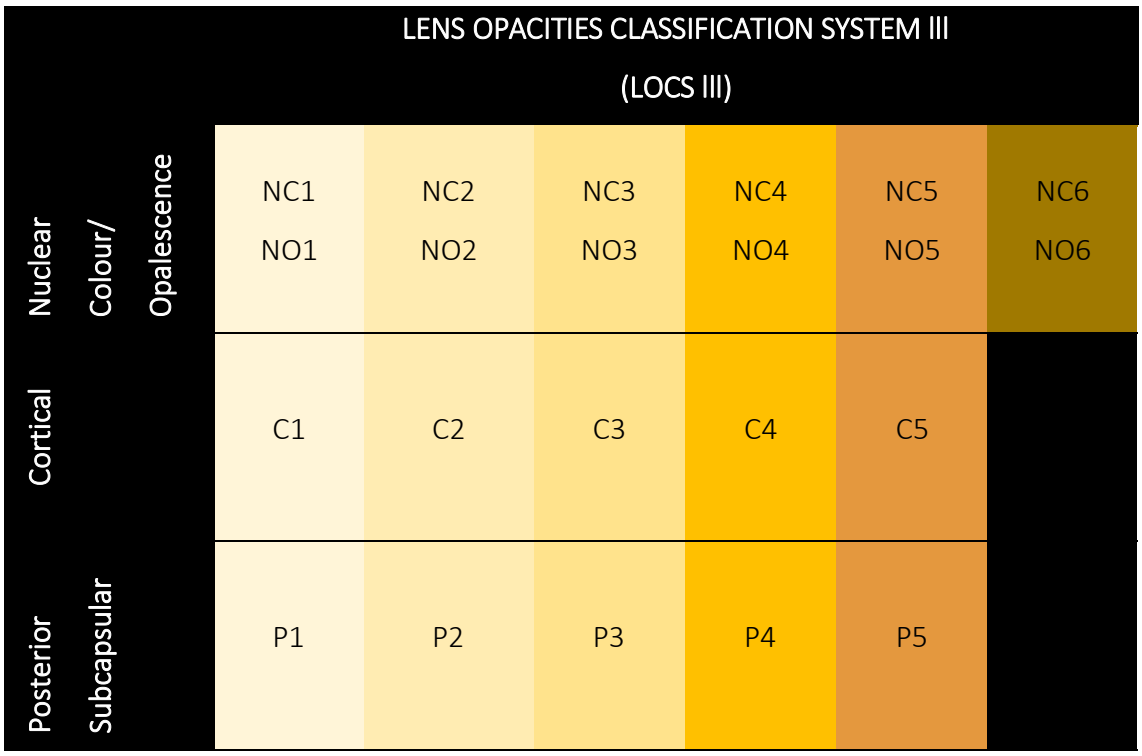

Figure 4. Lens opacities classification system lll (LOCS lll)

For the data analysis, research was conducted regarding what type of cataract and when the cataract affects the visual function the most. Central lens opacities was assumed to affect the central visual function more than cortical opacities (Shandiz et al., 2010), thus the presence of cataract was based on the nuclear colour and opalescence and posterior subcapsular cataract types. If they had a nuclear cataract ≥ grade NO3/NC3 or a posterior subcapsular cataract ≥ grade P1, it was determined that they had presence of cataract clinically significant for this study.

2.6 Ethics

The study was approved by REK (regional ethics committee) (project "REK-Sørøst sak 2018/804 Diabetes syn og øyehelse") and conformed to the tenets of the Declaration of Helsinki. All of the subjects in this study was participating voluntarily, and could, whenever they wanted, withdraw without giving any reason at any time. The different tests, eye examinations and optometric measurements are following the clinical guidelines, complied by the Norwegian Association of Optometry, and all the procedures include only non-invasive techniques. The patients were all informed of the light exposure from the flash of the KOWA fundus camera. This flash lasted for only a

slight second, and could cause a minimum discomfort for the patient, and lead to temporary after image in the visual field between 1-5 minutes. Tropicamide (0.5% Chauvin) is diagnostic dilating eye drops which is a standard ophthalmic drug used in optometric practice. A quite common side effect of this drop is a slight burning sensation that lasts only a few seconds after installation. Because of the large pupil size, the drop creates, patients can also become more sensitive to light, so they were advised to bring sunglasses to the appointment. One factor that is common, but still seldom experienced is acute angle closure glaucoma. The risk of this condition is 1/20 000 when using mydriatic eye drop (Liew, Mitchell, Wang, & Wong, 2006). All of the patient received information about this. They were also asked if they had been dilated using diagnostic eye drops before, if they have had any reactions to it and they underwent the Van Herick procedure to check if their anterior chamber angel was open in both eye before dilation.

2.7 Statistical analysis

All data that were collected, were anonymised and transferred into Microsoft Excel version 16.22 for mac and furthermore exported to IBM SPSS version 25 for statistical analysis. The results are expressed as scatter plots and linear regression to correlate retinal structure compared to retinal sensitivity as well as correlation between central foveal thickness and central retinal sensitivity, contrast sensitivity and best corrected visual acuity. Box plots and independent sample t-test illustrates correlation presence of cataract in the results of the measurements and how cataract impact on central retinal sensitivity and contrast sensitivity. A significance level of 5% was considered significant.

3 Results

85 test subjects were recruited. 13 were excluded due to poor retinal image quality, Perimetry and OCT was not possible to perform in some cases due to exhaustion, test subjects fell asleep or incorrect eye movement when measuring. 2 were excluded due to unfulfilled criteria in the OCT measurements. 11 subjects were excluded due to missing grading of the crystalline lens. In 4 cases, data about subject information, symptoms, medical history and diabetes duration were missing. 3 more cases of missing data occurred in subject vascular history. Despite the pilot study arranged to ensure the correct performance of the measurements and grading among the operators, some misunderstanding occurred. During the data collection, some of the operators miss graded the vascular disease regarding if the subject were having normal blood pressure if they were regulated by medicine. In the grading of the crystalline lens, there were some confusion regarding use of the LOCS III grading scale in the nuclear cataract type. Some of the operators didn't know the difference of nuclear color and nuclear opacity and didn't specify what grading they were using. Some of the data were missing due to unknown reasons, but if just some of the information were missing, they could still be in the database for other analysis.

3.1 Demographic data

Table 4. Test subject demography and characteristics

Patient demography	Study group (n)*	%	Min/max	Mean ± SD
Right eye	35/72	48.6		
Left eye	37/72	51.4		
Age (years)	72		44/81	66.89 ± 8.95
Male	36/68	52.9		
Female	32/68	47.1		
History of ocular disease**	34/68	50		
Vascular disease	20/65	30.8		

* Study group (n) varied because some data was missing in some of the measurements
** History of ocular disease consisted of whether or not the patient had one of the following: diabetic retinopathy, other retinopathy, AMD, glaucoma, cataract, other pathology and ocular surgery, diagnosed by ophthalmologist

Table 5. Duration of diabetes type 2

Duration of DB2	n = 68	%	Min/max age	Mean age
0-5 years	14	20.5	47/78	60.64
6-10 years	26	38.1	52/81	67.48
11-15 years	8	11.8	44/75	65.57
16-20 years	17	25	59/79	71.52
21-25 years	1	1.5	65/65	65
26-30 years	2	3	64/78	71

Table 6. Ocular and visual parameters

Ocular & visual parameters	n*	%	Min/max	Mean ± SD
Spherical equivalent (D)	68		-11.3/+7.3	-0.57 ± +2.71
BCVA (logMAR)	67		-0.2/0.44	-0.05 ± 0.11
Amsler - normal	62/68	91.2		
Amsler - metamorphopsia	6/68	8.8		
Contrast sensitivity (logCS)	68		1.12/1.80	1.59 ± 0.12
Central foveal thickness (μm)	70		183/359	269 ± 28.12
Nuclear colour cataract**	61		0/5	2.82 ± 1.16
Nuclear opacity cataract**	61		0/5	1.57 ±1.67
Posterior subcapsular cataract**	61		0/3	0.14 ± 0.54

* Study group (n) varies because some data was missing in some of the measurements
** Cataract based on the LOCS lll grading system
D = Diopters, BCVA = Best corrected visual acuity, logMAR = logarithm of minimum angle of resolution, logCS = logarithm of contast sensitivity, μm = micrometer

If we look at the age variety of the study population it reaches from 41 to 81 years with an average of 66.89 year of ages. But looking at figure 15, we see that most of the subjects are around the age of 70 years of age.

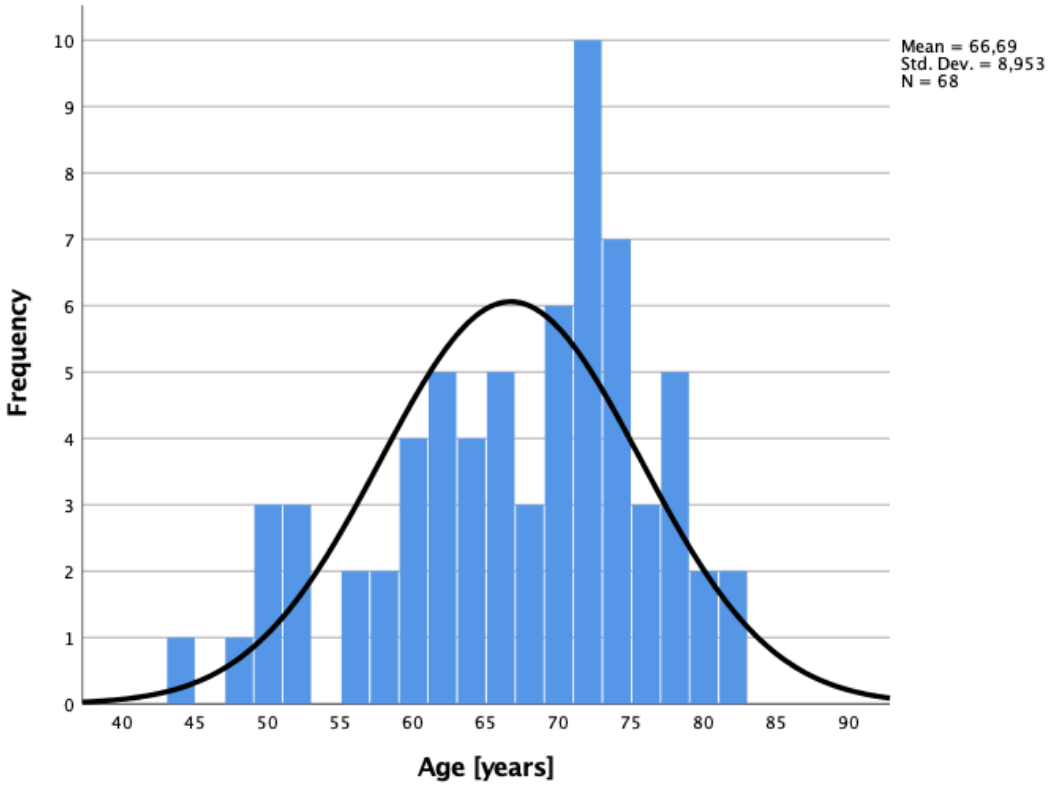

Figure 5. Histogram of age distribution in years in the test subjects

3.2 Structure vs. function

3.2.1 Retinal findings in fundus photo vs. retinal sensitivity

All the fundus images were taken with the KOWA nonmyd Wx 3D. Out of the 85 subject subjects that underwent retinal imaging, 13 were excluded, because they did not fulfil the image quality criteria in the grading scale.

Table 7. Frequency of test subjects with and without diabetic retinal findings and distribution of the individual findings

Frequency of test subjects **without** diabetic retinal findings					54/72 (75%)
Frequency of test subjects **with** diabetic retinal findings					18/72 (25%)
Test subjects	Distribution of retinal findings in the test subjects				
	MA	EX	HEM	CWS	SUM
1		4			4
2				5	5
3		2			2
4				1	1
5				1	1
6	1			1	2
7				1	1
8	2				2
9	12	3		1	16
10				5	5
11	1		1		2
12	3				3
13	4				4
14	3				3
15	1	1			2
16	1				1
17	20				20
18		6	1	1	8
Total	48	16	2	16	82

MA = microaneurysms, EX = exudates, HEM = dot & blot hemorrhages, CWS = cotton wool spots

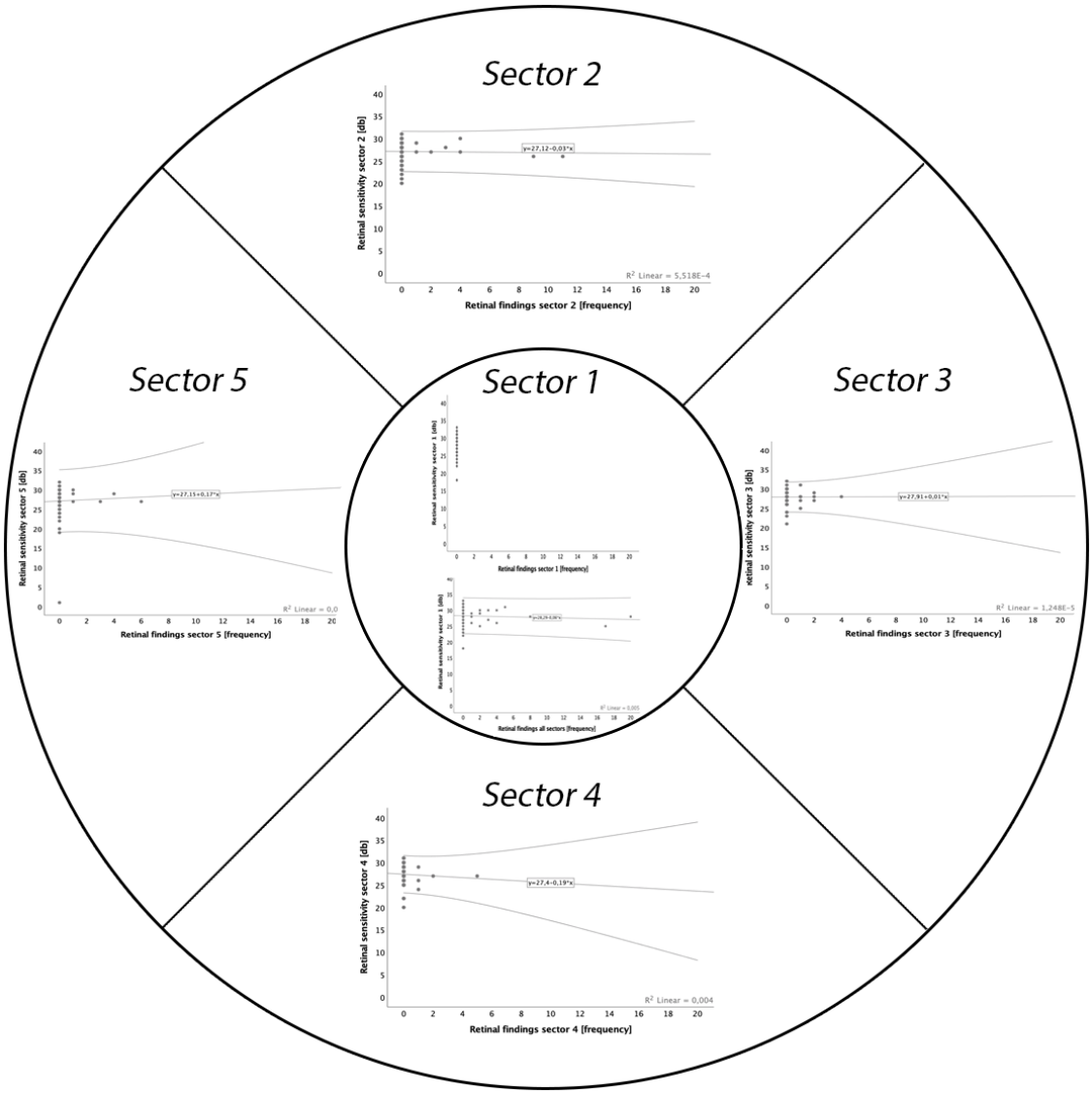

Figure 6. Sector diagram illustrating scatter plots of comparison between the retinal findings with the retinal sensitivity in each sector. Sector 1 in the figure represents retinal findings sector 1 vs retinal sensitivity sector one (upper scatter plot in the middle), total number of retinal findings in all sectors vs. retinal sensitivity sector 1 (lower scatter plot in the middle).

Figures 7-12 shows linear regression for the relationship between retinal findings and retinal sensitivity. As we can see of the scatter plots, the association in clinical macular findings (total number of microaneurysms, hemorrhages, exudates and cotton wool spots in sector 1) compared with retinal sensitivity measured with automated perimetry. The little symbol in the upper right corner is showing where the sectors are

in the macular area. Figure 12 illustrates the retinal findings in all of the sectors vs. retinal sensitivity in sector 1.

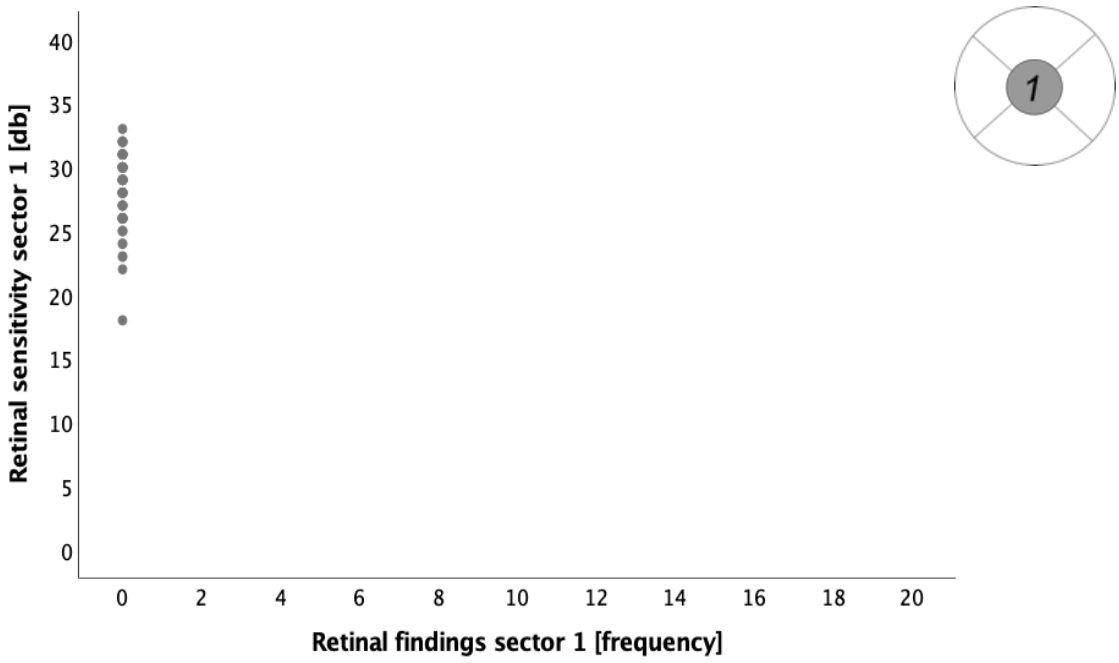

Figure 7. Scatter plot representing the numbers of retinal findings in sector 1 vs. retinal sensitivity (db) measured in sector 1 (n = 72).

There were no retinal findings like microaneurysms, hemorrhages, exudates or cotton wool spots in the central 1 mm sector.

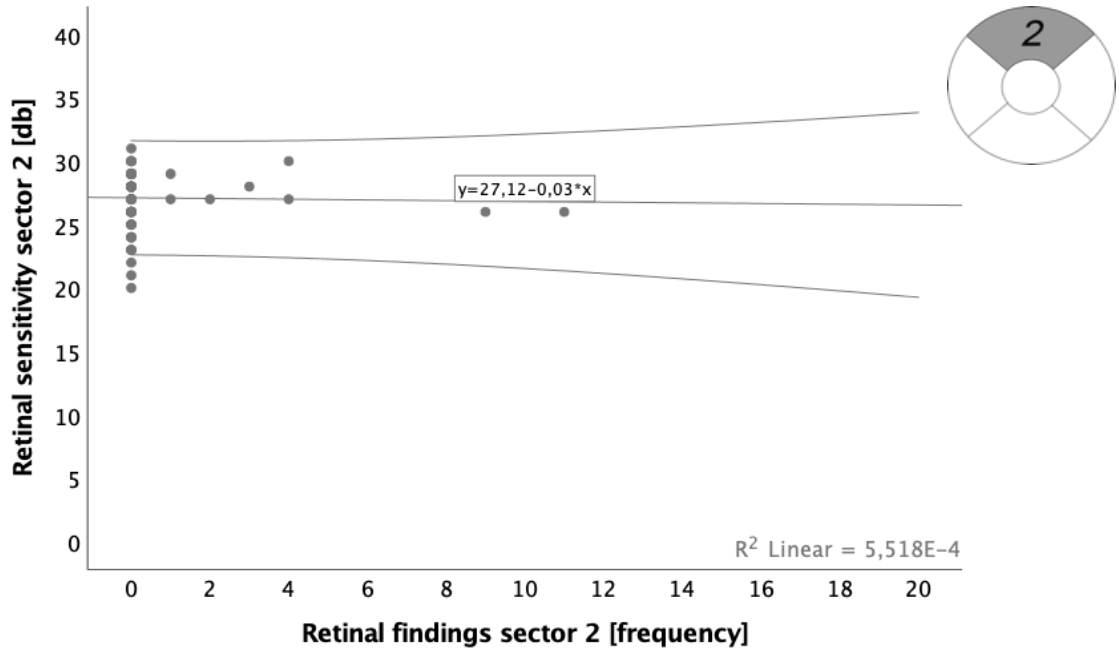

Figure 8. Scatter plot representing retinal findings sector 2 (superior retina) vs. retinal sensitivity sector 2 (inferior visual field). Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 72). ***p = 0.848***

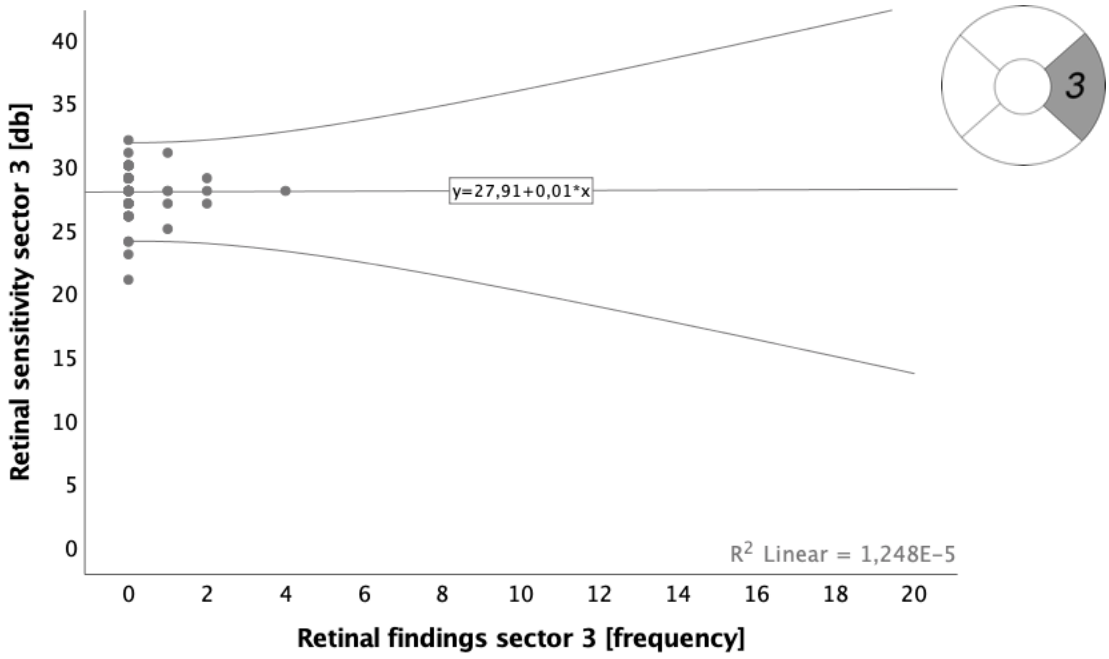

Figure 9. Scatter plot representing retinal findings sector 3 (nasal retina) vs. retinal sensitivity sector 3 (temporal visual field). Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 72). ***p = 0.977***

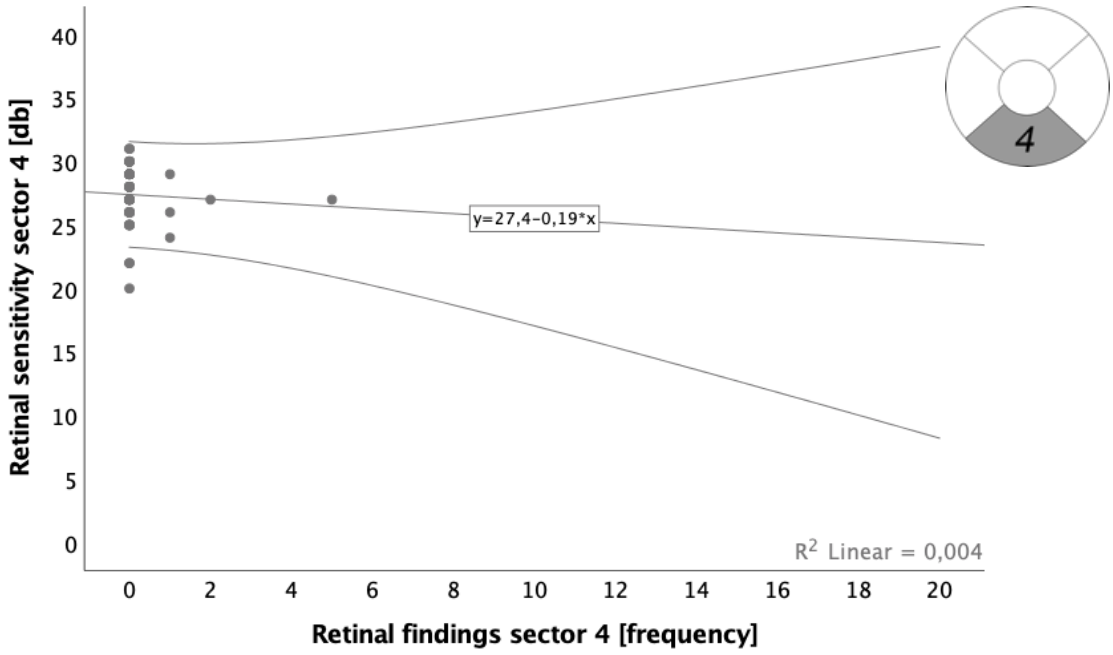

Figure 10. Scatter plot representing retinal findings sector 4 (inferior retina) vs. retinal sensitivity sector 4 (superior visual field). Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 72). ***p = 0.616***

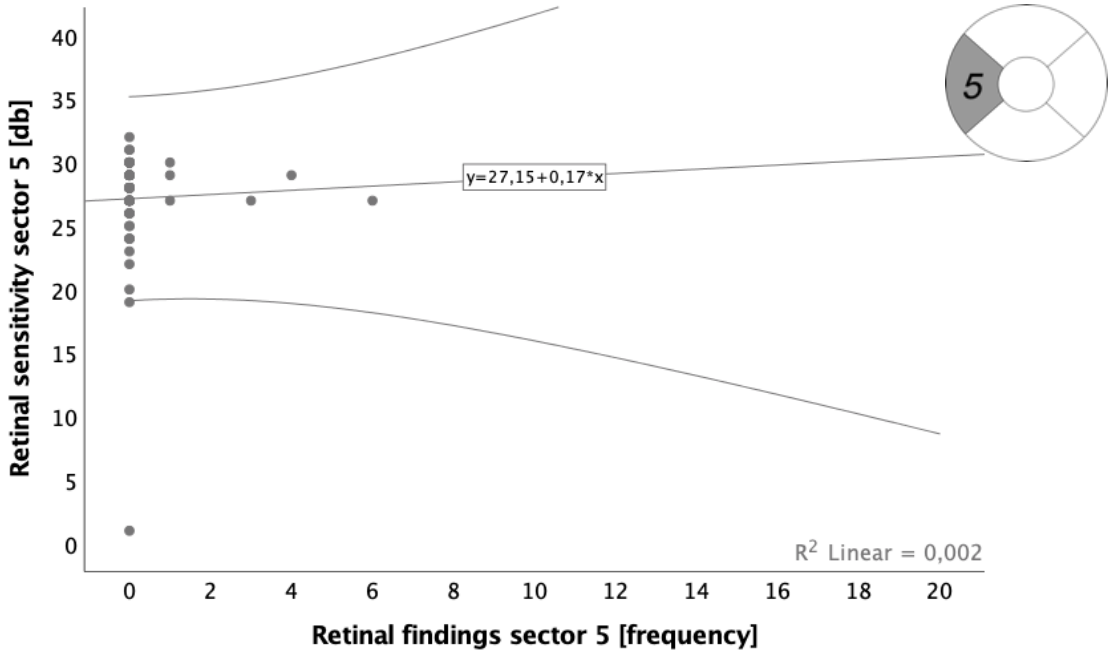

Figure 11. Scatter plot representing retinal findings sector 5 (temporal retina) vs. retinal sensitivity sector 5 (nasal visual field). Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 72). ***p = 0.748***

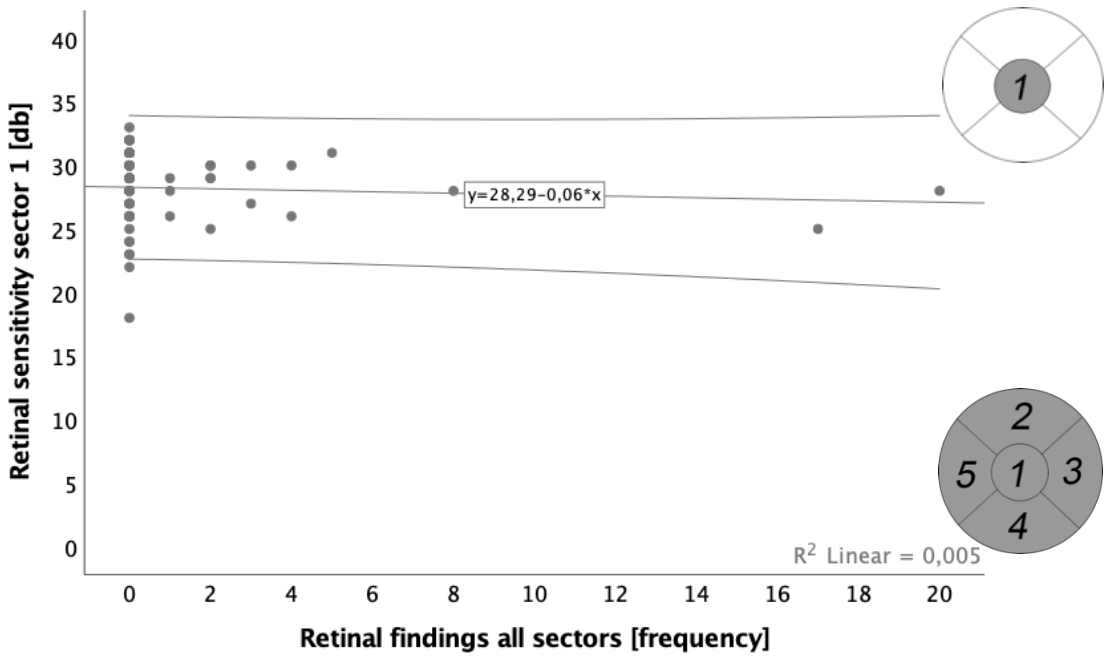

Figure 12. Scatter plot representing the total number of retinal findings in all sectors vs. retinal sensitivity sector 1. Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 72).
p = 0.564

The graphs show the coefficient of determination (R^2). This value represents the proportion of variation and is equally low for all the plots (< 0.7). This indicates that there is no significance. The number of microaneurysms, hemorrhages, exudates and cotton wool spots does not influence the retinal sensitivity in the central visual field within 10° in diameter.

3.2.2 Central foveal thickness vs. retinal function

Central foveal thickness was compeard with the retinal sensitivity in sector 1 in regard of influence. Also contrast sensitivity and BCVA was compared with central foveal thickness as well. (figures 13-15). Some of the OCT-images was not usable because the OCT Cirrus software failed to recognize the layers of the retina correctly, making the centre thickness value not trustworthy. 2 subjects were excluded from the analysis.

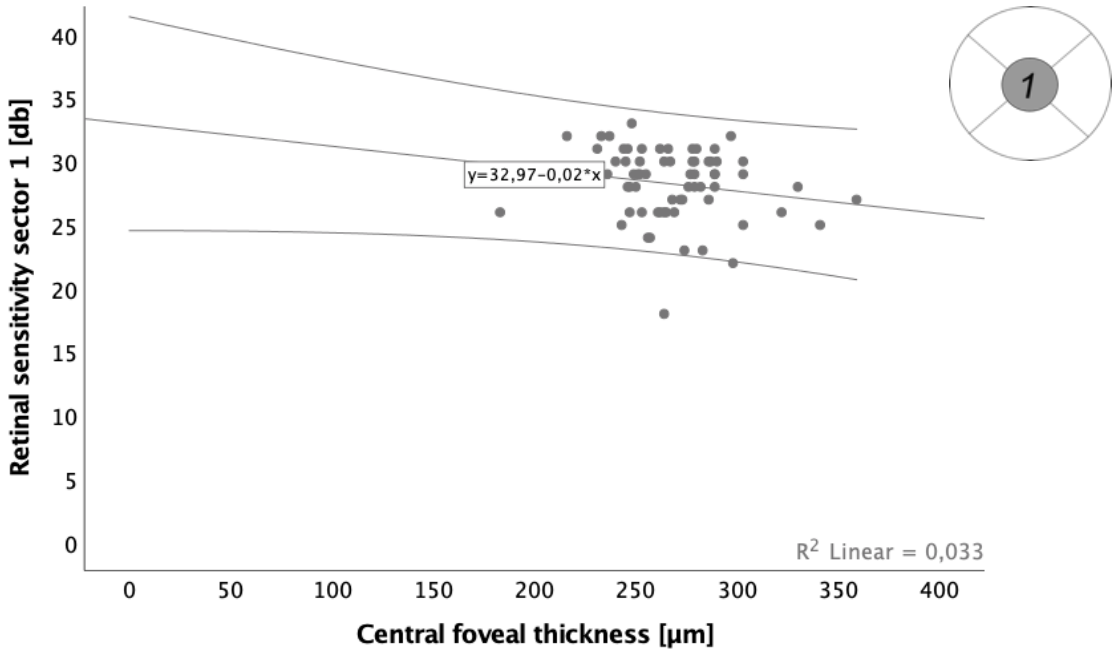

Figure 13. Scatter plot representing central foveal thickness vs. retinal sensitivity sector 1. Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 70). ***p = 0.140***

As we can see in this scatter plot in figure 13, there might be a trend. The regression line and the slope are showing correlation between the two variables, central foveal thickness and retinal sensitivity. R^2 is low, which means that it does not explain the relationship about the two factors, but there is a tendency suggesting that the retinal sensitivity in the central sector 1 (1°) is affected by the central foveal thickness.

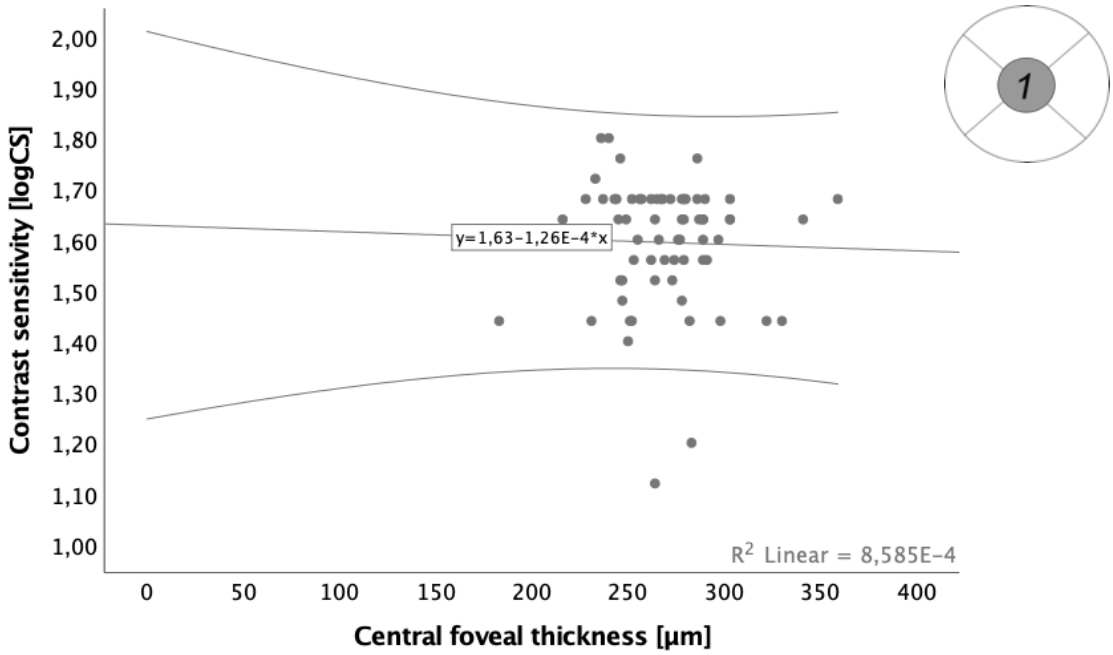

Figure 14. Scatter plot representing central foveal thickness vs. contrast sensitivity. Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 70). ***p = 0.815***

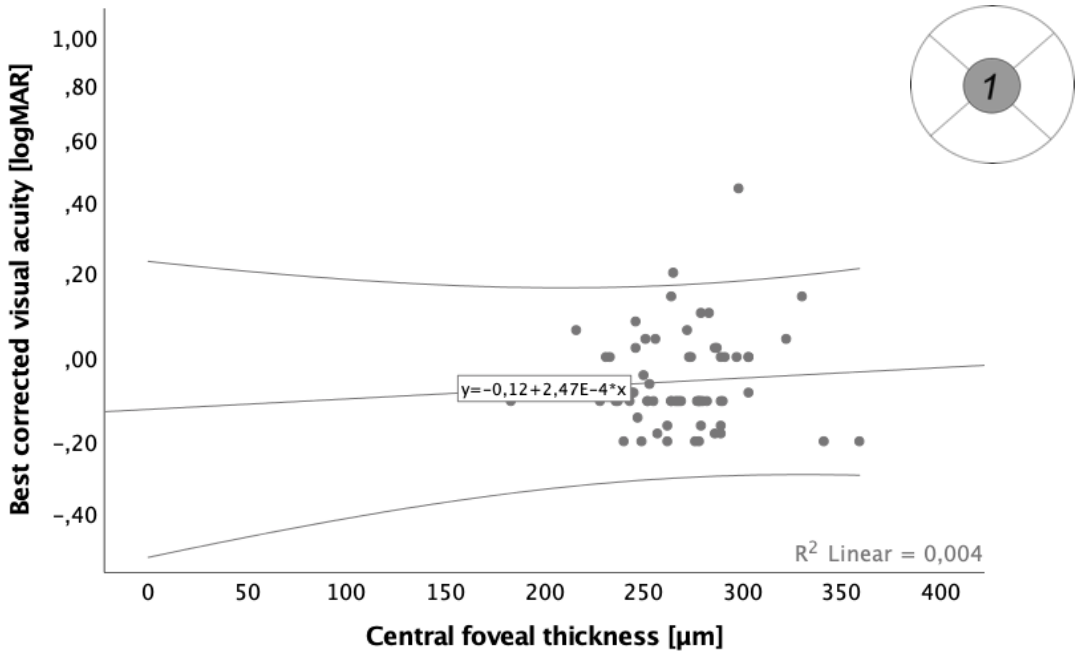

Figure 15. Scatter plot representing central foveal thickness vs. best corrected visual acuity (BCVA) in logMAR. Line in the middle indicates the line of best fit, upper and lower lines indicates upper and lower limits of 95% confident interval (n = 70)

p = 0.622

The symbol in the upper right corner is showing where the sectors are in the macular area.

Out of the statistical analysis and linear regressions made for the association of central foveal thickness vs central retinal sensitivity, as mentioned earlier, the significance show that the central foveal thickness may influence the central retinal sensitivity. The regression line and the slope are showing correlation between the two variables presented in each figure. In the linear regressions made for the association of central foveal thickness vs contrast sensitivity (figure 14) and for the central foveal thickness vs best corrected visual acuity (figure 15), there were no correlation (R^2 = 0.00086 and 0.004 respectively).

3.2.3 Cataract vs. retinal function

In this study, the cataract was graded with the LOCS lll grading scale, in the evaluation of central opacities like nuclear colour and opacity and posterior subcapsular cataract that potentially could affect the central retinal function. If the subject had a nuclear colour and/or opacity cataract of LOCS lll grade ≥ 3, or posterior subcapsular cataract grade ≥ 1, they had presence of cataract. 11 subjects were excluded due to missing grading of the crystalline lens. Out of the 61 subjects, 30 had no presence of cataract, 31 did have presence of cataract.

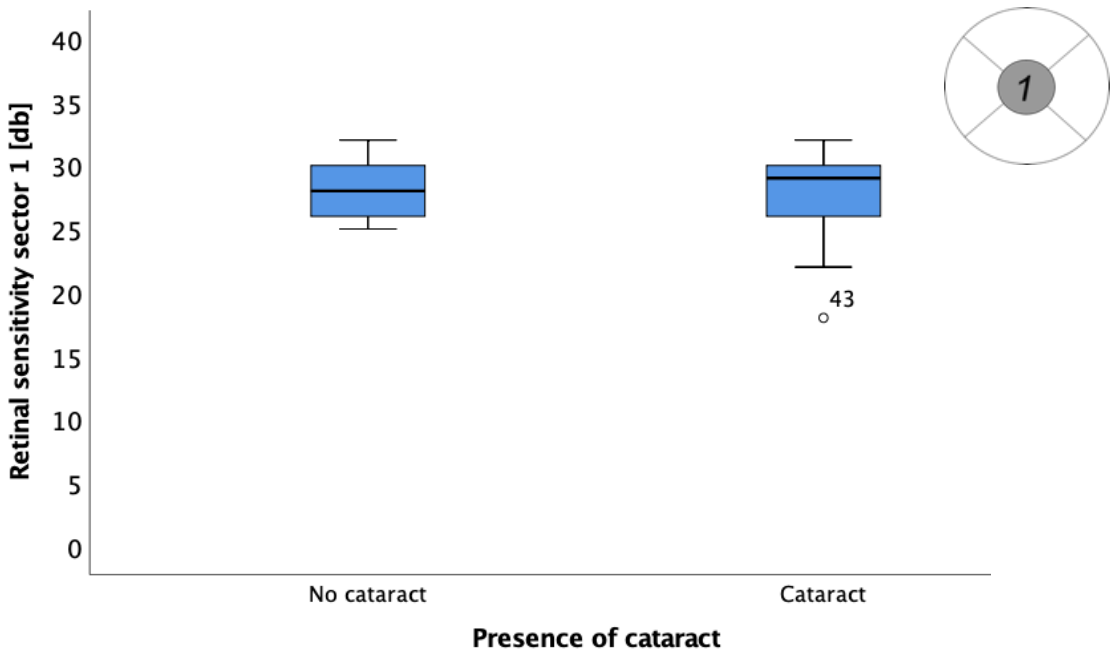

Figure 16. Box plot representing presence of cataract vs. retinal sensitivity sector 1 (n = 61). ***p = 0.129***

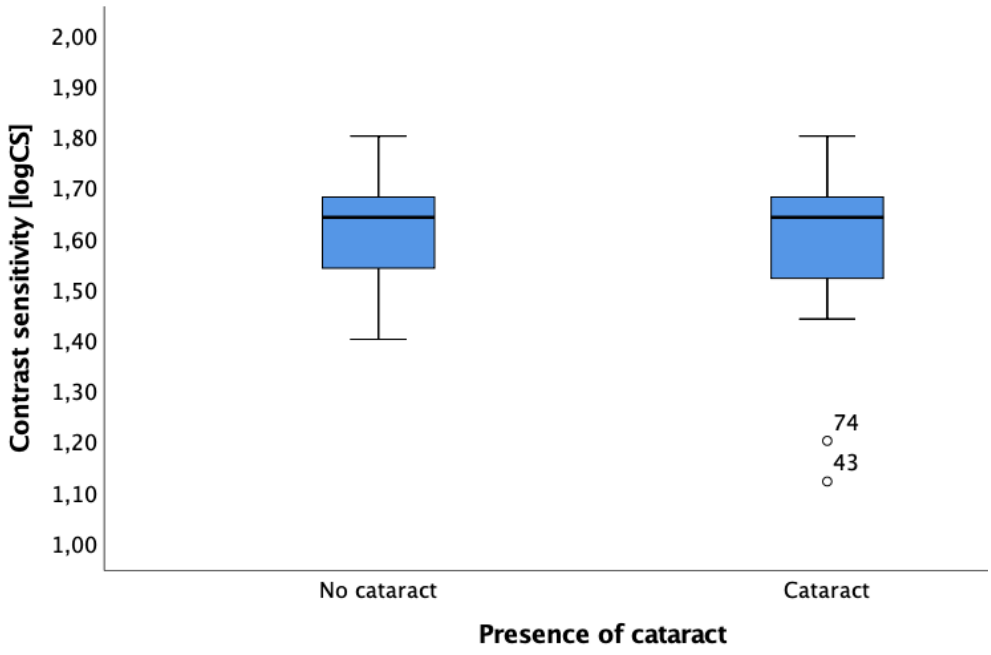

Figure 17. Box plot representing presence of cataract vs. contrast sensitivity (n = 61). ***p = 0.344***

The symbol in the upper right corner in figure 16 is showing where the sectors are in the retinal sensitivity in the visual field.

Out of the statistical analysis and the independent sample t-test made for the presence of cataract and its impact on central retinal sensitivity, there were no correlation between the influence of cataract on the central visual field. The same result was found when comparing the presence of cataract and its impact on contrast sensitivity; there were no correlation between the variables. As we can see of the plots in figure 16 and 17 there are some outliers as well, indicating that they had lower db-value and lower contrast sensitivity, that the rest of the subjects. In the comparison of presence of cataract and central retinal sensitivity, the size of the "whiskers" in the box plot in figure 16 are longer, which indicates more spread in db-values in the subjects having cataract.

3.3 Interrater- and intrarater reliability

In this study, an interrater and intrarater evaluation was conducted to look for reliability and validity in the data analysed in the retinal imaging. This was calculated in SPSS with a statistical analysis called "Cohens Kappa" (K) which is a measure of agreement between the two investigators (interrater or reproducibility) and for repeated measure by the same operator (intrarater or repeatability). The result of the kappa calculation was K = 0.167 and K = 0.219 for the interrater and intrarater respectively, when comparing the numbers of any retinal findings in any sector in total for a selection of 10 randomly test subjects (5 with findings, and 5 without any finding from the initial grading).

Table 8. Initial grading of retinal findings in 10 randomly selected test subjects

Test subjects	Initial grading of retinal findings				
	MA	EX	HEM	CWS	SUM
1	0	0	0	0	0
2	0	0	0	0	0
3	1	0	0	0	1
4	0	0	0	0	0
5	0	0	0	5	5
6	0	0	0	0	0
7	1	0	1	0	2
8	3	0	0	0	3
9	0	6	1	1	8
10	0	0	0	0	0
Total	5	6	2	6	19

MA = microaneurysms, EX = exudates, HEM = dot & blot hemorrhages, CWS = cotton wool spots

Table 9. Interrater and intrarater reliability grading in the same 10 test subjects

T.S.	Interrater					Intrarater				
	MA	EX	HEM	CWS	SUM	MA	EX	HEM	CWS	SUM
1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0
3	1	0	0	0	1	0	0	0	0	0
4	1	0	0	0	1	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0
6	1	0	0	0	1	0	0	0	0	0
7	5	2	1	0	8	1	1	1	0	3
8	7	0	1	0	8	3	0	1	0	4
9	1	33	2	0	36	1	18	1	0	20
10	0	0	0	0	0	0	0	0	0	0
Total	16	35	4	0	55	5	19	3	0	27

T.S. = test subjects, MA = microaneurysms, EX = exudates, HEM = dot & blot hemorrhages, CWS = cotton wool spots

4 Discussion

There are numerous studies regarding diabetic retinopathy with focus on pathophysiology and treatment on an ophthalmological level, but there isn't many that have looked at the retinal structure and macular findings and compared it to the central visual function systematically. Thus, the purpose of this study was to look at retinal structure in association with visual function in the macular area in subjects which had been diagnosed with diabetes mellitus type 2. The research questions were answered trough statistical methods and the results show no clear correlation between the variables in the different analysis.

4.1 Retinal structure vs. retinal sensitivity

There weren't many subjects in the current study with diabetic related changes in their retina (25% of the test subjects). According to table 7, the test subjects showed most signs of microaneurysms followed by exudates and cotton wool spots, and less signs of hemorrhages. Bek and Helgesen concluded that microaneurysms and hemorrhages were most present around the larger vascular arcades, in a study evaluating regional distribution of diabetic lesions (Bek & Helgesen, 2001). In the results of the current sturdy there are no statistical significances between clinical retinal findings related to diabetic retinopathy in the macular area compared to the retinal sensitivity measured with automated perimetry in the corresponding sectors ($p = 0.848$, $p = 0.977$, $p = 0.616$, $p = 0.748$ and $p = 0.564$). One of the reasons may be because the subjects did have well controlled diabetes type 2, and a low number of retinal findings. Considering the duration of diabetes as a strong risk factor, patients with type 2 hasn't had the condition since they were children, like in most cases of diabetes type 1 (American Diabetes, 2015).

In Malmö, Sweden, a research group wanted to compare outcomes of perimetric and visual acuity tests in patients with diabetic retinopathy. They took fundus photos and fluorescein angiography and measured logMAR visual acuity of 59 subjects and measured static automated perimetry using the 10-2 test program. They examined the perifoveal area of the macula and looked for damage across the perifoveal capillary network. There were no significant association between visual acuity and diabetic

retinopathy, but it was significance in the correlation between the severity of diabetic retinopathy and the perifoveal area measured with the automated perimetry (Bengtsson, Heijl, & Agardh, 2005). Another study looked at automated perimetry and capillary density in early diabetic maculopathy. They wanted correlate sensitivity perimetry with alterations of the perifoveal vascularity in early diabetic maculopathy. The study population consisted of 31 subjects with no clinically significant macular edema and with all different types of diabetic retinopathy. Fluorescein angiography and fundus photos were obtained from all the subjects and images were compared to the result of the automated perimetry measured with the 10-2 test program. The result showed no significance in diabetic findings in the perifovea compared to mean thresholds assessed with perimtry and that it was unrelated to diabetic changes in the perifoveal capillary network (Remky, Arend, & Hendricks, 2000). A study looking at the different stages of diabetic retinopathy and quantified the disturbances in the corresponding visual field. They looked at 63 subjects with different stages of diabetic retinopathy representing retinal changes like microaneurysms, exudates, hemorrhages and cotton wool spots and compared the findings to the retinal sensitivity measured in the area of 0° – 10°. The test results showed that there were significantly reduced retinal sensitivity in the central field of vision (Henricsson & Heijl, 1994). As we see of previous studies, there are different approaches and different results significance wise.

4.2 Central foveal thickness vs. central retinal sensitivity, contrast sensitivity and best corrected visual acuity

The results found in the current study, regarding association between central foveal thickness and contrast sensitivity suggest no statistical significance at all ($p = 0.815$) neither in the central foveal thickness compared with the BCVA ($p = 0.622$).
In the scatter plot comparing the thickness to contrast sensitivity, there are two outliers in the lower end of the contrast sensitivity axis. The reason for this, may be that these two subjects have higher grading of cataract, diabetic findings or other form of pathology. The final result may have been different if they would have been excluded. The subjects included in this study, were type 2 diabetics, and like mentioned earlier, the subjects may have their blood sugar levels under control, but they haven't had diabetes mellitus necessarily for as long as the type 1 patients (American Diabetes,

2015). Another reason that contradict the insignificance is the quality of the contrast sensitivity test performed. The MARS test is a recognised test with an equal or even better test-retest reliability than the Pelli-Robson test (Haymes et al., 2006). Meanwhile, there might be trend like mentioned before, in the plot representing the central foveal thickness vs central retinal sensitivity in sector 1 (figure 17). Normal central foveal thickness measured using a Carl Zeiss Cirrus HD-OCT in healthy individuals is 200.58 ± 19.22 μm (range 158.4 – 264 μm) (Arepalli et al., 2018). The retinal thickness is important to measure in subjects with diabetic retinopathy because of the presence of diffuse diabetic macular edema. This is characterized by extensively damaged capillaries and arterioles at the posterior pole with the result of widespread thickening of the macular area. This is measurable in retinal thickness, but not necessarily giving the same result as cystic macular edema (Bandello, Iacono, & Battaglia Parodi, 2011). Looking at the result of the comparison between central foveal thickness and central retinal sensitivity, there are not statistical significance ($p = 0.140$), but a slight trend may be seen in the influence the central thickness makes on the central retinal sensitivity. The reason for this might be due to early not detected macular pathology in some of the test subjects (Chiba, Imasawa, Goto, Imai, & Iijima, 2012).

A study from 2015 investigated retinal sensitivity over hard exudates in correlation with the central retinal thickness in the fovea measured with spectral domain OCT. The patient group consisted of 12 subjects with diabetic retinopathy with no other diabetic retinal feature than hard exudates. The researchers used microperimetry to evaluate the retinal sensitivity under dilated conditions and measured visual acuity with a logMAR visual acuity chart. The results revealed that visual acuity ranged from 0.20-1.20 logMAR, and an insignificant correlation was found between retinal sensitivity and retinal thickness were the hard exudates were localised and between retinal sensitivity and central foveal thickness (Raman et al., 2015). A team of researchers from America tested in 2017 whether quantitative functional tests and OCT-defined structure could serve as effective tools to diagnose and monitor early diabetic neural disease. Their subject group consisted of 57 (20 with no DR, 19 with mild NPDR, 15 with moderate NPDR and 18 controls) and were tested with OCT, contrast sensitivity and rarebit perimetry. This form for automated perimetry presents small light stimuli on a black

computer screen. The fovea testing strategy was used in this case. The contrast sensitivity was measured using the quick contrast sensitivity function (qCSF) method for evaluating the contrast thresholds over a wide range of contrast (0.002% - 100%) and spatial frequency. The results of the study showed that the contrast sensitivity were significantly reduced in diabetics with moderate compared to mild NPDR, and in subjects with no DR, compared to the controls. The central foveal thickness revealed significant thinning in the moderate NPDR subjects compared to the controls, and there were no statistical significance in the retinal sensitivity measurements of the central foveal area (Joltikov et al., 2017).

4.3 Presence of cataract and influence on the results

There was no statistical significant impact the cataract made on the central retinal sensitivity ($p = 0.129$), neither the contrast sensitivity ($p = 0.344$). The chosen level of cataract made it sure that only some degree of central lens opacities made it through the inclusion criteria. In other studies, it has been reported total exclusion of any degree of cataract or lens opacities (Nilsson, von Wendt, Brautaset, Wanger, & Martin, 2012) or like the current study, a custom made criteria of presence of cataract (Montesano et al., 2017).

4.4 Inter- and intrarater reliability using Cohens Kappa

Cohens Kappa is a popular descriptive statistical analysis for summarising the cross classification of two normal variables with identical categories (Warrens, 2011). The result of the interrater analysis was $\mathrm{K} = 0.167$ and $\mathrm{K} = 0.219$ for the intrarater analysis. Cohen suggested the kappa result to be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01-0.20 as none to slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as almost perfect (McHugh, 2012). As table 9 shows, the exudates were the diabetic retinal feature which was graded most differently when comparing the two operators. Exudates are one of the clinical signs on early development of diabetic retinopathy (Joshi & Karule, 2018) and due to the fact that they often evolve in cluster formation (Ram & Sivaswamy, 2009), makes them hard to count individually in the retinal image. In a Norwegian research from 2017, they investigated the effect of web-based targeted training on the optometrist's ability to

detect, classify and manage patients with diabetic retinopathy. The conclusion showed a potential for Norwegian optometrists to improve their skills in detecting diabetic retinopathy (Sundling & Aamodt, 2017).

4.5 Quantifying the structure and function

4.5.1 Macular area of interest

The measuring area of 1° was chosen in order to compare structural retinal changes in the fovea with the central foveal function like central 1° retinal sensitivity, contrast sensitivity and visual acuity. The measuring area of 10° was chosen in order to compare structural retinal changes in the macular area with central macular function like the 5° (diameter of 10°) retinal sensitivity.

4.5.2 The retinal features of diabetic retinopathy

The fundus abnormalities seen in diabetic retinopathy can be split up into three categories. Those findings resulting from leaking microvasculature (hemorrhages, lipid exudates and retinal edema), those findings resulting from structural damage to microvascular walls (microaneurysms) and those findings resulting from ischemia with a subsequent overproduction of vascular growth factors (cotton wool patches, intraretinal microvascular abnormalities (IRMA), preretinal neovascularisation, fibrous proliferation and vitreous hemorrhages) (Browning, 2010). Microaneurysms, exudates, hemorrhages and cotton wool spots were chosen as retinal features to look for in the macular area in the retina for this study. These diabetic changes were selected because they represent hallmarks from every category.

4.5.3 Retinal sensitivity measuring

In 2007 a study from Italy found that central retinal sensitivity measured with Octopus perimeter was 33.1 ± 1.7 db (range 27-38 db) obtained using the central 10° algorithm. Considering reliability using the 10-2 test program in the Octopus, different approaches to validation has been used to ensure test reliability. A comparison of size modulation standard automated perimetry and conventional standard automated perimetry with a

10-2 test program in glaucoma patients from 2017, reported reliability of false positive (FP) < 15% and not use of false negative's (FN's) at all (Hirasawa et al., 2017). Another study, also from 2017, using the 10-2 test program to assess the central visual function in patients with retinitis pigmentosa, reported reliability methods of FP < 15% and FN < 33% (Fujiwara et al., 2018). The test reliability in this study, was dependent on the FP and the FN as well, and for the test to be included, the FP and the FN had to be < 30%. This number was chosen to be sure to include as many subjects as possible due to the fact that the automated visual field test took place at the very end of the list of test procedures. It was expected for the subjects to be tired after all the other tests, so it was also expected that the FP and FN could be high for someone.

4.5.4 Central foveal thickness with OCT

In this study we used the Cirrus HD-OCT with the 'Macular Cube 200x200' test program, that generated the ETDRS (Early treatment diabetic retinopathy study) pattern. This is a figure of 3 concentric rings split up in a total of 9 sectors. The inner circle represents an area of 1 mm on the retina, the middle ring represents an area of 3 mm and the outer circle represents an area of 6 mm. The four sectors around the inner (central) circle is aligned to symbolise superior, inferior, nasal and temporal area of the retina (Huang et al., 2009). A study looking at macular area in patients with advanced retinitis pigmentosa used light stimuli to map the central macular sensitivity. The retinal area stimulated by the central stimuli was between 0° – 2.5° of the retinal visual field, and they reported that the central subfield (central sector) of the ETDRS pattern corresponded to the central stimulus (Vamos et al., 2011). This means that the 1° of visual field corresponds mainly to the central foveal thickness using the ETDRS pattern performed in this study. One of the grading criteria, was the correct segmentation by the build in algorithm in the Cirrus. This is one of the most crucial elements when measuring the central foveal thickness in order to measure correctly. An ophthalmological study done in Los Angeles compared central macular thickness in patients with dry AMD with two spectral-domain (SD)-OCTs, a Nidek OCT and the Zeiss Cirrus OCT. They reported that delineation of the retinal outer boundaries was clearly different in the two instruments as well as the image quality. In addition to difference in segmentation it is important to note the possibility of artefacts and pathologic

alteration which can significantly affect the inner/outer boundaries (Tepelus, Hariri, Balasubramanian, & Sadda, 2018).

4.5.5 Contrast sensitivity and visual acuity testing

Visual function in form of contrast sensitivity was tested at 50 cm with a MARS test for each eye in the current study. Visual acuity was measured with a logMAR visual acuity chart. Contrast sensitivity stimulates the central foveal area in the visual field corresponding to 1° (Clatworthy, Warburton, Tolhurst, & Baron, 2013). Diabetic retinopathy has been shown to reduce contrast sensitivity in both early and advanced stages of the pathology. There has been reported a significant reduction in only letter contrast sensitivity from a control group when the diabetic participants were grouped together but not when they were sub-categorised in terms of the level of diabetic retinopathy present. The same study also reported that when comparing letter contrast sensitivity results to visual acuity results, they found that the contrast sensitivity was significantly reduced for the patients who did not have macular edema compared to the controls, but the visual acuity was reduced. This demonstrates that for those at risk of developing damage to the macula, which includes all diabetics, letter contrast sensitivity is a more sensitive test than standard measurements of visual acuity (Stavrou & Wood, 2003).

4.5.6 Presence of cataract

Cataract was also tested on the subjects and it was evaluated in regard of the presence of cataract gave any impact on the retinal sensitivity and the contrast sensitivity. The American Academy of Ophthalmology states that different types of cataracts affect the visual system in regard of visual acuity, degree of myopia, growth rate and glare. Dividing the types of cataract into cortical, nuclear and posterior subcapsular cataracts, and describing their impact on visual acuity, cortical cataract has a mild impact on both distance visual acuity and near visual acuity. Nuclear cataract in general (both color and opalescence) has a moderate impact on distance visual acuity and no impact at all on near visual acuity. The posterior subcapsular cataract has a mild impact on distance visual acuity and a marked impact on near visual acuity (Ophthalmology, 2013). Clinical

experience of working with cataract patients taken into consideration along with the literature, the presence of cataract was based up on the significance of nuclear colour and opalescence and posterior subcapsular cataract types. Nuclear cataract ≥ grade NO3/NC3 or a posterior subcapsular cataract ≥ grade P1, was determined presence of cataract clinically significant for this study.

4.6 Limitations with this study

Some limitations were evident here in this study. To ensure quality in the measurements and less missing data, the operators could have been more thorough in the data collection. When analyzing the fundus images, the technique used and the image software of choice made it difficult to be sure where the foveal avascular zone (FAZ) were with only the normal mode, and the red-free filter, in order to place the measuring tool correctly. In many studies they use fluorescein angiography to better see the FAZ, but Norwegian optometrists are limited to only use of traditional fundus photos. Another technique used to measure the retinal sensitivity is microperimetry. One of the advantages with this instrument is that it combines testing both central retinal structure and central retinal function at the same time (Midena & Vujosevic, 2011). Based on the kappa analysis, more practice in grading of retinal findings on the fundus photos could have been achieved to strengthen the reliability of the measurements. Last was the fact that the perimetry testing was taken place at the very end of the eye examinations that had a duration of approximately 3 hours. Many of the subjects expressed tiredness and fatigue when performing the test. Some of the patient were recommended to come back for the perimetry test, and this caused some inconvenience. Ideally, to assure as reliable testing as possible, testing of the visual field could have been performed another day in every subject and also several times due to the learning effect.

4.7 Future studies

Future studies may include subject follow up in 1, 3 or 5 years to look for changes in the retinal structure and visual function. To more precisely investigate, microperimetry may be used to evaluate small alteration in the diabetic retina. Another function reduction to consider in diabetic retinopathy is the color vision. The Fransworth FM 100 Hue test is considered to be a more specific test in early detection of color vision defects in subjects with diabetic retinopathy (Shin et al., 2014).

5 Conclusion

The results suggest that diabetic retinal features such as microaneurysms, exudates, hemorrhages and cotton wool spots does not affect the retinal sensitivity, neither in the central 1° of the macular area, nor in the parafoveal part of the macula (10° diameter). Investigating the central foveal thickness with OCT in patients with type 2 diabetes and evaluating its effect on visual function like contrast sensitivity or best corrected visual acuity showed no statistical significant relationship. Looking at the relationship between central retinal thickness and central visual field may suggest that the central retinal field might be reduced as the foveal thickness increases, but further testing is warranted to make any conclusion about this. Presence of central opacities in the crystalline lens has no correlated impact on the visual function in diabetic retinopathy regarding the contrast sensitivity neither the central retinal sensitivity in 1° of the visual field.

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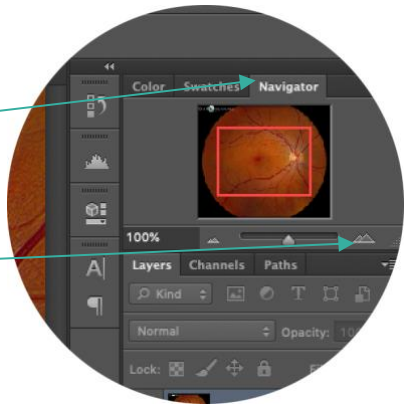
List of tables and charts

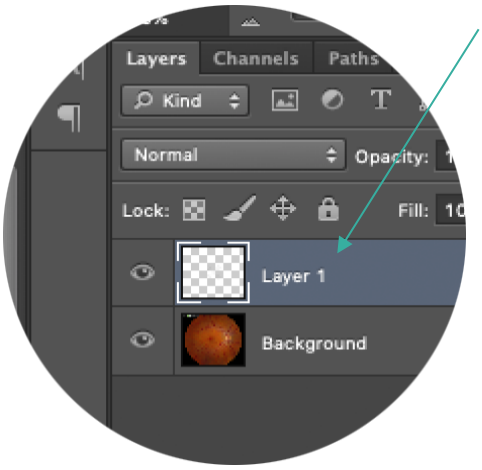
Annexes

Annex 1: Analyzing retinal findings in photoshop

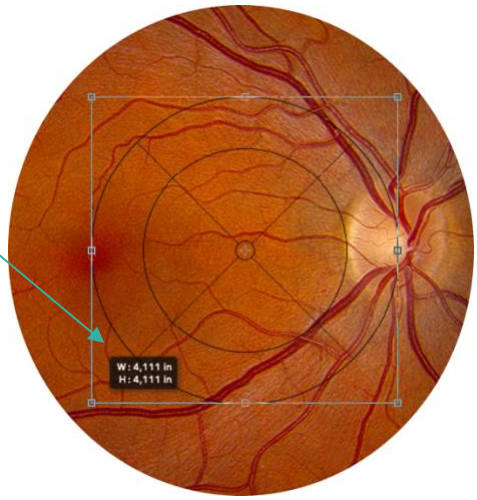
1) Open the program “VK-2” and “Photoshop Elements 4”. In the window in Photoshop, choose ‘Editor’ and drag the program to the “analyzing screen”.
2) Find the subject you want to look at in VK-2, by clicking ‘Database’ from the menu bar and then ‘Open Database List’. Search either by the ID-nr or by last name in the new window and click “START SEARCH”. Double click on the chosen patient.
3) Switch between the images with the arrow buttons on the keyboard to the best quality image of ‘Normal – macula’ is found.
4) When the best image is found, click ‘View’ from the menu bar and then ‘show file info’. A dialog window is coming up with the RAW-image location and the name of the image file you’re looking for; this is the last numbers (000xxx.tiff).
5) Navigate to this location in the folder directory by following the root in the pup-up window. When the image is found, right click, choose open in Photoshop Elements 4 and the image will open automatically in the Photoshop window on the Eizo screen.
6) Make sure the the ‘Navigator’ window in present in photoshop, if not, find it, by clicking it from ‘Window’ in the menu bar. Adjust the magnification to 100% with the button.



7) Look for the “grading tool”-file. It is located in the folder “Jonas” at the desktop and its named ‘measuring circles fundus’. Right click this image and choose ‘open in photoshop’. The image will open in a window for itself in Photoshop.
8) Go to this new window with the grading tool, select it by pressing ctrl + A, so that the whole image is marked, then press ctrl + C to copy the images.
9) Paste it on the fundus image as a new layer by pressing ctrl + V. This will now appear over the layer with the fundus image. Next you will want to orient the grading tool so the it is aligned correctly between the center of the optic nerve head and the fovea. This can be done by first clicking this button and the right click somewhere



on the image with the grading tool and choose ‘Free transform’. This allows you to move the image around. Place it so one side of the square touches center of the optic nerve head and opposite side touches the fovea, and make sure that the square/circles are symmetrical.



10) Now you know that the size of the circles is correct, drag the whole square so the inner circle is over the center of the fovea.
11) Double click on the square to make it disappear.
12) Name the different sectors of the circles (inner circle is sector 1, superior of the middle circle is nr 2, nasal is nr 3, inferior is nr 4 and temporal is nr 5). The sectors 3 and 5 switches places if its left eye.
Count the number of microaneurysms, exudates, hemorrhages and cotton wool spots in each sector.

ID-Number:

DIABETES, VISION AND OCULAR HEALTH

Name:

Date of birth:

Phone-number:

Mail address:

Date for examination 1:
Date for examination 2:
Date for examination 3:
Date for examination 4:

Date:

Signature:

ID-Number: _____

DIABETES, VISION AND OCULAR HEALTH

1 Patient history

1.1	Gender	☐ Female ☐ Male		
1.2	Year of birth	19		
1.3	Symptoms	☐ Blurred vision ☐ Variable vision ☐ Floaters ☐ Parts of the visual field is missing ☐ Double vision ☐ Metamorphopsia ☐ Photophobia		
1.4	Do symptoms disappear with glasses or contact lenses?	☐ Yes ☐ No		
1.5	Vision aids:	☐ Spectacles for distance ☐ Reading glasses / computer/VDU glasses ☐ Bifocal / progressive glasses ☐ Contact lenses ☐ Low vision aid		
1.6	Regular vision examination	☐ Yes ☐ No	☐ Optometrist ☐ Ophthalmologist	/12
1.7	Regular eye examination	☐ Yes ☐ No	☐ Optometrist ☐ Ophthalmologist	/12
1.8	Ocular health	Own: ☐ Diabetes retinopathy ☐ Other retinopathy ☐ AMD ☐ Glaucoma ☐ Cataract ☐ Other	Family: ☐ Diabetes retinopathy ☐ Other retinopathy ☐ AMD ☐ Glaucoma ☐ Cataract ☐ Other	
1.9	Diabetes type 2 duration:	_____ years		
1.10	Glucose level	_____ Mmol/l (%)		
1.11	Treatment of diabetes	☐ Lifestyle intervention ☐ Oral medication ☐ Insulin		
1.12	Diabetes in the family	☐ Yes ☐ No		
1.13	Vascular disease	☐ Yes ☐ No		
1.14	Blood pressure	☐ Low ☐ Normal ☐ High ☐ Not sure	_____ / _____ mmHg	
1.15	Cholesterol	☐ Low ☐ Normal ☐ High ☐ Not sure	Level LDL: Level HDL:	
1.15	Smoking	☐ Yes ☐ No		

ID-Number: _____

2 Visual function

2.0 Pd:

		OD	OS	OU
2.1	Habitual refraction	/ x	/ x	
2.2	Habitual visual acuity (logMAR)			
2.3a	Autorefractor			
2.3b	Pachymetry			
2.4	Subjective refraction	/ x	/ x	
2.5	Best corrected visual acuity (logMAR)			
2.6	Visual acuity with pinhole (logMAR)			
2.7	Near add			
2.8	Near visual acuity at 40 cm			

2.9 Cover test

Distance	Near
☐ Ortho	☐ Ortho
☐ ExoP ☐ ExoT	☐ ExoP ☐ ExoT
☐ EsoP ☐ EsoT	☐ EsoP ☐ EsoT
☐ HyperP ☐ HyperT	☐ HyperP ☐ HyperT

Comments:

2.10 Amsler at 30 cm

OD	OS
☐ Normal	☐ Normal
☐ Metamorphopsia	☐ Metamorphopsia
☐ Visual field loss	☐ Visual field loss

2.11 Contrast sensitivity - MARS

OD	OS

2.12 Color vision - HRR

OD	OS
☐ Normal	☐ Normal
☐ Deficiency	☐ Deficiency

2.13 Motility

☐ Normal
☐ Abnormal

2.14 Pupillary responses

☐ Normal
☐ Abnormal

The Mars Letter Contrast Sensitivity Test

Score Sheet

Patient _____ Administered by _____

Date _____ Correction _____ Test distance _____

Comments _____

Quick Instructions: Instruct patient to read letters left to right for each line, from top to bottom of the chart. Mark misses with an "X." Stop test on 2 consecutive misses.

Important: Allow *only* the letters C D H K N O R S V Z as responses.

FORM 1

Left eye ☐ Right eye ☐ Binocular ☐

C ☐ 0.04	H ☐ 0.08	V ☐ 0.12	O ☐ 0.16	S ☐ 0.20	N ☐ 0.24
D ☐ 0.28	S ☐ 0.32	Z ☐ 0.36	N ☐ 0.40	R ☐ 0.44	K ☐ 0.48
N ☐ 0.52	D ☐ 0.56	R ☐ 0.60	H ☐ 0.64	V ☐ 0.68	Z ☐ 0.72
C ☐ 0.76	S ☐ 0.80	O ☐ 0.84	N ☐ 0.88	K ☐ 0.92	H ☐ 0.96
K ☐ 1.00	N ☐ 1.04	V ☐ 1.08	D ☐ 1.12	S ☐ 1.16	R ☐ 1.20
Z ☐ 1.24	R ☐ 1.28	D ☐ 1.32	K ☐ 1.36	H ☐ 1.40	O ☐ 1.44
H ☐ 1.48	Z ☐ 1.52	C ☐ 1.56	V ☐ 1.60	R ☐ 1.64	K ☐ 1.68
S ☐ 1.72	C ☐ 1.76	Z ☐ 1.80	D ☐ 1.84	V ☐ 1.88	O ☐ 1.92

Value of final correct letter: _____

Number of misses prior to stopping _____X 0.04 = _____

Subtract

log Contrast Sensitivity _____

FORM 2

Left eye ☐ Right eye ☐ Binocular ☐

K ☐ 0.04	S ☐ 0.08	H ☐ 0.12	O ☐ 0.16	N ☐ 0.20	C ☐ 0.24
Z ☐ 0.28	D ☐ 0.32	C ☐ 0.36	R ☐ 0.40	V ☐ 0.44	O ☐ 0.48
C ☐ 0.52	K ☐ 0.56	O ☐ 0.60	N ☐ 0.64	R ☐ 0.68	S ☐ 0.72
N ☐ 0.76	S ☐ 0.80	Z ☐ 0.84	K ☐ 0.88	H ☐ 0.92	D ☐ 0.96
H ☐ 1.00	N ☐ 1.04	C ☐ 1.08	O ☐ 1.12	R ☐ 1.16	Z ☐ 1.20
V ☐ 1.24	K ☐ 1.28	S ☐ 1.32	N ☐ 1.36	D ☐ 1.40	R ☐ 1.44
K ☐ 1.48	R ☐ 1.52	V ☐ 1.56	Z ☐ 1.60	O ☐ 1.64	S ☐ 1.68
V ☐ 1.72	Z ☐ 1.76	C ☐ 1.80	D ☐ 1.84	V ☐ 1.88	H ☐ 1.92

Value of final correct letter: _____

Number of misses prior to stopping _____X 0.04 = _____

Subtract

log Contrast Sensitivity _____

FORM 3

Left eye ☐ Right eye ☐ Binocular ☐

H ☐ 0.04	R ☐ 0.08	Z ☐ 0.12	V ☐ 0.16	C ☐ 0.20	N ☐ 0.24
S ☐ 0.28	O ☐ 0.32	K ☐ 0.36	D ☐ 0.40	R ☐ 0.44	S ☐ 0.48
K ☐ 0.52	D ☐ 0.56	C ☐ 0.60	V ☐ 0.64	O ☐ 0.68	H ☐ 0.72
N ☐ 0.76	S ☐ 0.80	O ☐ 0.84	Z ☐ 0.88	C ☐ 0.92	D ☐ 0.96
R ☐ 1.00	H ☐ 1.04	N ☐ 1.08	K ☐ 1.12	Z ☐ 1.16	O ☐ 1.20
C ☐ 1.24	R ☐ 1.28	S ☐ 1.32	V ☐ 1.36	K ☐ 1.40	N ☐ 1.44
S ☐ 1.48	K ☐ 1.52	R ☐ 1.56	N ☐ 1.60	H ☐ 1.64	D ☐ 1.68
C ☐ 1.72	V ☐ 1.76	H ☐ 1.80	D ☐ 1.84	O ☐ 1.88	Z ☐ 1.92

Value of final correct letter: _____

Number of misses prior to stopping _____X 0.04 = _____

Subtract

log Contrast Sensitivity _____

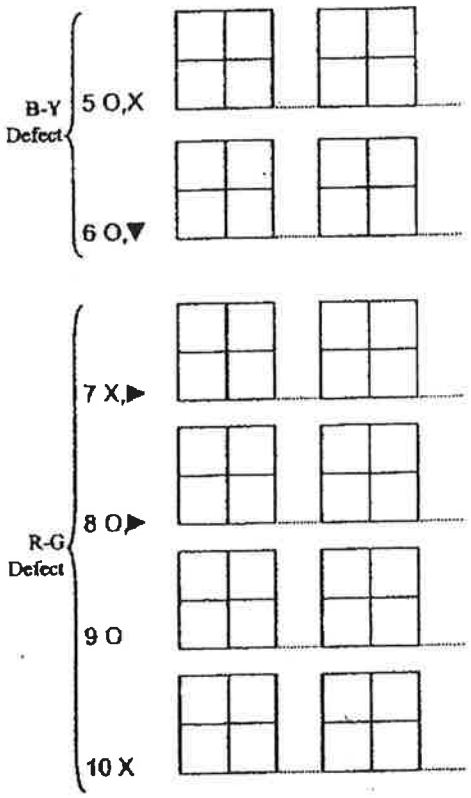
mars perceptrix

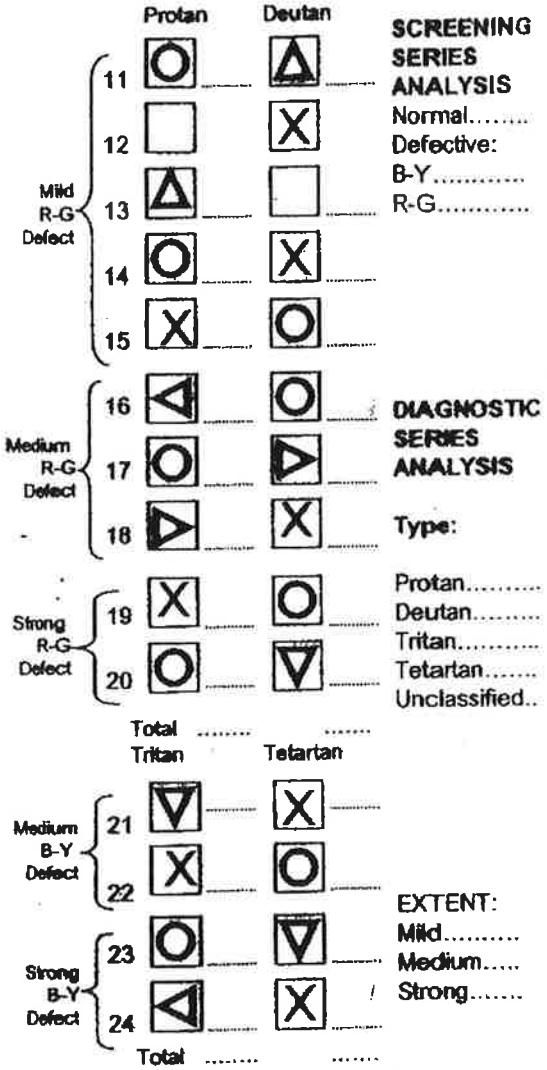
H R R PSEUDOISOCHROMATIC PLATES

NAME..... **DATE**..... **EXAMINER**.....

1-4 DEMONSTRATION SERIES
Four plates. Do NOT score.

SCREENING SERIES





SCREENING SERIES ANALYSIS
Normal.....
Defective:
B-Y.....
R-G.....

DIAGNOSTIC SERIES ANALYSIS

Type:
Protan.....
Deutan.....
Tritan.....
Tetartan.....
Unclassified..

EXTENT:
Mild.....
Medium.....
Strong.....

1021 South Rogers Circle Suite 6 Boca Raton, FL 33487

Laminated Version P/N 4458

ID-Number:

[3] Ocular health

OD					OS			
/min.				3.1a Blink rate	/min.			
60/.....= .....sec.				3.1b Inter blink interval 60/ blinks per minute	60/.....=.....sec.			
				KERATOGRAPH K5 3.2a Tear meniscus height				
…….. mm					…… mm			
Sec.	Sec.	Sec.	Mean	3.2b Non-invasive Keratograph Break-up Time	Sec.	Sec.	Sec.	Mean
Temporal:		Nasal:		3.2c Bubar redness	Nasal:		Temporal:	
Temporal:		Nasal:		3.2d Limbal redness	Nasal:		Temporal:	
☐ Yes ☐ No				3.2e. Lipid Layer Thickness Video sequence 20 sec	☐ Yes ☐ No			
mOsm/L				3.3. Tear osmolarity	mOsm/L			
☐ Exophtalmos ☐ Enophtalmos				3.4a Position	☐ Exophtalmos ☐ Enophtalmos			
☐ Yes ☐ No				3.4b Eye movemnets Free in all directions	☐ Yes ☐ No			
☐ Blepharitis (Efron grade ≥ 2) ☐ Collarets ☐ Telangiectasia ☐ Ectropion ☐ Entropion ☐ Trichiasis ☐ Eye lid tumor				3.4c Eye lids	☐ Blepharitis (Efron grade ≥ 2) ☐ Collarets ☐ Telangiectasia ☐ Ectropion ☐ Entropion ☐ Trichiasis ☐ Eye lid tumor			
				3.4d Conjuctiva				
☐ Scar ☐ Infiltrates ☐ Pigmentation ☐ Other				3.4e Cornea	☐ Scar ☐ Infiltrates ☐ Pigmentation ☐ Other			
				3.5 Van Herrick				
Sec.	Sec.	Sec.	Mean	3.6 Fluorescein break-up time	Sec.	Sec.	Sec.	Mean
Grade Temp.	Grade Corneal	Grade Nasal	Total	3.7a Ocular surface fluorescein staining (Oxford grading)	Grade Nasal	Grade Corneal	Grade Temp.	Total
Grade Temp. …….	Grade Corneal ……..	Grade Nasal …….	Total ……	3.7b Ocular surface lissamine green staining (Oxford grading)	Grade Temp. …….	Grade Corneal ……..	Grade Nasal …….	Total ……
☐ ≥ 2 mm ☐ ≥ 25%				3.8 Lid wiper epitheliopathy	☐ ≥ 2 mm ☐ ≥ 25%			
				3.9 Intra ocular pressure (I-care)				

ID-Number:

[3] Ocular health

<table>
<tr><th colspan="3">OD</th><th></th><th colspan="3">OS</th></tr>
<tr><td colspan="3">…… mm /5 min.</td><td>3.10 Schirmer 1 Test
15 minutes after ocular staining</td><td colspan="3">…… mm/5 min.</td></tr>
<tr><td colspan="3">☐ Meibomian glands in line
☐ Even lid margin:
Other:</td><td>3.11a Eye lid examination
Morphological features</td><td colspan="3">☐ Meibomian glands in line
☐ Even lid margin:
Other:</td></tr>
<tr><td colspan="2">No. of expressible glands OD
……...</td><td>Grade

……..</td><td>3.11b Meibum expressibility
(Central 5 glands)</td><td colspan="2">No. of expressible glands OS

……..</td><td>Grade

……..</td></tr>
<tr><td colspan="2">…. glands x 0 =
…. glands x 1 =
…. glands x 2 =
…. glands x 3 =</td><td>Total score</td><td>3.11c Meibum quality
(central 8 glands)
Clear fluid= 0
Cloudy fluid= 1
Cloudy particulate fluid = 2
Like toothpaste = 3</td><td colspan="2">…. glands x 0 =
…. glands x 1 =
…. glands x 2 =
…. glands x 3 =</td><td>Total score</td></tr>
<tr><td>Upper lid:</td><td>Lower lid:</td><td>Total</td><td>3.12 Meibography
Meibomian gland drop-out Upper and lower lid according to scale</td><td>Upper lid:</td><td>Lower lid:</td><td>Total</td></tr>
<tr><td colspan="3"></td><td>3.13 Corneal senstivity
(Cochet-Bonnet)*</td><td colspan="3"></td></tr>
<tr><td colspan="3"></td><td>3.14 Crystalline lens transparency
(LOCS III grading)</td><td colspan="3"></td></tr>
<tr><td colspan="3"></td><td>3.15 Pupille size
after dilation</td><td colspan="3"></td></tr>
</table>

*** Dilate after measuring corneal sensitivity. Check dilation after 10 minutes**

ID-Number:

3 Ocular health

3.16	Perimetry - Octopus	OD ☐ Normal ☐ Visual field loss	OS ☐ Normal ☐ Visual field loss
3.17a	OCT (Cirrus)	OD ☐ Macular Cube ☐ HD 1 line 100x ☐ HD Raster 5 lines ☐ Optic Disc Cube ☐ HD Radial	OS ☐ Macular Cube ☐ HD 1 line 100x ☐ HD Raster 5 lines ☐ Optic Disc Cube ☐ HD Radial
3.17b	Check pupille size and eyelid position	☐ Ok	☐ Ok
3.18	Retinal photography (Optomap)	OD ☐ Normal x 2 ☐ AF	OS ☐ Normal x 2 ☐ AF
3.19	Retinal photography (KOWA)	OD ☐ Normal - central ☐ Normal - macula ☐ Stereo disc	OS ☐ Normal - central ☐ Normal - macula ☐ Stereo disc

Retinal Assessment

3.20	Evaluation retina	OD ☐ Normal ☐ Abnormal	OS ☐ Normal ☐ Abnorma
3.21	Grading diabetes retinopathy	OD ☐ No ☐ Mild NPDR ☐ Moderat NPDR ☐ Severe NPDR ☐ PDR ☐ Macular edema	OS ☐ No ☐ Mild NPDR ☐ Moderat NPDR ☐ Severe NPDR ☐ PDR ☐ Macular edema

3.22 Comments:

4 Management of participants

4.1	Prescription provided	☐ Yes ☐ No	
4.2	Further managment	☐ Yes ☐ No	☐ Full eye examination ☐ Dry eye ☐ Referral ☐ Emergency
4.3	Reason for further managment		☐ Headache / symptoms ☐ Visual acuity ☐ Binocular vision ☐ Visual fields ☐ Colour vision ☐ Intraocular pressure ☐ Anterior segment / dry eye ☐ Cataract ☐ Retinopathy ☐ Maculopathy ☐ Headache ☐ Other

5 Comments:

Date:

Signature:

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

Diabetes, syn og øyehelse

Dette er et spørsmål til deg om å delta i ett forskningsprosjekt hvor formålet med prosjektet er undersøke hvordan synsfunksjon, øyehelse og livskvalitet påvirkes hos personer som har type 2 diabetes, og vurdere hvilke undersøkelsesmetoder som er mest effektive for å avdekke syn- og øyeproblemer hos optiker. Resultatene fra prosjektet forventes å gi et vesentlig bidrag til å gjøre optikere i bedre stand til å avdekke syn- og øyeproblemer og håndtere disse målrettet og effektivt, og redusere antallet henvisninger til øyelege.

Du forespørres om å delta fordi du har diabetes type 2 og har blitt invitert gjennom Nasjonalt senter for optikk, syn og øyehelse (NOSØ), Diabetesforbundets lokallag i Buskerud, Telemark og Vestfold, eller gjennom optikere i disse fylkene. Forskningsprosjektet og alle undersøkelser gjennomføres ved NOSØ, Institutt for optometri, radiografi og lysdesign, Fakultet for helse og sosialvitenskap, Høgskolen i Sørøst-Norge, avdeling Kongsberg.

HVA INNEBÆRER PROSJEKTET?

Ved deltakelse i prosjektet vil du bli bedt om å fylle ut spørreskjemaer som avdekker syn- og øyesymptomer og din oppfattelse av livskvalitet knyttet opp mot syn. Du vil gjennomgå undersøkelser som er etter Norges Optikerforbund's retningslinjer. Dette innebærer blant annet: innledende samtale og spørsmål, måling av synsevne, utmåling av eventuelle synsfeil på avstand, samt mikroskopiundersøkelse av fremre og bakre del av øynene. Det vil bli målt øyetrykk, samt at netthinnen din blir avbildet med forskjellige instrumenter. Noen målinger krever at vi drypper med pupilleutvidende dråper. Undersøkelsene som inngår i prosjektet er fordelt over tre besøk, og tidsforbruket vil være ca. 2 timer for hvert besøk. Vi vil også be deg om å komme tilbake til oppfølgende undersøkelse etter 1, 5 og 10 år.

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 grundig syn- og øyeundersøkelse. Undersøkelsen inkluderer undersøkelse av tårefilmen, det ytre øyet og netthinnen, og undersøkelser av hvor godt du ser. Det vil bli gitt veiledning og råd som kan gi deg best mulig syn og lindre eventuelle plager for eksempel hvis du har tørre øyne. Dersom det oppdages noen unormale funn, vil vi følge opp dette og sørge for at du får informasjon og eventuell henvisning til øyelege eller lege.

Det er ikke knyttet risiko, betydelig ubehag eller bivirkninger til noen av undersøkelsene. Det vil være nødvendig å bruke øyedråper (Tropikamid 0,5% minims) for å utvide pupillene. Dette kan av noen oppleves litt

ubehagelig da dråpene kan svi noe, og at man blir mer lysømfintlig i etterkant. Effekten av øyedråpene vil avta gradvis og opphører helt etter noen timer.

Det er gratis å delta i prosjektet.

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 NOSØ. 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 førsteamanuensis Tove Lise Morisbakk (tlf 31 00 97 55, tovelm@usn.no) eller førsteamanuensis Vibeke Sundling (tlf 31 00 89 55, vibeke.sundling@usn.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, Institutt for optometri, radiografi og lysdesign, Fakultet for helse og sosialvitenskap, Høgskolen i Sørøst-Norge 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, sett inn saksnr. hos REK (xx/yyy).

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