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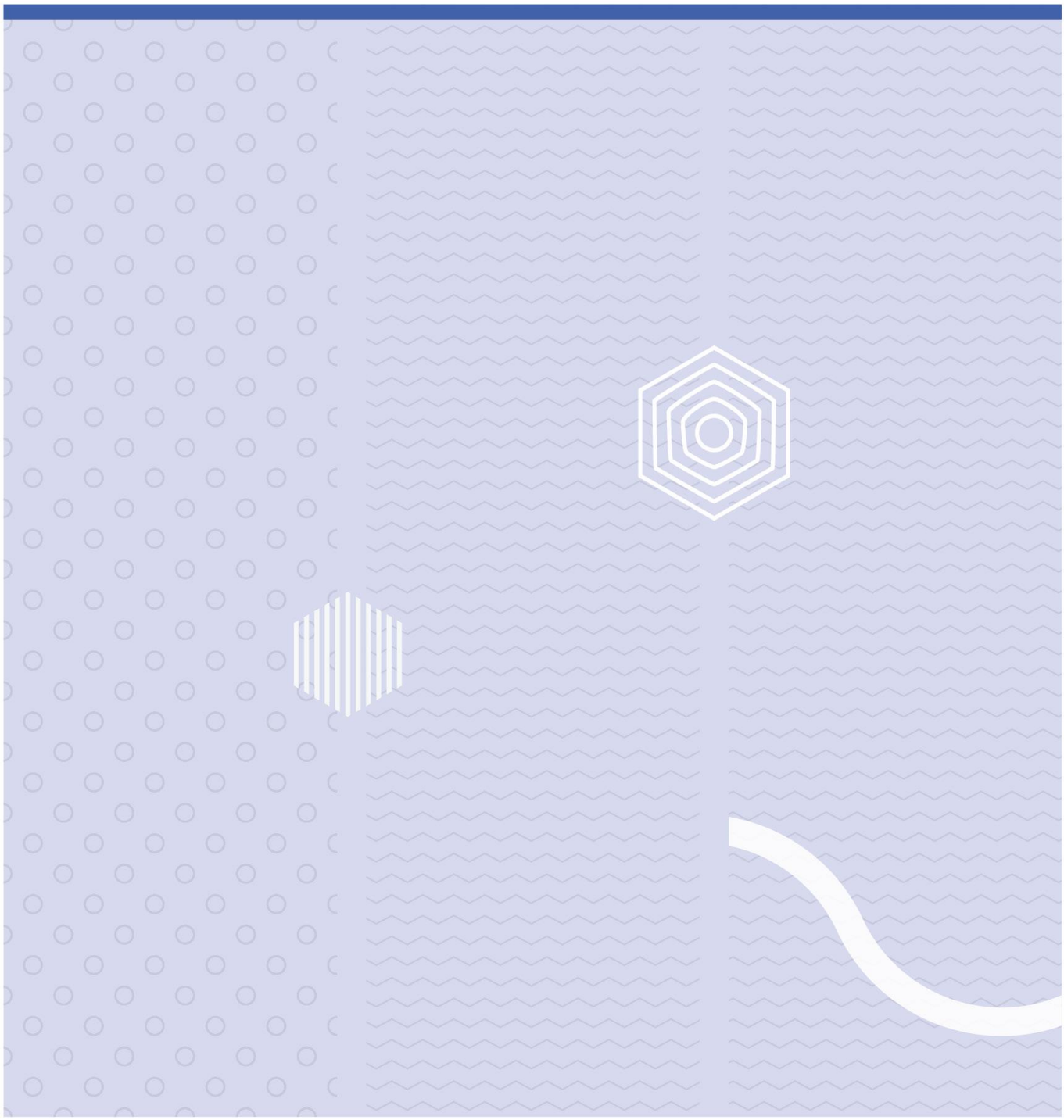
The peripheral diabetic retinopathy in type 2 diabetes: a cross-sectional study



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This thesis is worth 30 study points.

Abstract

Purpose

The main objective of this study was to investigate whether peripheral ultra-widefield high resolution digital images (Optomap model California, Optos) detect more diabetic retinal findings than central 45-degrees retinal images (KOWA VK-2, Kowa American Corporation).

Methodology

This cross-sectional study included adult Norwegian participants with known Diabetic Mellitus type 2 who attended the clinic at the USN for the project "Diabetes, Vision and Ocular Health" from August 2018 to October 2019. The captured images from Optomap (model California) and the 45-degree fundus camera, KOWA VK-2 were obtained with mydriasis and with the macula in centre. The number of microaneurysms, haemorrhages, hard exudates, cotton-wool spots, venous beading, intra retinal microvascular abnormalities, neovascularisation and vitreous haemorrhages were counted in each peripheral and mid-peripheral quadrant and for the central retina, in both eyes. As a quality assurance, 11.2% of the images were re-graded, and 34.8% of the images from KOWA VK-2 were graded by a senior optometrist. The diabetic retinopathy severity was assessed based on the International Classification of Diabetic Retinopathy (ICDR) grading scale. The data was analysed using of frequency and summation tables, and R commander software Version 2.7-2. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 89 DMT2 participants were included in the study, the mean age was 67.4 years (range, 37-82 years). When grading DR by using Optomap, 42 (47.2%) of the participants have DR within the central 45-degree area, 61 (68.5%) when including the mid-peripheral retina, and 65 (73.0%) when including the peripheral retina. One (1.1%) participant have only peripheral lesions.

A total of 45 (50.6%) participants had peripheral diabetic findings. Mean (sd) of DR for the peripheral retina were microaneurysms 12.3 (4.3), haemorrhages 12.5 (2.7), hard exudates 0.5 (0.6), cotton-wool spots 0.5 (0.6), IRMA 0.5 (0.6), venous beadings 1.0 (0.8). Neovascularization and vitreous haemorrhages were not found in this study.

Mean (sd) number of lesions in the peripheral ST quadrant were 4.0 (6.2), the SN quadrant 4.0 (7.0), the IT quadrant 3.1(5.4) and the SN quadrant 2.1 (4.0).

32 (36.0%) and 35 (39.3%) participants had an increased severity of DR using the wide field image (Optomap) compared to a central area of 45-degrees captured with Optomap and KOWA VK-2 image, respectively. A linear model found a relationship between DR found in the peripheral retina and the central retina. Weighted kappa statistics showed moderate and good agreement when comparing the severity of DR in central 45-degrees with UWF (KOWA VK-2: κ= 0.45 vs 45-degree Optomap: κ= 0.75). Intraobserver agreement were good (κ= 0.75 to κ= 0.84, and interobserver agreement were fair (right eye: κ= 0.29 and left eye κ= 36). Wilcoxon ranked sum test showed the two means are significant different (Optomap vs KOWA VK-2: p= 0.005 and 45-degree Optomap: p= 2.46e-7).

Conclusion

The use of peripheral high-resolution digital retinal images was found to detect additional diabetic retinal findings that increased the grade of DR compared to retinal imaging. There was no significant difference in retinopathy in the four peripheral retinal quadrants. The study found a moderate and good correlation between peripheral and central diabetic retinopathy and showed that improved retinal visualization using widefield imaging, and examination of the peripheral retina may alter the classification of diabetic retinopathy and therefore can influence the treatment and follow-up of these patients.

Key words

Peripheral retina, ultra-widefield imaging, Optomap, diabetic retinopathy, Diabetic Mellitus type 2

Abstrakt

Hensikt

Hensikten med denne studien var å undersøke om perifere høyoppløselige digitale bilder (Optomap modell California, Optos) oppdager flere diabetiske netthinnefunn enn sentrale 45 graders netthinnebilder (KOWA VK-2, Kowa American Corporation). Studien undersøkte hvor hyppig diabetisk retinopati forekommer i perifer retina, forskjellene i diabetisk retinopati i de fire perifere netthinne kvadrantene, og forskjellene i diabetisk retinopati i perifer retina sammenlignet med de sentrale 45-grader ved bruk av Optomap og KOWA VK-2.

Metode

Deltagerne i denne tverrsnittstudien var voksne nordmenn diagnostisert med Diabetes Mellitus type 2, som deltok i USN sin kliniske studie «Diabetes, syn og øyehelse» fra august 2018 til oktober 2019. Bildene ble tatt ved hjelp av Optomap, og et 45-graders fundus kamera, KOWA VK-2, med mydriasis og med makula i sentrum. Antall mikroaneurismer, blødninger, harde eksudater, myke eksudater, venøse kalibervekslinger, intraretinale mikrovaskulære abnormiteter, neovaskularisering og glasslegemeblødninger ble talt i hver perifer og midtperifer kvadrant og for den sentrale netthinnen, i begge øyne. Som en kvalitetssikring av graderingen, ble 11.2% av bildene gradert på nytt, og 34.8% av bildene fra KOWA VK-2 ble gradert av en seniorforsker. Alvorlighetsgraden av DR ble vurdert i henhold til International Classification of Diabetic Retniopathy (ICDR) graderingsskala. Datainnsamlingen ble analysert ved bruk av frekvens og summeringstabeller, og R Commander programvare versjon 2.7-2. En p-verdi på mindre enn 0.05 ble ansett som statistisk signifikant.

Resultat

Totalt 89 DMT2 deltagere ble inkludert i studien med en gjennomsnittsalder på 67.4 år (fra 37-82 år). Gradering av DR ved bruk av Optomap viste at 42 (47.2 %) av deltakerne hadde DR innenfor det sentrale 45-graders området, 61 (68.5 %) ved inkludering av den midt-perifere

netthinnen, og 65 (73,0 %) ved inkludering av den perifere netthinnen. Én (1,1 %) deltaker hadde kun perifere DR.

Totalt 45 (50,6 %) deltakere hadde perifere diabetiske funn. Gjennomsnittlig antall (sd) mikroaneurismer i periferien var 12.3 (4.3), blødninger 12.5 (2.7), harde eksudater 0.5 (0.6), myke eksudater 0.5 (0.6), IRMA 0.5 (0.6), og venøse kaliberendringer 1.0 (0.8). Neovaskularisering og glasslegemeblødninger ble ikke funnet i denne studien.

Gjennomsnittlig (sd) antall funn med DR i den perifere ST-kvadranten var 4.0 (7.4), i SN-kvadranten 4.0 (7.3), i IT-kvadranten 4.7 (6.5) og i IN-kvadranten 4.3 (5.3).

Henholdsvis 32 (36,0 %) og 35 (39,3 %) deltakere hadde en økt alvorlighetsgrad av DR ved bruk av Optomap sammenlignet med 45-graders Optomap og KOWA VK-2. En lineær modell fant en sammenheng mellom DR funnet i den perifere netthinnen og den sentrale netthinnen. Vektet kappa-statistikk viste moderat og god enighet ved sammenligning av alvorlighetsgraden av DR i sentrale 45-grader med UWF (KOWA VK-2: κ= 0,45 vs 45-grader Optomap: κ= 0,75). Intraobserverer enighet var god, (κ= 0.75 til κ= 0.84) og interobserverer enigheten for KOWA VK-2 bildene var rimelig (høyre øyet κ= 0.29 og venstre øye κ= 0.36). Wilcoxon rangerte sumtest viste at de to gjennomsnittene er signifikant forskjellige (Optomap vs KOWA VK-2: p= 0,005 og 45-graders Optomap: p= 2,46e-7).

Konklusjon

Bruken av perifere høyoppløselige digitale netthinne bilder viste seg å oppdage flere diabetiske netthinnefunn som ytterligere økte graden av DR sammenlignet med sentrale netthinne bilder. Det var ingen signifikant forskjell i retinopati i de fire perifere kvadrantene. Studien fant en moderat og god sammenheng mellom perifer og sentral diabetisk retinopati, og viste at forbedret netthinne visualisering ved bruk av Optomap og undersøkelse av perifer retina kan endre klassifiseringen av diabetisk retinopati. Bruk av perifer avbildning kan påvirke behandlingen og oppfølgingen av disse pasientene.

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Oslo, April 2023

Linda Huseby

List of Abbreviations

DM	Diabetic Mellitus
DR	Diabetic Retinopathy
DME	Diabetic Macula Edema
DMT2	Diabetes Mellitus type 2
NOF	Norges Optikerforbund
WF	Wide Field
UWF	Ultra-Wide Field
PL	Peripheral lesion
PPL	Predominantly peripheral lesions
ETDRS	Early Treatment Diabetic Retinopathy Study
PDR	Proliferative Diabetic Retinopathy
NPDR	Non-Proliferative Diabetic Retinopathy
FA	Fluorescein Angiography
USN	University of South-Eastern Norway
ST	Superior temporal
SN	Superior nasal
IT	Inferior temporal
IN	Inferior nasal
Mic	Microaneurysms
Ha	Haemorrhages
Ex	Hard exudates
CWS	Cotton-wool spots
IRMA	Intraretinal microvascular abnormalities
Vb	Venous beading
NV	Neovascularization
Vh	Vitreous haemorrhages

1.0 Introduction

Diabetic retinopathy (DR) is a complication of Diabetes Mellitus (DM) that causes a progressive damage to the blood vessels in the retina. DR is a major cause of visual impairment in the adult working population and elderly, and screening is a cost-effective strategy for preventing blindness (Wong, Cheung, Larsen, Sharma & Simó, 2016a). Studies have shown that screening programs using colour fundus photography may enable early detection of diabetic retinopathy along with an appropriate referral (Flaxel et al., 2020). Until recently the standard 2-field colour fundus photography is the most used in DR screening (Fenner, Wong, Lam, Tan & Cheung, 2018). With newer techniques ultra-wide field photography, allows evaluation of the peripheral retina which is not visible on standard photographs of the fundus. As of today, there is a lack of consensus on the best mode of screening and there is no standardized follow-up of the peripheral retina. This study investigates the frequency of DR in the peripheral retina in adult Norwegian subjects.

Parts of this thesis has been presented in the project protocol, as the final exam in MRES019 Research methods (Linda Huseby, 2021) at USN (unpublished).

1.1 Diabetic Retinopathy

DM is a global health burden (M. A. B. Khan et al., 2020) and DR is the most frequent microvascular complication of diabetes, and a significant cause of visual impairment and blindness in the working age group (Lin, Gubitosi-Klug, Channa & Wolf, 2021). Screening for DR is therefore recommended to detect sight threatening complications prior to vision loss.

At the entrance to 2020 the estimated prevalence of patients with Diabetic Mellitus Type 2 (DMT2) in Norway in the age group 30-89 years were between 6.8% and 7.5%, and about 20% of the patients were undiagnosed (Stene et al., 2020). A Norwegian study by Kilstad et al. (2012) found the prevalence of DR in patients with DMT2 in Norway to be 24%, not very different from J. Q. Li et al. (2019) who found the prevalence of DR in patients with DMT2 in Europe to be 25.0%. The pooled mean annual incidence of any DR and Diabetic Macula Edema (DME) in persons with DMT2 was respectively 4.6% (95% CI 2.3–8.8%) and 0.4% (95%

CI 0.5–1.4%). They estimated that persons with DMT2 affected by any DR in Europe will increase from 6.4 million today to 8.6 million in 2050.

1.2 Classification of Diabetic Retinopathy

Persistent increase in the blood glucose level damages the retinal blood vessels and causes DR. The presence and the quantity of abnormalities like microaneurysms, haemorrhages, hard exudates, cotton-wool spots, intra retinal microvascular abnormalities, neovascularization and venous beading defines the severity of the disease.

Microaneurysms (Mic): Are focal dilatation of capillary walls and appears as round red intraretinal lesions, 10 to 100 micrometres in diameter (Bowling & Kanski, 2016).

Haemorrhages (Ha): Leakage of vessels due to disruption of tight junction in the capillaries, and the form (flame, dot/blot, or cluster) is dictated by the layer of the retina within which the haemorrhage lies (Bowling & Kanski, 2016).

Cotton-wool spots (CWS): Appear as localised white elevations of the nerve fibre layer. They represent the arrest of axoplasmic material at the margin of a microvascular infarct or retinal ischaemia (Bowling & Kanski, 2016).

Hard exudates (He): Extracellular lipid which has leaked from abnormal retinal capillaries. Appear as waxy cream white lesions with distinct margins at the border between thickened and non-thickened retina (Bowling & Kanski, 2016).

Venous beading (Vb): Venous beading refers to localised dilatation, looping and sausage-like segmentation of veins. It occurs where capillary non-perfusion extends up to the vein wall, causing it to lose its glial support (Bowling & Kanski, 2016).

Intra retinal microvascular abnormalities (IRMA): Consist of vascular elements within the retina that branch with a frequency, number, and angulation unlike normal retinal vessels. Within the retina, they typically lie between artery and vein, and unlike new vessels they do not overlie other vessels (Bowling & Kanski, 2016).

Neovascularisation (NV): Retinal neovascularisation consists of a vascular network, often overlying other retinal vessels, with a branching structure unlike that of normal retinal vessels, arising anywhere in the retina or from the optic disc (Bowling & Kanski, 2016).

Vitreous haemorrhages (Vh): Haemorrhage occurring into the vitreous gel or into the retrohyaloid space (Bowling & Kanski, 2016).

DRs are categorized as Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR). Further, depending on the severity of the disease, NPDR patients are distinguished as mild-stage, moderate-stage, and severe-stage NPDR patients (Shanthi & Sabeenian, 2019).

Table 1: Classification of diabetic retinopathy (Wong et al., 2018). International classification of DR and DME.

Diabetic retinopathy	**Findings observable on fundus**
No apparent diabetic retinopathy (DR)	No abnormalities found on retinal image
Mild non-proliferative DR	Microaneurysms only
Moderate non-proliferative DR	Microaneurysms and other signs (e.g., dot and blot haemorrhages, hard exudates, cotton-wool spots), but less than severe non-proliferative DR
Severe non-proliferative DR	Moderate non-proliferative DR with any of the following: • Intraretinal haemorrhages (≥20 in each quadrant) or • Definite venous beading (in 2 quadrants) or • Intraretinal microvascular abnormalities (in 1 quadrant) • and no signs of proliferative retinopathy
Proliferative DR	Severe non-proliferative DR and 1 or more of the following: • Neovascularization • Vitreous/preretinal haemorrhage

Diabetic Macula Edema (DME)	Findings Observable on Dilated Ophthalmoscopy*
No DME	No retinal thickening or hard exudates in the macula
Noncentral-involved DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter
Central-involved DME	Retinal thickening in the macula that does involve the central subfield zone that is 1mm in diameter

* Hard exudates are a sign of current or previous macular edema. DME is defined as retinal thickening, and this requires a three-dimensional assessment that is best performed by a dilated examination using slit-lamp biomicroscopy and/or stereo fundus photography.

1.3 Screening for Diabetic Retinopathy

The onset of diabetic retinal complications is typically insidious, and patients remain often asymptomatic during the early stages when treatment and medical management are most effective. The asymptomatic presentation of DR emphasizes the importance of retinal examinations to detect and evaluate disease severity and identify patients at risk for vision loss. Without treatment, DR progresses from mild NPDR to moderate- and severe NPDR before the occurrence of proliferative DR. Sight threatening DME can occur at any stage of the retinopathy (Cheung, Mitchell & Wong, 2010). Mild DR is a warning sign of increased retinopathy complications and that the number of microaneurysms is an important factor for long-term outcome (M. L. Rasmussen et al., 2015).

Vision loss and blindness can be prevented by improved access to DR screening using modern screening methods that may help improve detection, followed by referral and early treatment of DR (Lin et al., 2021). Screening is indicated to identify patients with DR in order to prevent vision loss, and it is a cost-effective step to decrease this health burden. Patients with severe degrees of DR have reduced quality of life and use many health-care resources (Wong, Cheung, Larsen, Sharma & Simó, 2016b).

In Norway DMT2 patients are advised to undergo screening at or soon after diagnosis by an ophthalmologist, and then annually or after individual follow-up (Das et al., 2021; NOF, 2016).

1.4 Imaging Technologies

Studies have shown that retinal photography interpreted by trained graders has a high sensitivity (61–90%) and specificity (85–97%) for detection of retinopathy signs and can guide appropriate ophthalmic referral (Cheung et al., 2010).

Traditional fundus cameras capture the central 45° or 60° of the retina. The current gold standards for photography, the Early Treatment Diabetic Retinopathy Study (ETDRS) photographs, consist of seven single 30° images taken after pupil dilation which covers the central and mid-peripheral retina. In these two photographs techniques, the peripheral retina remained undocumented. The introduction of ultrawide field (UWF) imaging has allowed the visualization of approximately 82% of the total retinal area compared to only 30% using seven-standard field ETDRS photography, and 15% using a traditional 45°fundus camera (Oh et al., 2021).

UWF imaging allows examination of the peripheral retina, for up to a 200° view of the retina captured in a single image which exceed the area of the ETDRS photographs. This is made possible by a special optical design of the scanning laser ophthalmoscope (SLO), which also has the advantage of being much less susceptible than fundus cameras to any media opacities such as cataracts. Therefore, the Optomap widefield SLO appears to be a promising technology to screen for DR (Neubauer et al., 2008).

In Denmark a study by Malin L. Rasmussen et al. (2015) showed that the mydriatic as well as the non-mydriatic widefield image taken with the Optos SLO is equally good in grading DR compared to seven 45° fields taken in accordance with the ETDRS protocol. They found that the Optos SLO was superior especially in identifying mild NPDR where a larger proportion of patients had haemorrhages in the periphery. In images with grading discrepancies, a higher level of DR was detected in the non-mydriatic widefield images compared to ETDRS seven-field images. Reasons for this discrepancy were DR in the periphery in the non-mydriatic

widefield images which were not covered in ETDRS seven-field images. A study by L. D. Price, S. Au og N. V. Chong (2015) also showed that UWF imaging improves the detection of DR lesions and leads to a more precise grading of DR, and compared to the ETDRS seven-field images, UWF imaging detects a higher retinopathy level in around 10-15% of cases. Although UWF images are better than ETDRS seven-field images in terms of DR detection and gradeability, Singh et al. (2019) found that UWF imaging has only moderate agreement and lower gradeability rates than dilated fundus examination.

UWF imaging also helps in predicting the risk of post-vitrectomy bleed which tends to be higher in eyes with greater peripheral lesions, and UWF imaging has found utility in telemedicine programs for DR screening because of greater speed of acquisition and patient comfort (Kumar et al., 2021).

A systematic review by Kárason, Vo, Grauslund og Rasmussen (2022) concluded that retinal imaging of traditional fundus camera and UWF both provide acceptable performance compared to the gold standard EDTRS seven-field. Given the time-consuming nature of the seven-field, retinal imaging with traditional fundus cameras could be reasonable options in DR screening, even though a high number of ungradable images in non-mydriatic 45° or 60° fields may pose a clinical challenge.

Compared to wide field fundus fluorescein angiography, as the gold standard, colour UWF images has a high sensitivity and specificity in detection NV in all quadrants and at the disk. Coloured UWF may be used as a non-invasive tool for screening and aid detection of eyes that need treatment (Haridas, Indurkhya, Kumar, Giridhar & Sivaprasad, 2021).

1.5 Peripheral Lesions

Recommended definitions of widefield (WF) and UWF imaging are given by The International Widefield Imaging Study Group who have evaluated modern imaging methods (Choudhry et al., 2019). The group recommends the incorporation of retinal landmarks to describe the retinal field of view (Table 1).

Table 2: Retinal landmarks to describe the retinal field of view (Choudhry et al., 2019).

Region within the retina	Field of view	Anatomic location
Posterior pole	Approximate 50 degrees	Retina beyond disk and arcades
Mid peripheral	60 degrees to 100 degrees (widefield)	Retina up to posterior edge of vortex vein
Far peripheral	110-200 degrees (ultra-wide field)	Anterior edge of vortex vein ampulla to pars plana

Several studies have investigated predominantly peripheral lesions (PPL). PPL are any haemorrhages, microaneurysms, venous beading, intraretinal microvascular anomalies, or retinal neovascularization that are present predominantly in any peripheral field in eyes with DR. The lesions are considered predominantly peripheral when more than 50% of the lesions were posterior to the seven standard EDTRS field (P. S. Silva, J. D. Cavallerano, et al., 2015).

Some patients with DMT2 have only peripheral DR. Using UWF imaging is particularly important in patients with PPL since PPL have shown to have significantly greater progression rates compared to eyes without PPL (Ashraf, Shokrollahi, Salongcay, Aiello & Silva, 2020) (Lim et al., 2020).

A study by P. S. M. D. Silva et al. (2015) found that the presence and increasing extent of PPLs were associated with increased risk of DR progression over 4 years, independent of baseline DR severity and HbA1c levels, and increasing extent of PPLs substantially increased the risk of DR progression and progression to PDR, especially in eyes with less severe DR at baseline. Another study by P. S. Silva, A. J. Dela Cruz, et al. (2015) the same year found that the clinical identification of PPLs may reflect the extent of nonperfusion and ischemia, thus accounting for the increased risk of DR progression. These findings demonstrate that detailed peripheral retinal evaluation provides important information that is necessary to completely assess the risk of DR progression.

A later study by Cherian et al. (2022) has also shown that the presence of PPL in UWF colour photos is a marker for coronary artery disease, and an early referral to cardiology is warranted.

2.0 Aims and Research Questions

2.1 Study Rationale

Optometric practice has potential for shared care in terms of detection, identification, and management of ocular complications of DM and ocular disease in DM. The Royal College of Ophthalmologists and Norwegian Association of Optometry (NOF) have produced guidelines for diabetic eye care to improve the quality of eyecare. Current guidelines are used in all research and patient examinations, even when different retinal areas are investigated. It is therefore questions about the peripheral retina. What is the impact and importance of detecting and grading peripheral diabetic retinopathy, and how frequent are diabetic retinal changes in the periphery? The results from this study are expected to give us improved knowledge whether the images taken with mydriasis by using Optomap detect more diabetic retinal findings than traditional fundus photo done with mydriasis in adult Norwegians with DMT2. The results will contribute to improve the Norwegian national professional guidelines with possible recommendations regarding examination of the peripheral retina for patients with DM, and to improve our understanding of the impact and importance of changes in the peripheral retina.

When investigation patients with DM, the Norwegian guidelines recommend that examination of the posterior segment should be done by indirect ophthalmoscopy and fundus photography with dilated pupils since photos taken with Optomap without mydriasis have in smaller studies shown to have comparable sensitivity as regular fundus photo in mydriasis. The Norwegian clinical guidelines say that more knowledge is needed about the clinical significance of the peripheral lesions using UWF images (NOF, 2016). In this study an UWF scanning laser ophthalmoscope Optomap model California, has been used to investigate DR in the far periphery in adult Norwegian patients with DMT2.

2.2 Objective

The main objective is to investigate whether peripheral ultra-widefield (UWF) high resolution digital images (Optomap model California, Optos) detect more diabetic retinal findings than central 45 degrees retinal images (KOWA VK-2, Kowa American Corporation).

2.3 Research Questions

The main objective is based on the following research questions:

1. How frequent are diabetic retinopathy in the peripheral retina, graded outside the vortex vein ampullas, on retinal Optomap (model California) images, and what are the differences in DR in the peripheral retina when comparing the four retinal quadrants?
2. What are the differences in DR in the peripheral retina, graded outside the vortex ampullas, on retinal Optomap (model California) images compared to DR graded in the central retinal on retinal Optomap (model California) images?
3. What are the differences in DR in the peripheral retina, graded outside the vortex ampullas, on retinal Optomap (model California) images compared to DR graded in the retinal on central 45-degrees retinal images (KOWA VK-2)?

3.0 Methods

3.1 Study Design

This is a cross- sectional study of adult patients with Diabetes Mellitus type 2.

3.2 Setting and Participants

This is an ongoing single-centre cross-sectional study performed at the clinic at the University of South-Eastern Norway (USN), Department of Optometry, radiography and

lighting design, Faculty of Health and Social Sciences, National Centre for Optics, Vision, and Eye Care in Kongsberg, Norway. This study is a part of a larger study, “Diabetes, Vision and Ocular Health” (DVOH), and data used in the current thesis were collected during the period between August 2018 and October 2019.

Adult men and women were included in the study if they were over the age of 18 at the time of examination and diagnosed with diabetes mellitus type 2 (According to The Norwegian Directorate of Health, the current diagnostic criteria for diabetes in Norway are – HbA1c ≥48 mmol/mol (≥6.5 %), or fasting plasma glucose ≥ 7.0mmol/l or 2–hours plasma glucose ≥ 11.1mmol/l).

3.3 Recruitment

Patients with DMT2 from the outpatient clinic at the USN have been asked to participate in this study. Recruitment have also been done by advertisements on the website of University of South-East Norway (USN)(Nasjonalt senter for optikk, 2018). Optometric practices and Norwegian Diabetes Associations in the earlier Buskerud, Vestfold and Telemark counties have been invited to ask their patients/members with known DMT2 if they are interested in participating in this study. Advertisements in general practitioners’ offices in Kongsberg, in the local newspaper and by information campaigns at the largest companies in the local area have been done to recruit patients with DMT2.

3.4 Data Collection

Participants attended the clinic voluntarily, and they were given written information (Appendix 1) and an informed consent (Appendix 2) to be signed before participating in the study.

The participants underwent a thoroughly eye examination following the recommended clinical guidelines according to the Norwegian Association of Optometry (NOF, 2016). All

procedures are standard procedures in optometric clinics, included a dry eye examination, visual field testing and imaging of the retina. Optomap (model California) imaging and fundus photography (KOWA VK-2) which were analysed in this thesis, were performed with pupil dilatation (Tropicamide 0.5%)

In addition to an eye examination, data was collected concerning visual quality of life using three different questionnaires (the NEI-VFQ-25 questionnaire, the MacMonnies and the OSDI questionnaire). Data from these are not included in this thesis and will be presented elsewhere.

Some of the subjects has attended the clinic at the National Centre for Optics, Vision and Eye Care in Kongsberg a second visit for investigations for this study. Only the retinal images from the first visit are included in this study. Eyes were excluded if the image quality were not sufficient, making grading not possible (Table 2 and Table 3).

3.5 Imaging

3.5.1 KOWA VK-2 Imaging

The 45-degree KOWA (Kowa American Corporation, Torrance, CA) coloured retinal camera is used to capture high resolution images for best detailed images possible. The VK-2 is a high-performance digital imaging software system and are connected to the high-resolution KOWA camera and used to review the retinal images. The image can be processed by using a toolbar containing filters and zoom functions, according to diagnostic needs. The retinal images were captured by trained optometrists, and for this study the images were obtained with mydriasis. The image process involved taking several images before storage, including optic disk in centre, macula in centre plus stereo photo of optic nerve head, but only images with macula in centre were analysed in this thesis. Each image took only seconds to capture, and the two most gradable images were stored. The images were stored in the patient journal on the server at the USN clinic. The images were anonymised and not linked to this project.

The Eizo CG277, 27 inches screen were used as the viewing screen with software allowing the use of the toolbar for zooming functions, and filters for manipulation of the images to increase lesion detection.

3.5.2 Optomap imaging

The Optomap model California (Optos California®, Optos PLC, Dunfermline, United Kingdom) consists of a scanning laser ophthalmoscope (SLO), with two laser wavelengths: one green (532 nm) and one red (633 nm) laser. The two images are then either viewed separately (Image 3 and 5) or superimposed by the software to yield semi-realistic colour imaging, making a composite image (Image 4). The instrument requires a small optical path of only 2 mm and, by a special mirror design, is able to obtain wide-field images of approximately 180–200° without pupil dilation. The optical resolution with the instrument used in this study was 1984 × 1984 pixels for that angle, resulting in approximately 10–11 pixels per degree. The SLO produce images of high contrast and sharpness, which show less susceptibility to media opacities than conventional photography (Neubauer et al., 2007).

The retina images were loaded from the server to a viewing station equipped with an Eizo CG277, 27 inches calibrated colour screen, and assessed with the Optomap viewing software. This software allows important image manipulations to increase lesion detection such as a zoom function up to 150%, enhancement and image markings. It offers viewing in both the composite colour and the single wavelengths. The images obtained by the different wavelengths was compared to better differentiate the level at which lesions were located, as the green laser cannot penetrate significantly below the retinal pigment epithelium, while the longer red laser wavelength will (Neubauer et al., 2007).

All the retinal images were obtained with mydriasis and with the macula in the centre. The images were captured by trained optometrists. The imaging process involved taking at least two images selecting the two images that provided the largest retinal area and best image quality for each eye before storage. Each image took only seconds to capture with the Optomap (mod California). Total scanning requires approximately 3–5 min including patient positioning. The images were stored in the patient journal on servers at the USN clinic. The images were anonymised and not linked to this project.

3.6 Procedures

3.6.1. Procedure for Analysing KOWA VK-2 Images

The images were stored at a USN server and were analysed by using the VK-2 application. The database and the database list were opened, and the patient ID was entered for allowing the images to be viewed. The multiple image button was ticked, and all the images captured of the patient were seen. The images from the first visit with the macula in centre were carefully looked at, to choose the most gradable image (Table 3). Both the image and the toolbox were moved to the EIZO screen before evaluating the image.

No filter, high magnification, and medium size lens were first used to evaluate the image, then the green filter was used to evaluate the red components in the image. A transparent overlay with macula in centre were used to count the number of haemorrhages and venous beading in the right quadrant. Starting at the disk and following the arcades until the end of the image in a clockwise manner, the number of microaneurysms, haemorrhages, hard exudates, cotton-wool spots, IRMA, venous beadings, neovascularisations, and vitreous haemorrhages were counted. The number of findings were noted down in the data registration booklet (Appendix 6).

The procedure was repeated for the left eye and for each subject (Appendix 3).

3.6.2. Procedure for Analysing Central 45-Degree of the Optomap Images

The images were stored at a USN server. The Optomap application was opened on the EIZO screen, and the patient ID were entered in the dialogue box. The correct date for imaging were chosen, and the right eye were double clicked to be evaluated fist. The most gradable image (Table 2) was chosen, and the central 45-degrees area (Image 1) was produced. A line from the fovea to the centre of the disk was made. The distance from the fovea to the disk centre are approximately 15-degrees (Rohrschneider, 2004), and were used as a tool to produce the central 45-degree of the Optomap image. The length in pixels from the macula to the disk centre was multiplied with 3, to find the number of pixels in the diameter of the circle. The radius of the 45-degree circle was calculated, and the marker were put in the

fovea and a line were produced in the temporal, nasal, superior, and inferior direction equal to the radius of the circle. The Ellipse-tool were ticked, and a circle were produced with the macula in centre, and with the radius equal to the bar length. This produced an image of the central 45-degree of the posterior pole (Image 1).

The Enhancement button was ticked, and the enhancement was increased to 3 for best possible contrast. The macula was evaluated first by using the SmartZoom function allowing both the use of zoom and the blend function. The blend function allowed the image to be evaluated from the 100% red channel to the 100% green channel. The image was evaluated with composite colours (50% red channel and 50% green channel) first, and then with single wavelength filters (100% green channel). The 100% green channel made microaneurysms and haemorrhages more visible. After evaluating macula, the image was increased until the quadrant filled the screen (Image 2). The superior temporal (ST) area was evaluated first by the use of the SmartZoom function allowing the use of zoom and blend function, followed by the superior nasal (SN), inferior temporal (IT) and then the inferior nasal (IN) area. A note of each finding was made in the excell- sheet (Appendix 6).

The procedure was repeated for the left eye, and for all participants (Appendix 4).

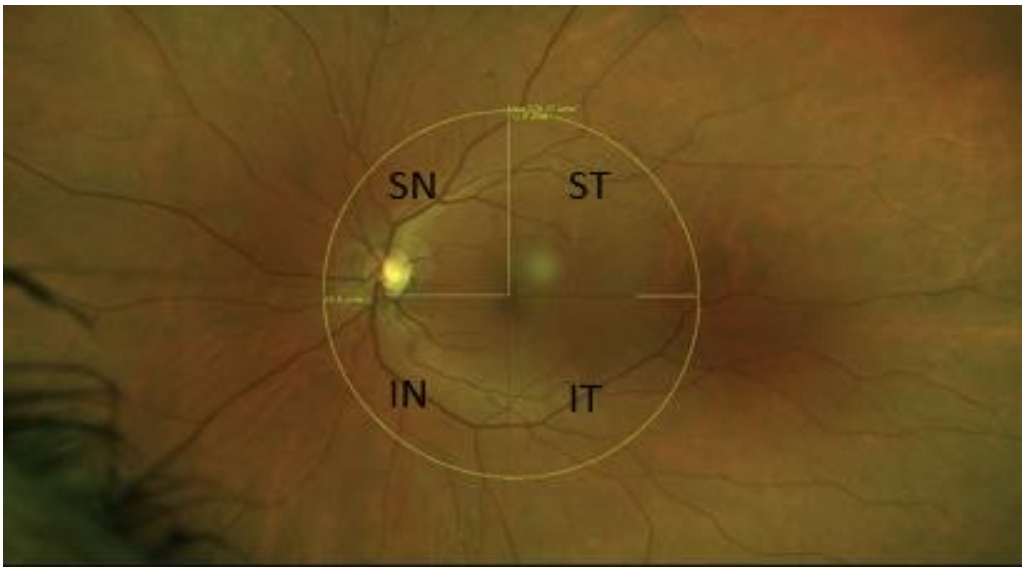


Image 1: A magnified composite Optomap model California image of the central retina. The central 45-degree circle and the central retinal quadrants are marked.

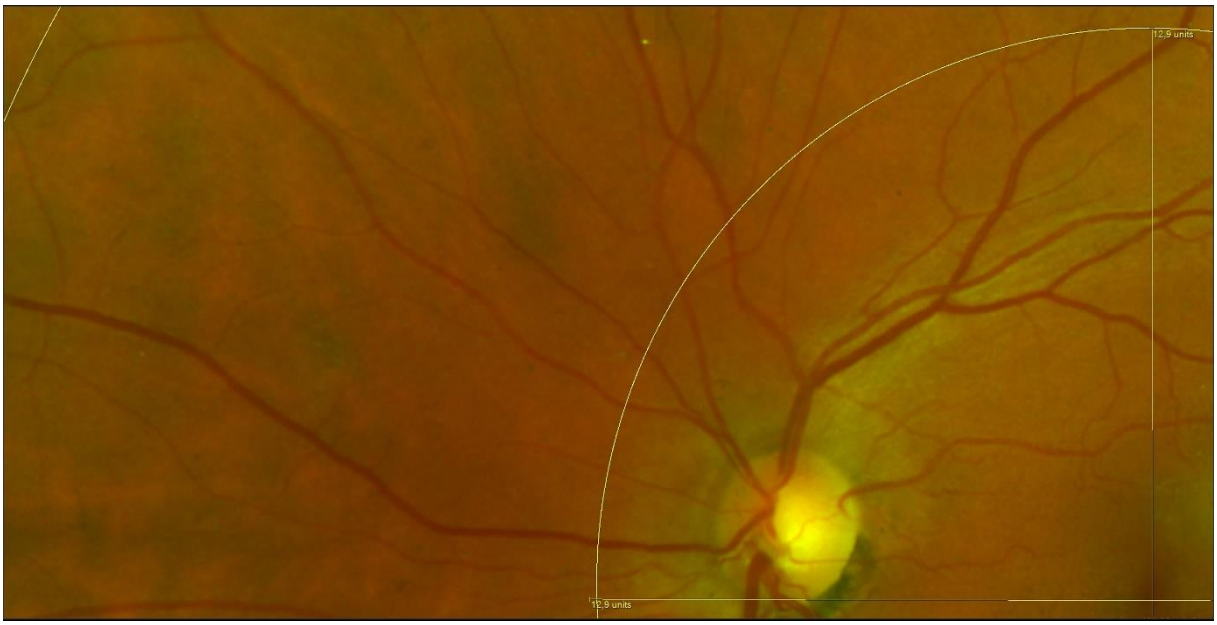


Image 2: A colour composite image captured by Optomap model California. Here the magnification is increased to easier count the findings in the superior nasal quadrant of the central retina.

3.6.3. Procedure for Analysing Optomap Peripheral- and Mid-Peripheral Retina.

The Optomap application was started on the EIZA screen, and the patients ID was entered in the dialogue box. The correct examination was chosen and by doble clicking on the right image, only the right eye appeared on the screen. The most gradable image (table 4) with the largest peripheral field were evaluated. In most cases this image was the same as for the central 45 degrees of the retina which was already marked with a yellow line.

The filter was changed to the 100% red channel for allowing the vortex ampulla to be visible (Image 3). The Area button was ticked and a circle covering the vortex ampulla with the fovea in centre was made. The ring was made parallel to the central 45-degree ring. The area within the circles were defined as the mid- peripheral retina, and the area outside were defined as the peripheral retina.

The peripheral retina and the ST quadrant were evaluated first. The enhancement was increased to 3 for best possible contrast, and the image size were increased until the whole ST quadrant filled the screen. The SmartZoom button with the zoom and blend function were used to evaluate the image. Fist with composite colours (Image 4) and then with the

100% green channel (Image 5). The number of microaneurysms, haemorrhages, hard exudates, cotton-wool spots, IRMA, venous beading, neovascularisations, and vitreous haemorrhages were counted, and the results were written down in the data registration booklet. Some pictures had a lot of artefacts, and it was allowed to flick between the two captured images to avoid the artefacts to be counted when in doubt.

The procedure was repeated for the SN, IT, and IN areas for both eyes.

After finishing the peripheral retina, the same procedure was used for evaluating the mid-peripheral retina, the area between the two circles (Image 4). The right eye was evaluated first, starting with the ST field to see if the image was gradable or not (Table 3). The number of microaneurysms, haemorrhages, hard exudates, cotton-wool spots, neovascularizations, venous beadings, and vitreous haemorrhages were counted and written down in the data registration booklet (Appendix 5). The procedure was repeated for the SN, IT and IN field, and for the participants left eye.

These procedures were repeated for all participants.

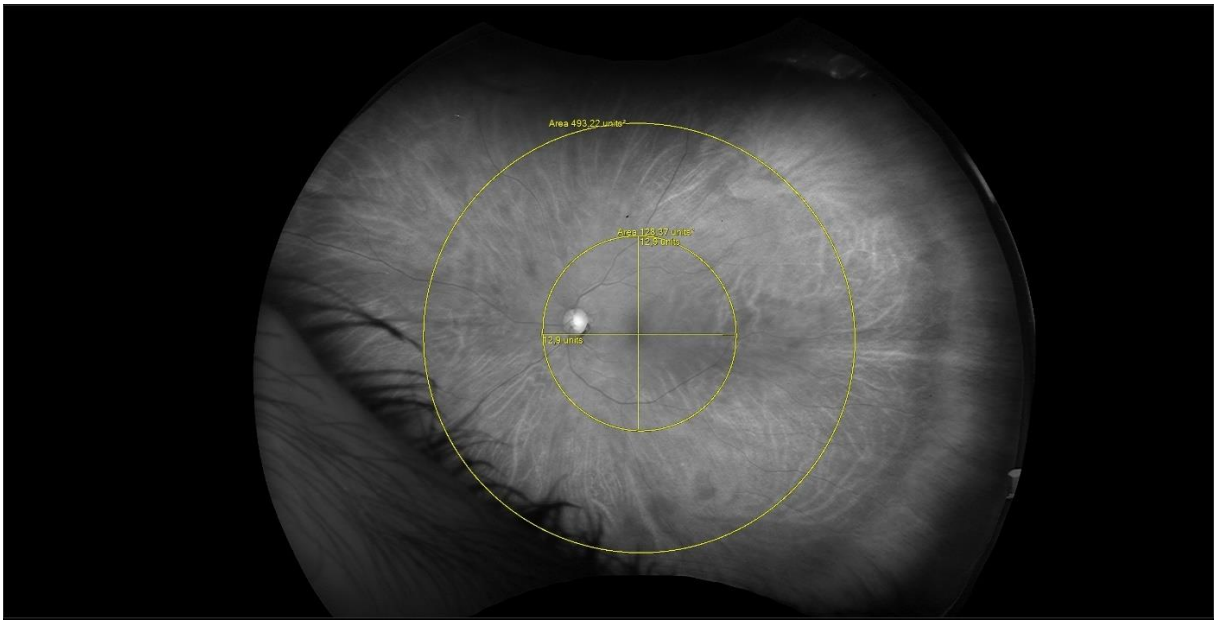


Image 3: Image of retina taken by Optomap model California with 100% red free channel used to find the vortex ampulla to outline the peripheral area. The outer circle goes through the anterior part of the vortex ampullas.

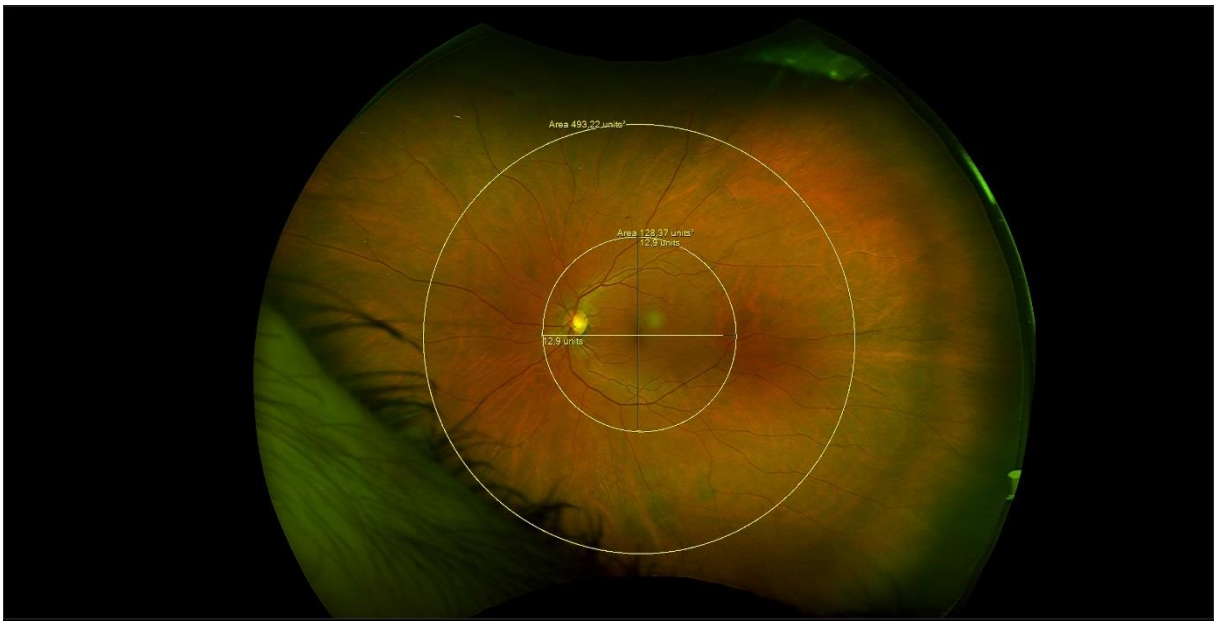


Image 4: Colour composite image of the retina captured by Optomap model California. The peripheral, mid-peripheral and the central retina are seen.

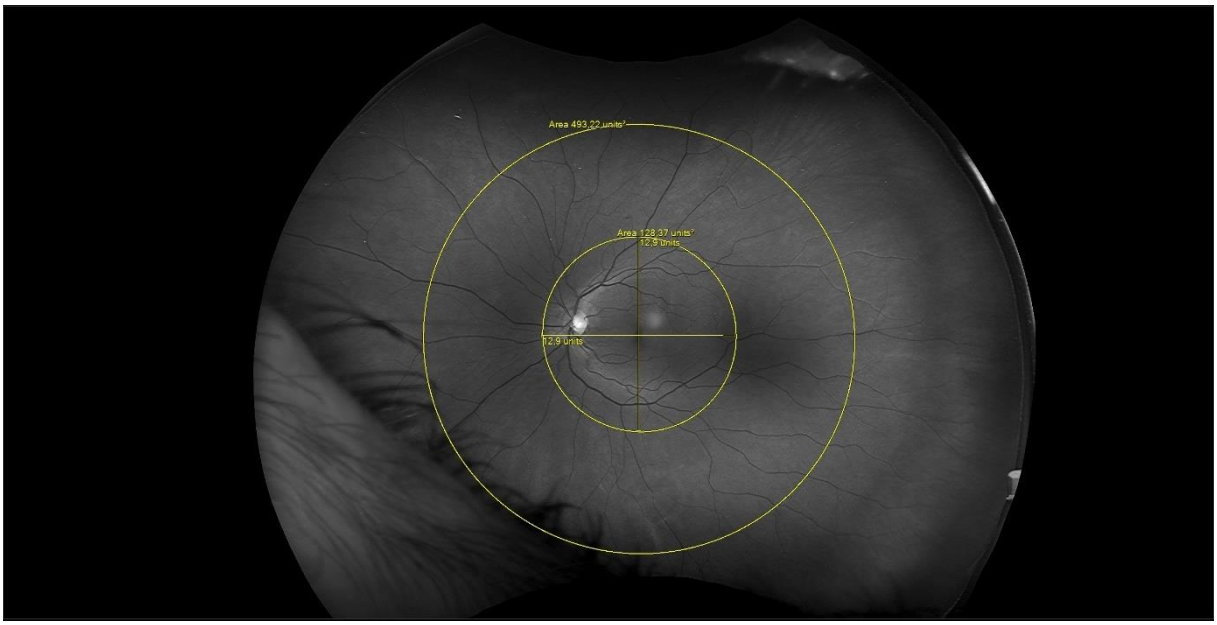


Image 5: Image by Optomap model California with 100% green channel and max enhancement for easier detecting haemorrhages and microaneurysms.

3.6.4 Analysis

All images were assessed in the same room, at the same desk with the same illumination. The lumen when viewing the images were close to 250lux measured with a LUX light meter on a mobile phone app on the tabletop. All images were assessed on the Eizo CG277, 27 inches screen with resolution 2560 x 1440 (109 ppi). The screen was colour calibrated before use. All Optomap and KOWA VK-2 images were assessed for the presence of lesions and graded for the severity of DR based on the International Classification of Diabetic Retinopathy (ICDR) grading scale (Table 4). The scale for grading diabetic retinopathy was developed for use with dilated ophthalmoscopy (Wong et al., 2018). In this study, it is adapted for use in grading of both the Optomap UWF-SLO images and the KOWA VK-2 images and the original grading nomenclature is retained for simplicity. The images are graded by trained optometrists who had completed the VIOLA program by a Danish ophthalmologist, Jakob Grauslund at Syddansk universitetet. VIOLA is a virtual learning course for grading diabetic retinopathy.

The main outcome measures of DR were graded within specific fields in the two eyes, and for the central 45-degrees. The KOWA VK-2 images were graded first, then the central 45-degree Optomap images before the peripheral and mid-peripheral Optomap images. The grading was done at different times to avoid the grader to remember the results. The results were noted down in a data registration booklet (Appendix 6). Two booklets were made for each patient, one for each grader to avoid copying and remembering the earlier grading results.

Macular oedema is a thickening of retina in the macula area. To detect macula oedema, an enlarged Optomap image were viewed separately with two wavelengths, red and green, to better assess at which level the changes were located. This together with visible signs as hard exudates allows clinically significant macular oedema to be assessed to some degree (Neubauer et al., 2007).

The image grader had previously not participated in examination of the patients and the grader was masked to all additional information such as gender, age, visual acuity, duration of diabetes, and other clinical symptoms. The grader had to choose the images to grade and to decide if the images were gradable or not. Only gradable images were analysed.

Data from both eyes have been obtained, since there is a high correlation between the two eyes the data from only one eye has been used in the calculation. The mean grade of DR for the peripheral retina in the right eye is 0.67 (95%CI: [0.48-0.86]) where 0 is no DR, 1 is mild DR, 2 is moderate DR, 3 is severe DR and 4 is proliferative DR, and mean of peripheral DR in the left eye is 0.89 (95%CI: [0.69-1.09]). The mean grade of DR for KOWA VK-2 for right eye is 1.02 (95%CI: [0.81-1.23]) and for the left eye the mead DR is 1.03 (95% CI: [0.82-1.25]). In this study the mean of peripheral DR for the left eyes and for the central 45-degree KOWA VK-2 images are higher than the right eye and therefor the left eye is used for all calculations, both for the periphery and for the central retina.

3.7 Image Quality

The fundus images were evaluated if they were gradable or not before evaluating the retina to exclude insufficient image quality. A grading scale for the central and mid-peripheral retina (Table 3) and one for the peripheral retina (Table 4) were made for this study. The grading scale for the periphery were made less strict to allow most pictures to be gradable since the capture's images were done with macula in centre and without eye steering making the peripheral area smaller than the possible 200°.

Table 3: Grading scale used to exclude insufficient image quality making grading not possible for the central 45-degrees and the mid-peripheral retina.

Grade*	Field definition	Clarity
1: Excellent	Artifacts covers less than ¼ of the image.	Sharp image, all capillaries and lesions on image is visible. Normal colour, high contrast and even illumination
2: Acceptable	Artefacts are presented in more than ¼ of the image, but less than ½.	Not focused. Blurring or glare is presented in less than ½ of the image, vessels and lesions are visible.
3: Not gradable	Artefacts are presented in more than ½ of the image.	Dark image, blurring or glaring covers more than ½ of the image, vessels and structures cannot be clearly identified

Images grade 1 and 2 are gradable, grade 3 is not gradable.

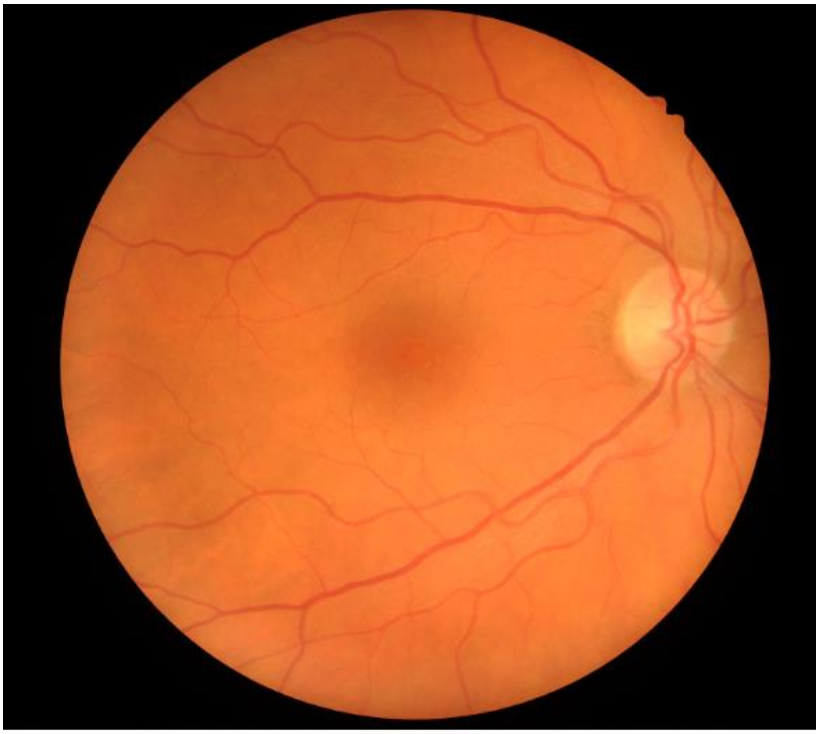


Image 6: Grade 1. KOWA VK-2 image. Excellent gradable image, sharp image and all vessels are visible.

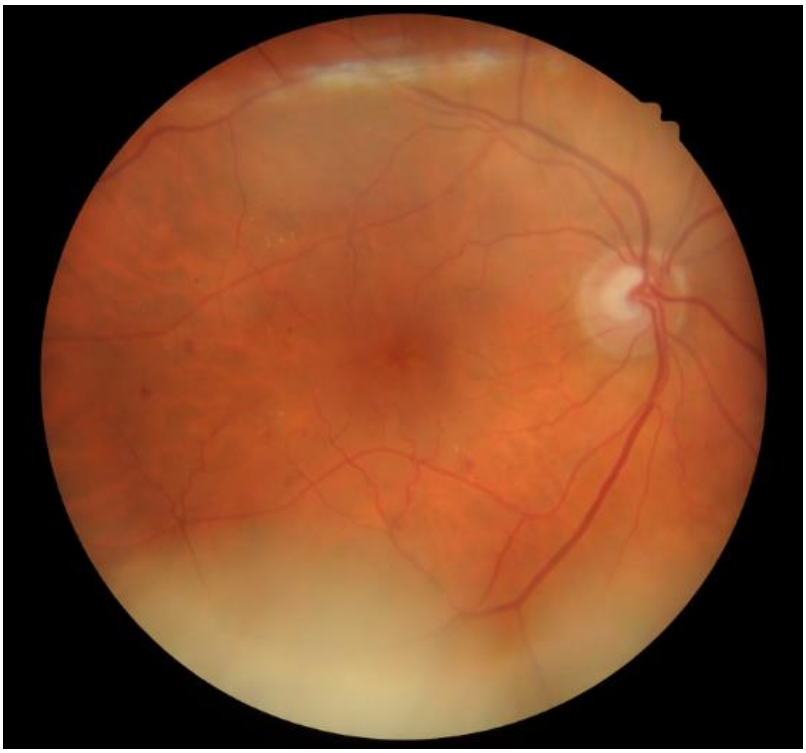


Image 7 Grade 2. KOWA VK-2 image. Acceptable gradable image, artefacts are covering less than ½ of the image.

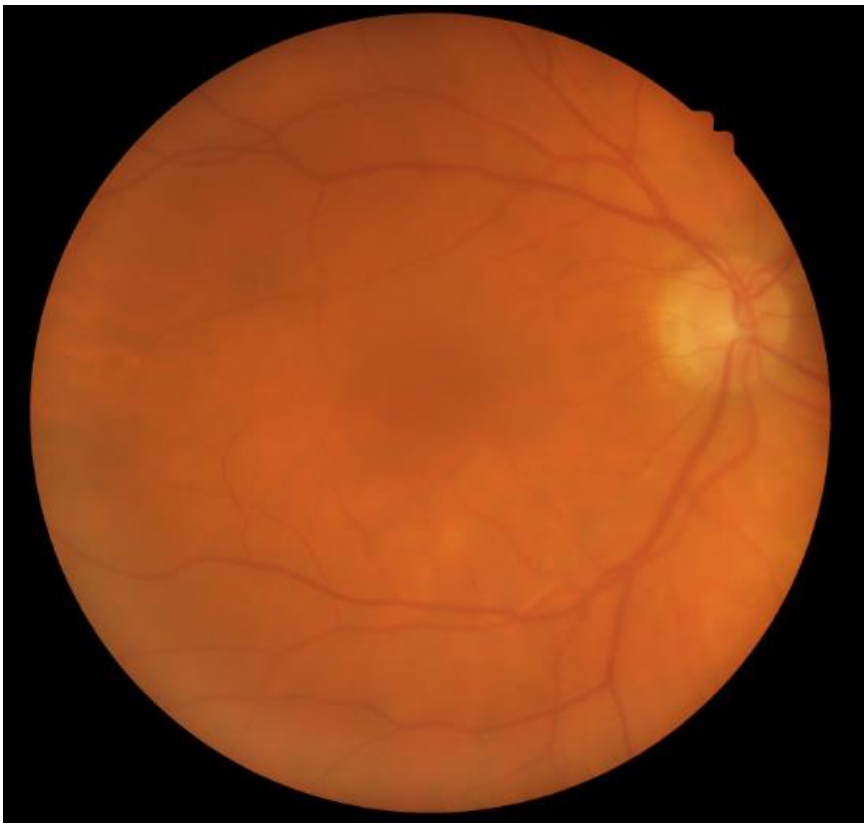


Image 8: Grade 2. KOWA VK-2 image. Acceptable gradable image. Not focused, vessels and lesions are visible.

Table 4: Grading scale used to exclude insufficient image quality making grading not possible, used when evaluating the peripheral retina.

Grade*	Field definition	Clarity
1: Excellent	Far peripheral retina is visible, and vortex ampulla is clearly visible.	Sharp image, all capillaries and lesions on image is visible. Normal colour, high contrast and even illumination.
2: Acceptable	Far peripheral retina visible, Vortex ampulla is not visible	Small vessels are not clearly visible, but are sufficient clear to identify branches
3: Not gradable	Far peripheral retina is not visible	Dark image, blurring, glaring, or artefacts covers the peripheral retina. Vessels cannot be identified.

*Images grade 1 and 2 are gradable, grade 3 is not gradable.

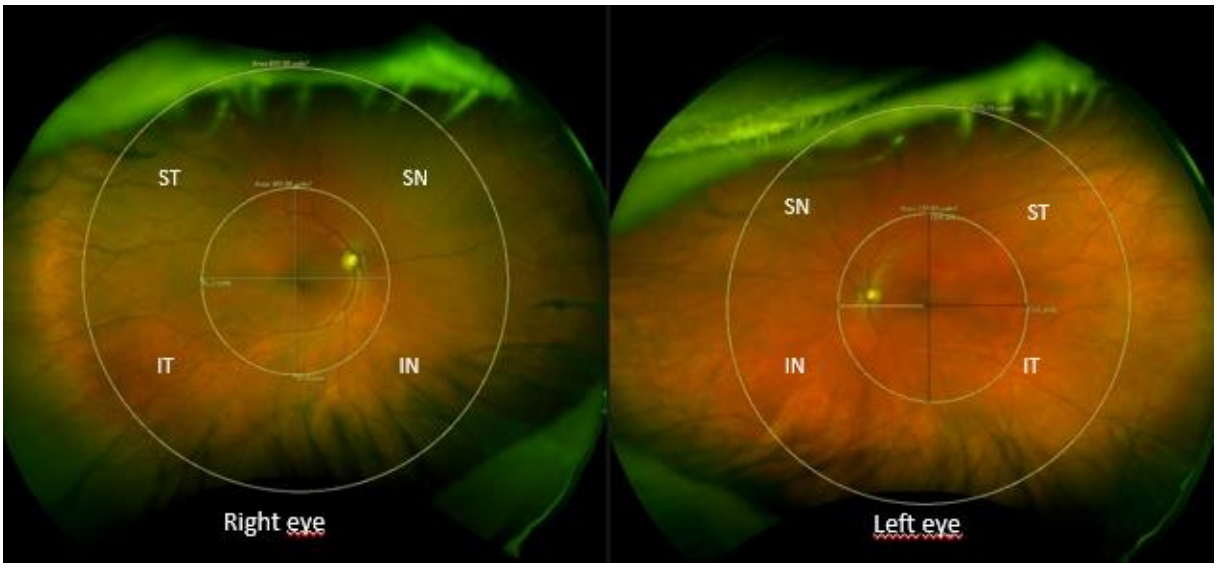


Image 9: Optomap images of right and left retina with composite colours. Here are all areas in both images gradable.

Image 9 show examples of two retina where the peripheral, mid-peripheral and the central retina are gradable. The peripheral, mid-peripheral and central 45-degree are marked with yellow lines.

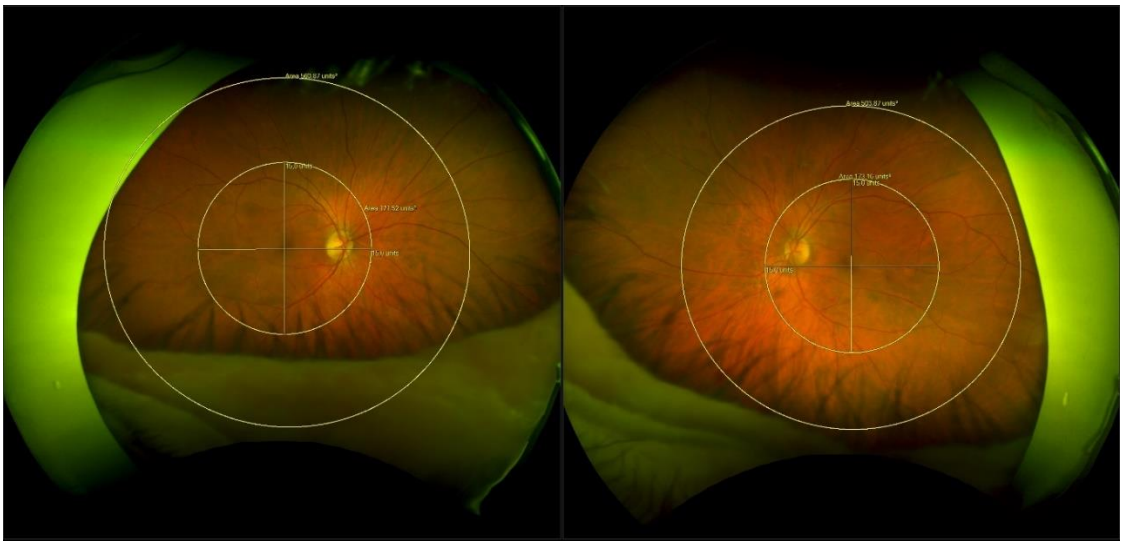


Image 10: Image captured by Optomap model California with composite colours. The visible areas are smaller due to artefacts.

Some of the images have not gradable areas (Image 10). When looking at the right eye, the peripheral retinal is not graded in the ST and IT areas. These areas are not visible and therefore not gradable. The right eyes mid-peripheral retina IT and IN areas is not gradable since the lower eyelid covers ½ of the areas. The right eye central retina is gradable. The left eye has only gradable images.

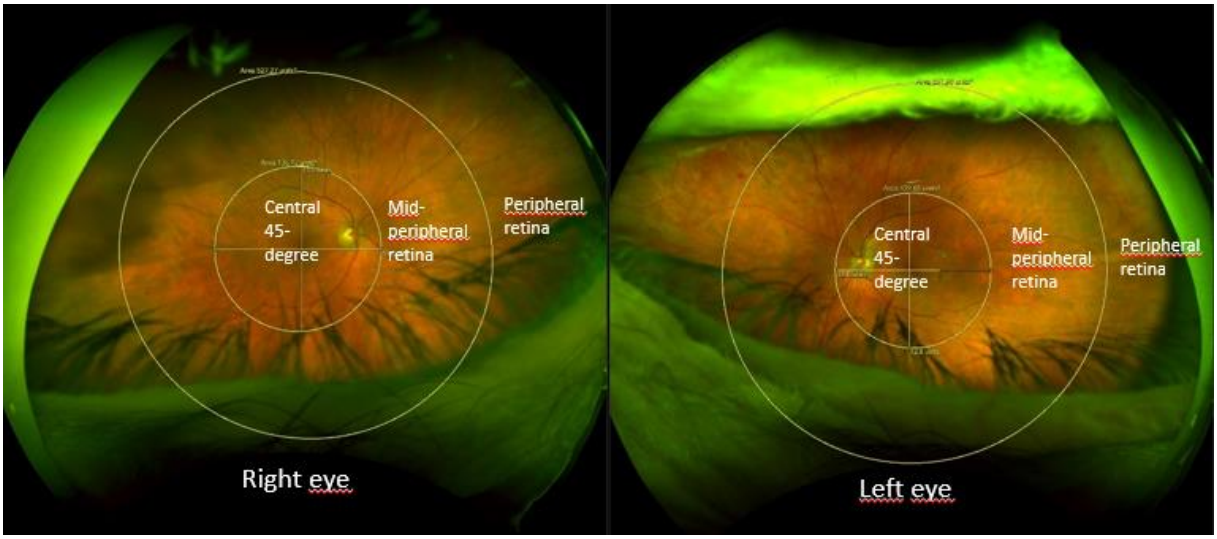


Image 11: Optomap images of central, mid- peripheral and peripheral retina for right and left eye.

Image 11 show examples where the central retina is gradable in both images. The mid peripheral retina for the right eye is not gradable in the ST, IT and the IN quadrant since the eyelashes and shadows cover more than ½ of the area. The mid peripheral for the left eye is not gradable in the IN and IT quadrant since lids and lashes cover more than half of the area looked at. The peripheral retina in the right eye is not gradable in the ST, IT and IN areas, and in the left eye only the peripheral IN are not gradable since that area is not visible.

Looking at these pictures the gradable area in the peripheral retina varies a lot among the participants, while the central areas are relatively equal in size.

3.8 Statistics

All data were collected in an MS Excel 2000 spreadsheet (Microsoft, Redmond, WA, USA) and analysed using R Commander. The analyses were conducted using R software version 2.7-2 and p-value of <0.05 was used to determine statistical significance.

Frequency with mean and standard deviations are calculated, summation tables and graphs are used to present data.

Variables are described as mean (standard deviation) or count (percentage) as appropriate. Shapiro-Wilk were used to determine if the data were normally distributed. Paired t-test were used for determining the mean and confidence intervals (CI), Wilcoxon signed rank test were used to compare the data, ANOWA for determining mean and standard deviation (sd), and Linear model were used to calibrate degree of linearity.

Kappa statistics were used to calculated intrarater and interrater reliability and assessed as proposed by Neubauer et al. (2007): <0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 very good agreement. Weighted Cohens kappa were used.

3.9 Research Ethics

Ethical approval has been obtained for this study as a part of the ongoing DVOH study by the Regional Committees for Medical and Health Research Ethics (REK) in Norway

(2018/804/REK sør-øst), and then submitted and approved by the Norwegian Centre for Research Data (NSD).

The consent includes information about the study. They have been informed that they can drop out whenever they want, without giving any reason why. If they drop out it will not have any consequences for their further treatment at the clinic in the National Centre for Optics, Vision and Eye Care at the USN. If the participant withdraws from the project, he or she can demand to have the collected samples and information, unless the information has already been included in analyses or used in scientific publications. Their information and test results will during the project period be linked to a list of names through a code. The code key is deleted when the data collection is completed. The information stored will not subsequently be linked to the person.

The procedures are non-invasive, but the eyedrop Tropicamide (0.5%, Chauvin) might have caused some discomfort for the participants. If any suspect conditions or pathology are discovered, the patient was given appropriate follow-up and referral to general practitioner or ophthalmologist.

Tropicamide (0.5%, Chauvin) is a standard drug used in optometric practice and will be used to dilate the eye to allow better quality when imaging the retina. When instilling the Tropicamide the participant will feel some stinging soon after insertion of the eye dops, this will last for about 10 seconds. After instilling the Tropicamide, the pupil dilation last for 4-8 hours. During this time, the participant may be more sensitive to light and notice that close objects become more blurred. The participants will be advised to bring sunglasses. Tropicamide may, in very rare cases, cause an attack of acute angle-closure glaucoma. This tends to be in participants with narrow anterior chamber angles. Participants with an angle ≤2 measured with Van Herick's method, will be closely monitored and if needed referred to an ophthalmologist for treatment. The participants will be informed about side effects the drug have, and they will also get information of who to contact if they have any problems after they have left the clinic. These are standard routines recommended from the Norwegian Association of Optometry.

4.0 Results

4.1 Prevalence

In this study a sample of 89 participants with DMT2 aged from 37 to 82 years, mean age 64.7 years (95% CI: [62.7 – 66.7]), agreed to participate. The mean duration of DMT2 (self-reported) were 10.3 years (95% CI: [8.8-11.3]) ranging from 1 to 36 years. The distribution of gender were 56.2% males and 43.8% women.

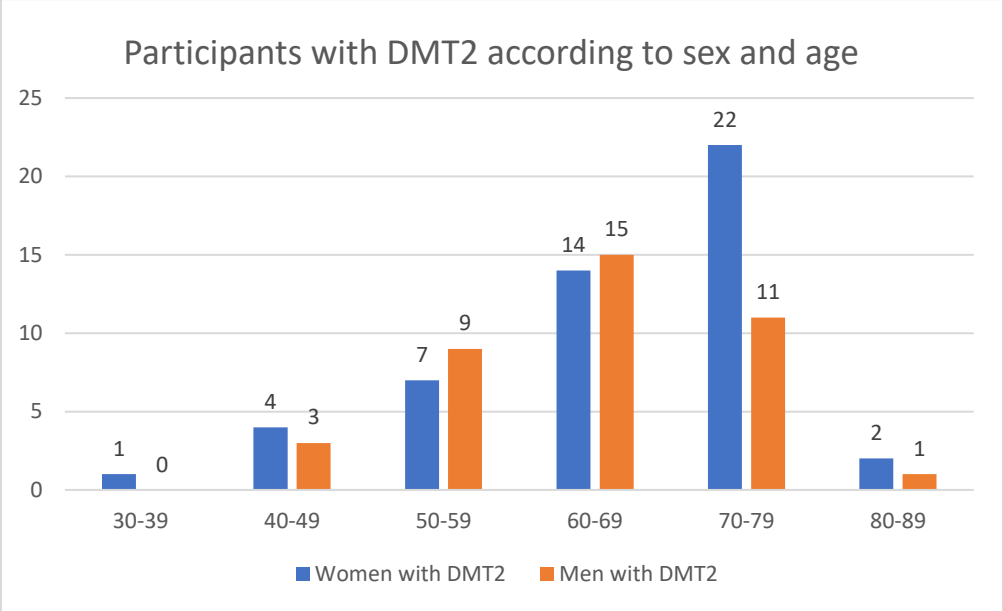


Figure 1: Distribution of participants with DMT2 according to sex and age.

A total of 50 women and 59 men with DMT2 participated in the study. The Figure 1 show that most of the participants are between 60 and 79 years old and the number of subjects is not evenly distributed according to age.

The prevalence is defined as the proportion of individuals who have a disease at or during a time period. In this study the number of participants with DR were counted, the images were taken during their visit between August 2018 to October 2019.

When grading the left retina by using Optomap, 42 (47.2%) of the participants had any DR within the central 45-degree area, when including the mid-peripheral retina 61 (68.5%) of

the participants had any DR, and when including the UWF 65 (73.0%) of the participants had any DR. One (1.1%) participant had only peripheral lesions.

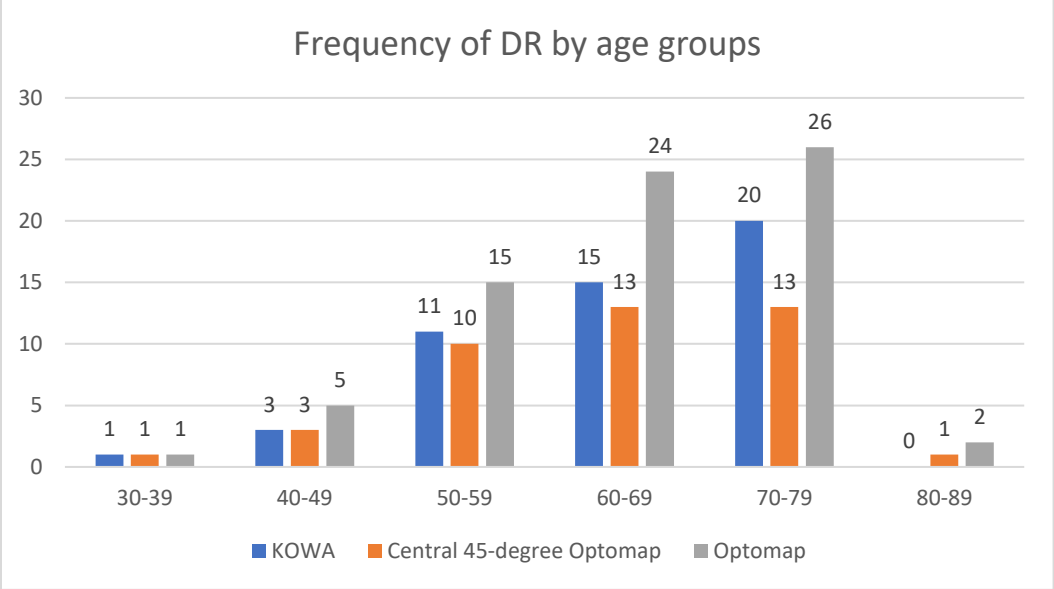


Figure 2: Frequency of DR by age groups for KOWA VK-2, central 45-degree Optomap area and for the total Optomap area. The left eye is used for calculations.

Figure 2 indicates that the KOWA VK-2 fundus camera is more likely to detect central DR than the 45-degree Optomap image. The frequency of DR increases with age until 80 years and also when the peripheral area (Optomap) is investigated.

4.2 Image Quality

The image quality depends on the pupil size. Ramesh et al. (2022) found that pupil size is a significant predictor of image quality for non-mydriatic photographs. In this study all participants were dilated with Tropicamide 0.5%. The mean pupil size for right eyes was 6.7mm (range 4.0-8.5) and for the left eye 6.7mm (range 5.0-8.5).

Table 5: Number of gradable and non-gradable images.

Area	**Quadrant**	**N**	**Gradable (n/%)**	**Non-gradable (n/%)**
Ultra-wide-field, peripheral retina, Optomap	ST*	178	175(98.3%)	3(1.7%)
	SN*	178	176(98.9%)	2(1.1%)
	IT*	178	171(96.1%)	7(3.9%
	IN*	178	170(95.5%)	8(4.5%)
Mid- peripheral field, Optomap	ST*	178	177(99.4%)	1(0.6%)
	SN*	178	176(98.9%)	2(1.1%)
	IT*	178	174(97.8%)	4(2.2%)
	IN*	178	173(97.2%)	5(2.8%)
45-degree area, Optomap		178	177(99.4%)	1(0.6%)
45-degree field, KOWA VK-2		178	175(98.3%)	3(1.7%)

N= Number of images. *ST= Superior temporal area, SN= superior nasal area, IT= Inferior temporal area and IN= Inferior nasal area. n= number of gradable images (percent)

The majority of the images are gradable according to table 3 and 4. The IN area is the least gradable area for both the peripheral and mid-peripheral area. A slightly higher rate of ungradable images was found with the KOWA VK-2 compared to the Optomap image for the central retina.

Table 6: Number of images where peripheral graded area is less than ¼ of the total area possible.

	Number of right and left eyes N/N	Right eye where peripheral graded area is less than ¼ (n, %)	Left eye where peripheral graded area is less than ¼ (n, %)
Peripheral ST*	89/ 89	13 (14.6%)	8 (9.0%)
Peripheral SN*	89/ 89	1 (1.1%)	5 (5.6%)
Peripheral IT*	89/ 89	17 (19.1%)	13 (14.6%)
Peripheral IN*	89/ 89	56 (62.9%)	49 (55.1%)

n= number of images where graded area is less than ¼ of the total image possible. (%) and in percent. N= total number of captured images for right and left eye. *ST= Superior temporal area, SN= superior nasal area, IT= Inferior temporal area and IN= Inferior nasal area.

When grading the images initially, many of them had a small area visible compared to theoretical possible in the periphery. The table above (Table 6) show the number of images that have less than ¼ of the peripheral areas visible. The numbers shoe that the peripheral SN retina have most frequent an area possible to grade followed by ST, IT, and IN. The peripheral IN area is most often not very visible due to eyelids. In this study 62.9% and 55.1% (Table 6) of the images had an area less than ¼ of the area that is possible to capture, making the results less reliable. Image 10 is an example where the whole peripheral image in the left eye has been graded, and where IN has a small area visible.

4.3 Frequency of Diabetic Retinopathy in the Peripheral Retina.

The frequency of diabetic retinopathy in the peripheral retina, graded outside the vortex vein ampullas.

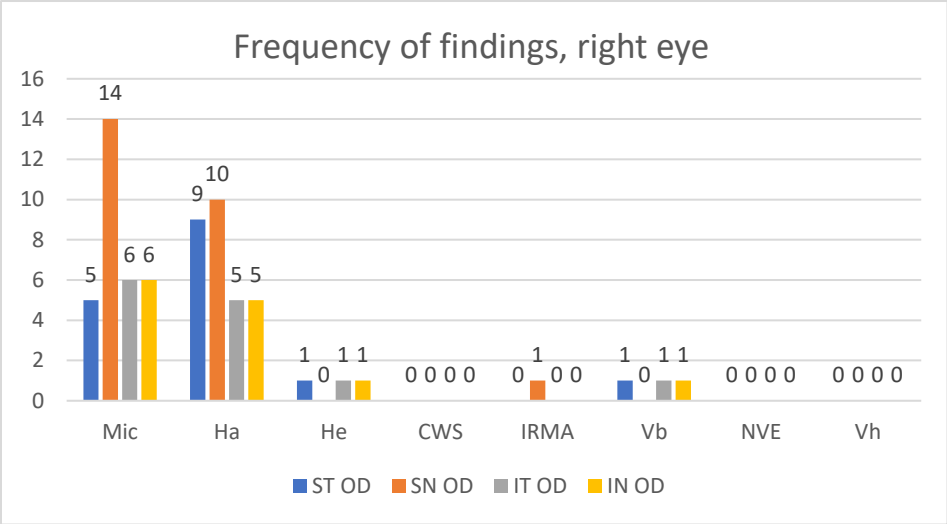


Figure 3: Frequency of peripheral diabetic retinopathy for the right eye.

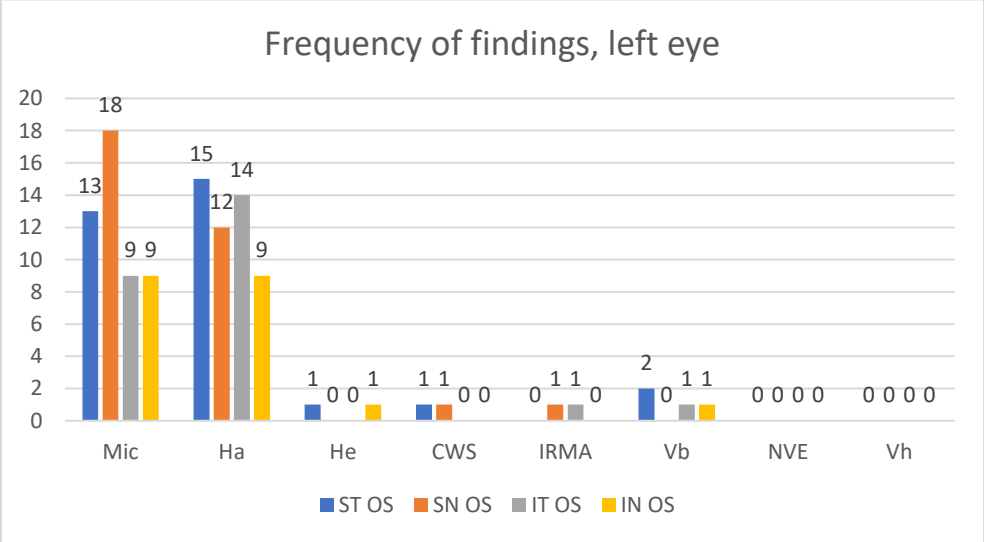
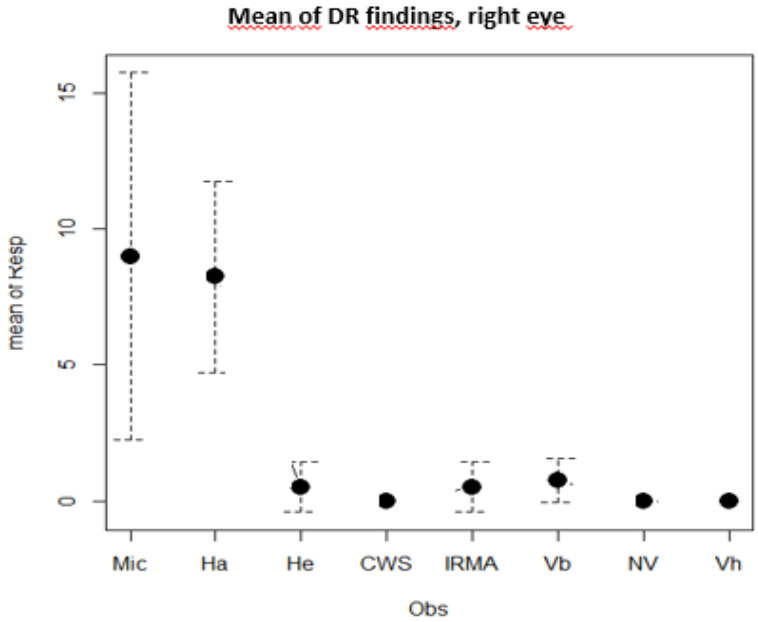


Figure 4: frequency of peripheral diabetic retinopathy for the left eye.

Figures 3 and 4 show the frequency of peripheral diabetic retinopathy for the right eye and left eye. For both eyes, microaneurysms and haemorrhages are most frequently found followed by venous beading, hard exudates, cotton-wool spots, intraretinal microvascular abnormalities, neovascularisation, and venous haemorrhages. Since the left eye most frequently has peripheral diabetic lesions, the left eye is used for calculations.



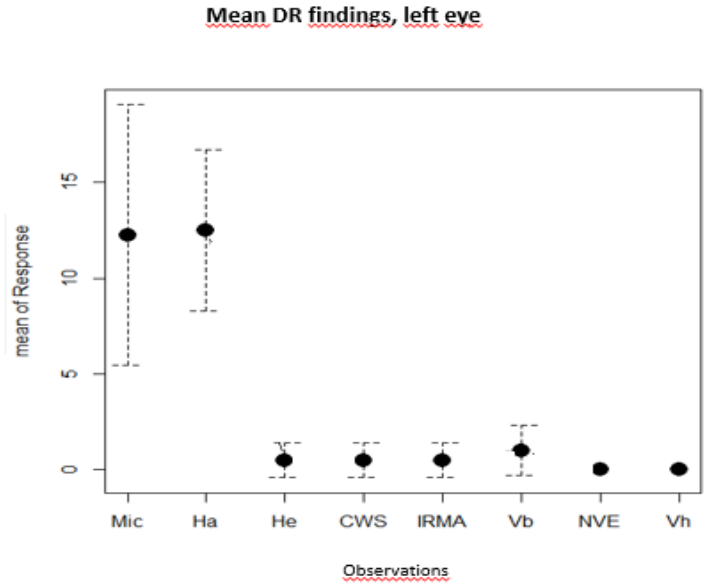


Figure 5: The mean of DR findings in the peripheral retina for the right eye top and left eye bottom using Optomap. The arrows indicate 95% CI.

When investigating the peripheral retinas, grade “no DR” are most frequently found. 53 (59.6%) images from the right eye and 44 (49.4%) images of the left eye do not have any DR in the UWF. Thus, 36 (40.4%) and 45 (50.6%) of the participants have any DR in the far periphery. When investigating the findings and using the one-way ANOVA model, the mean

number of images with microaneurysms (sd) for the right eye were 9.0 (4.2), haemorrhages were 8.3 (2.2), hard exudates were 0.5 (0.6), cotton-wool spots were 0.0 (0.0), IRMA were 0.5 (0.6), venous beading were 0.8 (0.5), neovascularization were 0.0 (0.0) and vitreous haemorrhages were 0.0 (0.0). For the left eye the mean number of images with of microaneurysm were 12.3 (4.3), haemorrhages were 12.5 (2.7), hard exudates were 0.5 (0.6), Cotton-wool spots were 0.5 (0.6), were IRMA 0.5 (0.6), venous beading were 1.0 (0.8), neovascularization were 0.0 (0.0), and vitreous haemorrhages were 0.0 (0.0%).

The linear model show that it is statistically significant to find haemorrhages (right eye p= 8.32 e-7, left eye p=5.29e-9) and microaneurysms (right eye p= 0.221e-7, left eye p= 7.58e-9) in the peripheral retina.

When looking at the number of participants with microaneurysms and haemorrhages which is most frequently found in the peripheral retina and using the left eye and Optomap. The number of participants with microaneurysms in the UWF area are 21 (23.6%), 21 (23.6%) more than when investigating the central 45-degree retina, and the number of participants with haemorrhages in the peripheral retina are 29 (32.6%), 18 (22.2%) more than when investigating only the central 45-degree retina. The number of microaneurysms increases with 250 (30.6%) when including the UWF area compared to the WF area, and the number of haemorrhages increases with 384 (61.2%) when including the UWF area compared to the WF area.

4.4 The Differences in Diabetic Retinopathy in the Peripheral Retina When Comparing the Four Retinal Quadrants.

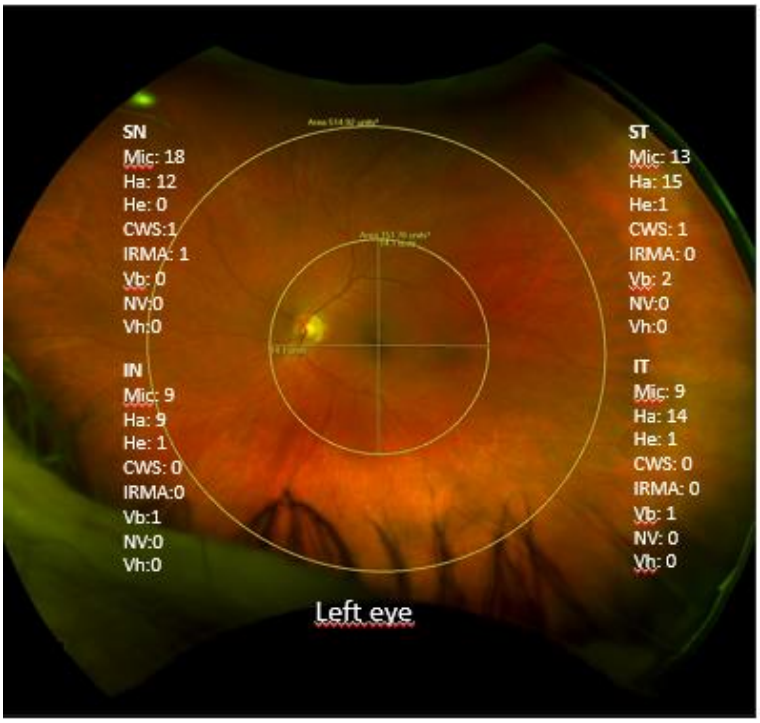


Figure 6: Number of images with findings in each peripheral quadrant for the right eye (top) and the left eye (bottom).

When investigating each peripheral quadrant (Figure 6), the superior nasal areas have the highest number of findings in both eyes and the inferonasal areas with the least number of findings. The superior areas are often more gradable (Table 7) compared to the inferior quadrants which often also has the least gradable area (Table 6).

Table 7: Number of subjects with peripheral findings in each peripheral quadrant for the right eye.

DR in peripheral retina	**Number of images with peripheral DR for the right eye (n,N(%)**			
	ST	**SN**	**IT**	**IN**
No DR	73/87(83.9%)	67/88(76.1%)	68/86(79.1%)	77/88(87.5%)
Microaneurysms	5/87(5.7%)	14/88(15.9%)	11/86(12.8%)	6/88(6.8%)
Haemorrhages	9/87(9.2%)	10/88(11.4%)	9/86(10.5%)	5/88(5.7%)
Hard exudates	1/87(1.1%)	0/88(0%)	0/86(0%)	1/88(1.1%)
Cotton-wool spots	0/87(0%)	0/88(0%)	0/86(0%)	0/88(0%)
IRMA	0/87(0%)	1/88(1.1%)	1/86(1.2%)	0/88(0%)
Venous beading	1/87(1.1%)	0/88(0%)	1/86(1.2%)	1/88(1.1%)
Neovascularization	0/87(0%)	0/88(0%)	0/86(0%)	0/88(0%)
Vitreous haemorrhages	0/87(0%)	0/88(0%)	0/86(0%)	0/88(0%)

n= number of participants with peripheral diabetic retinopathy, N= number of gradable images, (%) = the percentage of participants with peripheral diabetic retinopathy.

Table 8: Number of subjects with peripheral findings in each peripheral quadrant for the left eye.

DR in peripheral retina	**Number of images with peripheral DR for the left eye (n,N %)**			
	ST	**SN**	**IT**	**IN**
No DR	62/88(70.5%)	62/88(70.5%)	69/85(81.1%)	66/82(80.5%)
Microaneurysms	13/88(14.8%)	18/88(20.5%)	9/85(10.6%)	9/82(11.0%)
Haemorrhages	15/88(17.0%)	12/88(13.6%)	14/85(16.5%)	9/82(11.0%)
Hard exudates	1/88(1.1%)	0/88(0%)	0/85(0%)	1/82(1.2%)
Cotton-wool spots	1/88(1.1%)	1/88(1.1%)	0/85(0%)	0/82(0%)
IRMA	0/88(0%)	1/88(1.1%)	1/85(1.2%)	0/82(0%)
Venous beading	2/88(2.3%)	0/88(0%)	1/85(1.2%)	1/82(1.2%)
Neovascularization	0/88(0%)	0/88(0%)	0/85(0%)	0/82(0%)
Vitreous haemorrhages	0/88(0%)	0/88(0%)	0/85(0%)	0/82(0%)

n= number of participants with peripheral diabetic retinopathy, N= number of gradable images, (%) = the percentage of participants with peripheral diabetic retinopathy.

The tables 7 and 8 show that microaneurysms and haemorrhages are most frequently found in the peripheral retinal quadrans. The superior nasal quadrant has more retinopathy than the other quadrants, and the superior areas have slightly more findings than the inferior areas. The superior nasal area has often a larger area to grade (Table 6). The inferior-nasal area has the least number of findings, also most often the smallest visible area (Table 6).

Table 9: Mean and standard deviation of number of images with diabetic retinal findings in each quadrant for the peripheral retina.

Peripheral area*	**Mean (sd) number of images with DR, Right eye**	**Mean (sd) number of images with DR, Left eye**
ST	2.00 (3.29)	4.00 (6.23)
SN	3.13 (5.59)	4.00 (6.99)
IT	2.75 (4.53)	3.13 (5.36)
IN	1.63 (2.45)	2.50 (4.04)

*ST= superior temporal, SN= Superior nasal, IT= Inferior temporal, IN= inferior nasal

In the peripheral retina, the superior areas show more images with DR than the inferior areas. When using the one-way ANOVA (table 9), the mean number (sd) of images with DR in the superior nasal quadrant were for the right eye 3.1(5.6) and for the left eye 4.0 (7.0) and in the superior temporal quadrant mean number were 2.0 (3.3) for the right eye and 4.0 (6.2) for the left eye. The mean number of images with DR in the inferior quadrant is lower. The mean number in the inferior temporal quadrant were 2.8 (4.5) for the right eye and 3.1 (5.4) for the left eye, and the inferior nasal quadrant were 1.6 (2.5) for the right eye and 2.5 (4.0) for the left eye. When comparing the four retinal quadrants there is no statistical significance between the quadrants, p= 0.883 for right eye and p= 0.942 for the left eye, and we do not reject the hypothesis that the means are equal. In this sample peripheral DR is likely to occur in any quadrant.

When looking at PPL using the left eye with most findings, this study found 13 (14.6%) of the participants to have PPL. The PPL were distributed in all the peripheral quadrants. PPL were most frequently found in the SN quadrant, 10 (11.2%) followed by the ST quadrant 8 (9.0%), the IT quadrant 6 (6.7%) and the IN quadrant 3 (3.4%). One (1.1%) of the participants had only peripheral lesions, the subject was 55 years and had a self-reported duration of DMT2 of 10 years. The mean age of the participant with PPL was 61.9years (95%CI: [56.8-67.1]) and mean duration were 10.4 years (95%CI: [4.9-15.8]).

4.5 Differences in Diabetic Retinopathy in the Peripheral Retina when Comparing Retinal Optomap image with 45-degree Optomap image.

Differences in DR in the peripheral retina, graded outside the vortex ampullas, on retinal Optomap (model California) images compared to DR graded on central retinal Optomap (model California) images, here the left eye is used for calculations.

For simplicity reasons microaneurysms, haemorrhages, hard exudates, cotton-wool spots, IRMA, venous beading, neovascularization, and vitreous haemorrhages are graded as mild DR, moderate DR, severe DR, and proliferative DR as appropriate for the peripheral retina.

When using the Shapiro-Wilk normality test, the p-value are significant at alpha level 0.05 for both the 45-degree Optomap and the Optomap images, and we cannot reject the null hypothesis that the findings are normally distributed.

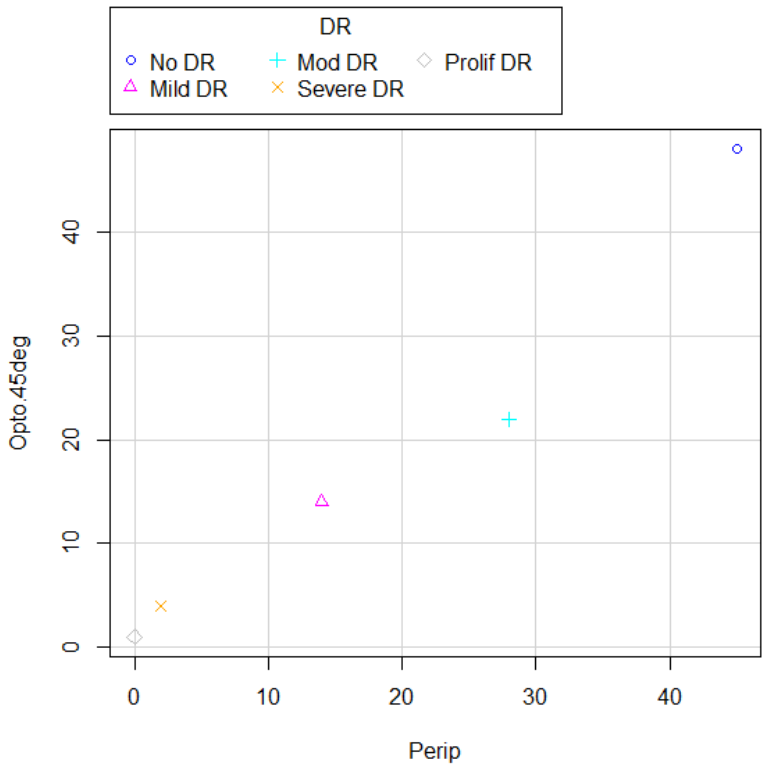


Figure 7: Comparison of DR between the central 45-degree Optomap image with the peripheral part of the Optomap image for the left eye.

The figure 7 above shows that there is a linear relationship between Optomap 45-degree images and UWF part of the Optomap images. There is more likely to find no DR and moderate NPDR in both the peripheral and the central retina, and less likely to find proliferative DR, severe NPDR and mild NPDR. When using the linear model, the results indicates that there is a linear relationship between DR found in the images captured by 45-degree Optomap images and in the peripheral part of the Optomap images (p-value= 0.003).

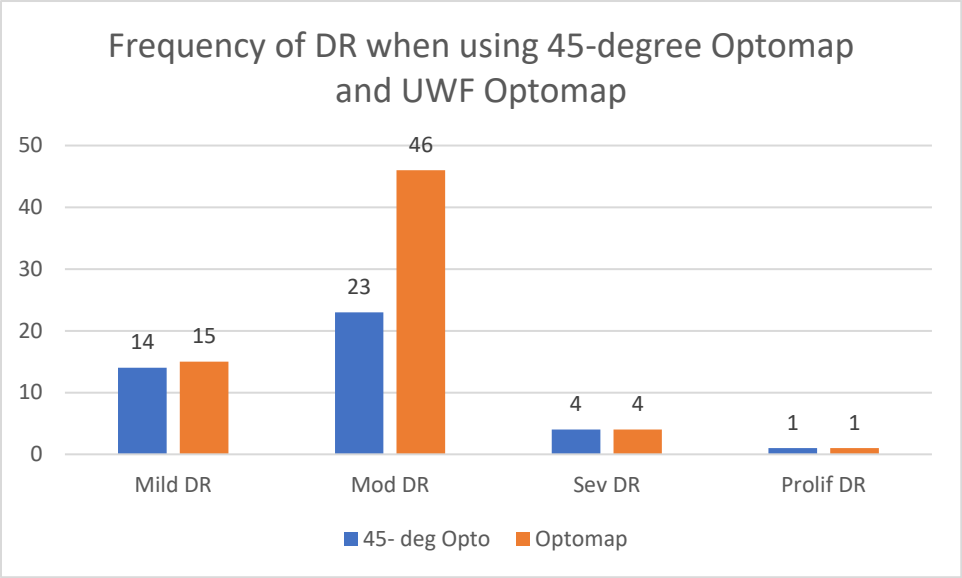


Figure 8. DR found in the 45-degree central Optomap image compared to the UWF Optomap image for the left eye.

Figure 8 show that when including the peripheral retina moderate DR are more frequent found when using UWF Optomap. Mild DR, severe DR and Proliferative DR are equally likely to be found when using 45-degree Optomap images. Using kappa-statistic when comparing the UWF Optomap image with the 45-degree Optomap image weighted Kappa statistic $\kappa = 0.75$ indicating a good agreement between DR found when using 45-degree Optomap images and the UWF Optomap images.

Table 10: Changes in diabetic retinopathy from central to peripheral retina when using Optomap for the left eye.

Diabetic retinopathy, N=89	**45-degree Optomap (n/N, %)**	**Wide field Optomap (n/N, %)**	**Ultra-wide field Optomap (n/N, %)**
No DR	47/89(47.2%)	28/89 (31.5%)	22/89 (24.7%)
Mild DR	14/89 (15.7%)	22/89 (24.7%)	15/89 (16.9%)
Moderate DR	23/89 (25.8%)	34/89 (38.2%)	46/89 (51.7%)
Severe DR	4/89 (4.5%)	4/89 (4.5%)	5/89 (5.6%)
Proliferative DR	1/89 (1.1%)	1/89(1.1%)	1/89(1.1%)

N=number of participants, n= number of findings, (%) and in percent.

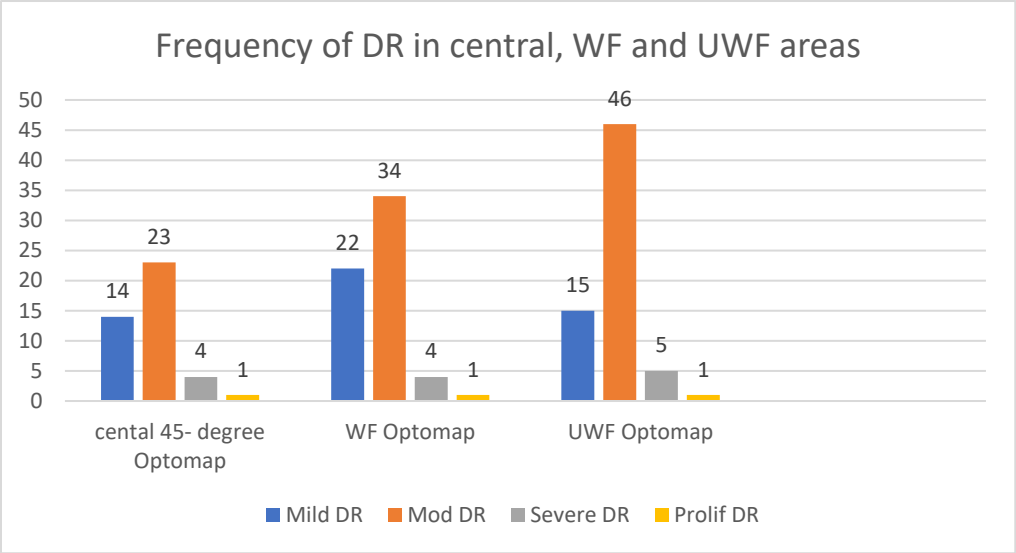


Figure 9: Distribution of DR in the central, mid-peripheral (WF Optomap) and peripheral (UWF) Optomap images for the left eye.

When using Optomap to investigate DR, the number of participants with DR increases with the area investigated. When increasing the area from the central 45-degrees to mid-peripheral retina the number of participants with DR increases with 19 (21.3%), and when increasing the area to the peripheral retina the number of participants with DR increases with 6 (6.7%).

Table 11: Changes in the degree of DR when comparing the images from 45-degree Optomap with Optomap.

Changes in DR from 45-degree Optomap to UWF Optomap, N=32	**Number of participants with changes (n, %)**
From No DR to mild DR	10 (31.5%)
From mild DR to moderate DR	7 (21.9%)
From No DR to moderate DR	*14 (43.8%)*
From moderate DR to severe DR	1 (3.1%)

When looking at the grading of DR, 22 (24.7%) of the participants have an increased grade of DR when including the mid-peripheral retina, and another 15 (16.9%) have an increased grade of DR when including the peripheral retina. When comparing the central 45-degree Optomap image with the UWF Optomap image (table 10), 32 (36.0%) of the participants have an increased grade of DR.

The paired t-test gave, when comparing the central 45-degree Optomap image with the UWF Optomap image, the mean difference equal to -0.56 (95% CI: [-0.7-(-0,4)]), (p= 2.39e-9). The Wilcoxons signed rank test show the p-value is p= 2.47e-7 which is <0.05 and we can reject the null hypothesis that the means are equal. The DR found by using central 45-degree Optomap images are significantly different from the DR found by grading the whole UWF Optomap image.

4.6 Differences in Diabetic Retinopathy in the Peripheral Retina when Comparing Retinal Optomap Images with KOWA VK-2 Images.

Differences in DR in the peripheral retina, graded outside the vortex ampullas, on retinal Optomap (model California) images compared to DR graded on central retinal images (KOWA VK-2). Here the left eye is used for calculations.

When using the Shapiro-Wilk normality test, the p-value are significant at alpha level 0.05 for both the KOWA VK-2 and the Optomap images, and we cannot reject the null hypothesis that the findings are normally distributed.

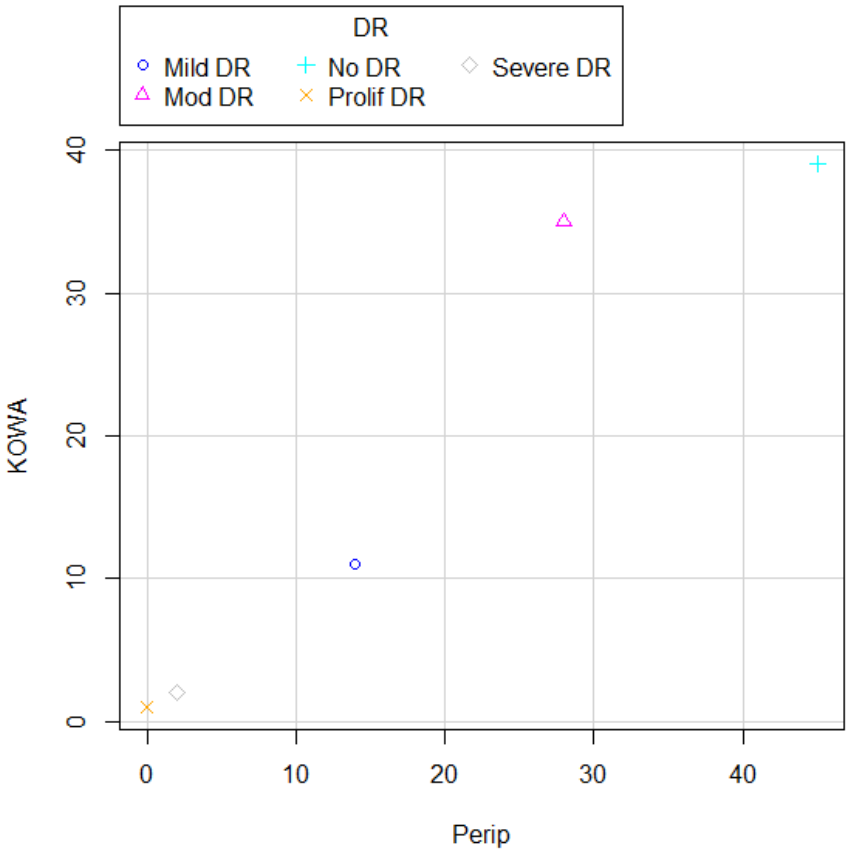


Figure 10: Linear relationship between DR found with KOWA VK-2 and peripheral part of the Optomap images for the left eye.

Figure 10 show the linear relationship between DR found in KOWA VK-2 images and in the UWF part of the Optomap images. When comparing the two different areas by the two different imaging methods, the results show that there is most likely to find no DR followed by moderate DR, mild DR, severe DR, and proliferative DR. When using the linear model, the study indicates that there is a linear relationship between DR found in the peripheral part of the UWF Optomap images and DR found by KOWA VK2 images (p= 0.007).

Table 12: Comparing DR results when using KOWA VK-2 and Optomap for the left eye.

Diabetic retinopathy, N=89	**KOWA VK-2 (n, %)**	**Wide field Optomap (n, %)**	**Ultra-wide field Optomap (n, %)**
No DR	39 (43.8%)	28 (31.4%)	22 (24.7%)
Mild DR	11 (12.3%)	22 (24.7%)	15 (16.7%)
Moderate DR	35 (39.3%)	34 (38.2%)	46 (51.7%)
Severe DR	2 (2.2%)	4 (4.5%)	5 (5.6%)
Proliferative DR	1 (1.1%)	1 (1.1%)	1 (1.1%)

N= total number of participants, n= number of findings, (%) and in percent.

The table (Table 12) show when increasing the area investigated by using KOWA VK-2 for the central, and Optomap for the WF area, 11 (12.3%) more participants have DR, and when comparing KOWA VK-2 with Optomap UWF area another 6 (6.7%) participants have DR. When comparing KOWA VK-2 with UWF Optomap, 35 (38.2%) participants have an increased severity of DR.

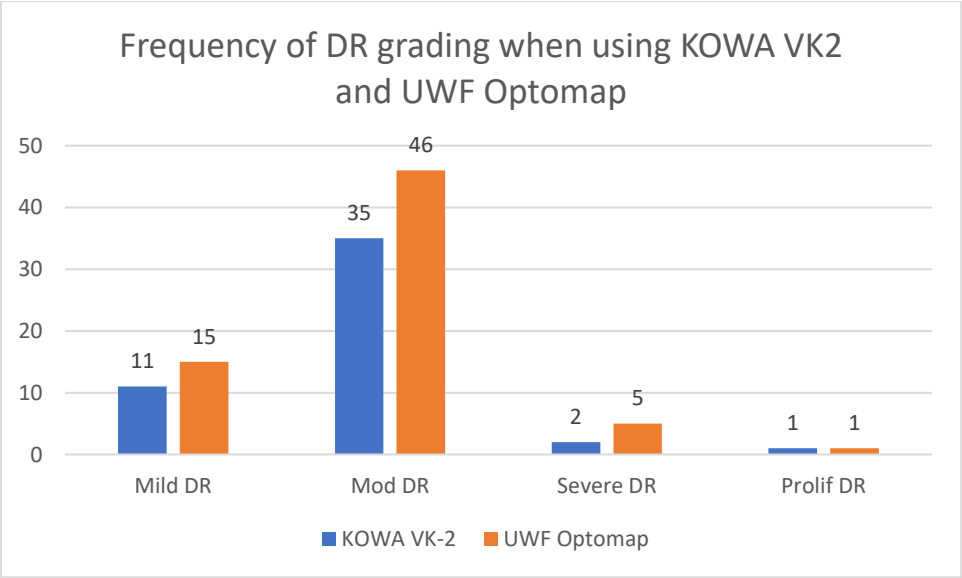


Figure 11: The frequency of DR when using KOWA VK-2 and UWF Optomap for the left eye.

Figure 11 compare the results from KOWA VK-2 with the UWF Optomap image. The frequency of moderate DR is higher when using Optomap (model California) than when

using KOWA VK-2 images, and more similar at mild DR, severe DR, and proliferative DR. The paired t- test show a mean difference of -0.38 (95% CI: [-0.6-(-0,1)]) (p= 0.002), and the Wilcoxon signed rank test show p= 0.005 which is significant at alpha level 0.05. The Wilcoxon test show the p-value <0.05 and we can reject the null hypothesis that the means are equal. The DR found by using KOWA VK-2 are significant different from the DR found by using UWF Optomap.

When using kappa-statistic, weighted kappa κ= 0.46 (-0.01-0.98), indicating a moderate agreement between the DR found by KOWA VK-2 and Optomap.

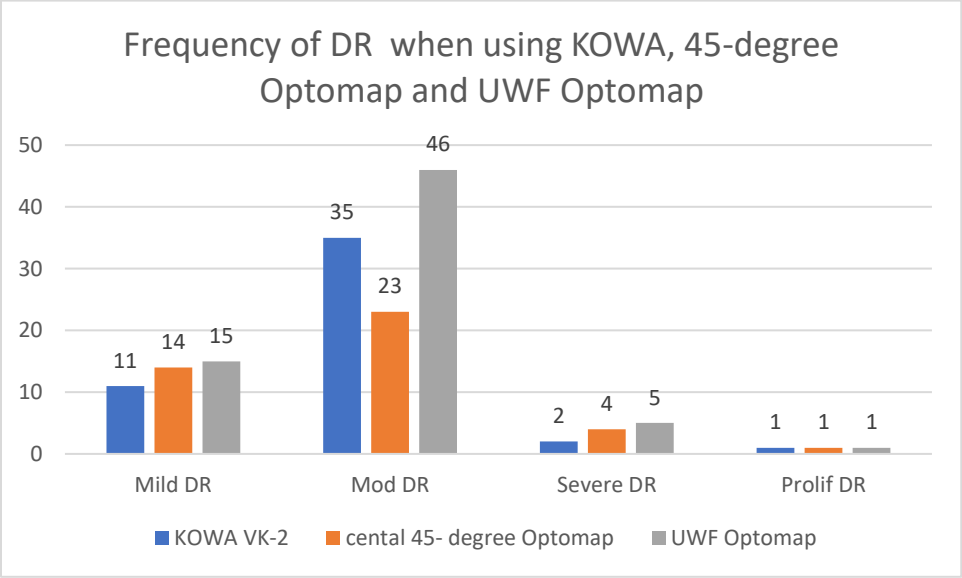


Figure 12: Grading of DR when using KOWA VK-2, 45-degree Optomap and UWF Optomap images for the left eye.

When comparing the three methods (Figure 12) the frequency of moderate DR is higher when using UWF Optomap compared to 45-degree Optomap images and KOWA VK-2 images. KOWA VK-2 is superior to 45-degree Optomap images to detect moderate DR. For mild DR, severe DR, and proliferative DR the results are more equal. Mean (sd) for grading the average DR for the three methods were for mild DR 13.0 (1.7), for moderate DR 34.7 (11.5), for severe DR 3.3 (1.2) and for proliferative DR were 1.0 (0.0). The results show that moderate DR varies most between the methods.

4.7 Reliability and Validity

31 (34.8%) of the central KOWA VK-2 images were re-graded the degree of DR by the senior grader to check for interobserver reliability, and 10 (11.2%) of the participants were re-graded to calculate intraobserver repeatability for both Optomap images and fundus KOWA VK-2 images.

Table 13: Interobserver reliability.

	KOWA VK-2, right eye n/N (%)	**KOWA VK-2, left eye n/N (%)**
Equally graded	15/31(48.4%)	15/30 (50.0%)
Graded within 1 degree of DR	23/31(74.2%)	22/30(73.3%)

N= total number images, n= number of graded images, (%) and in percent.

Interobserver reliability for grading DR with KOWA VK-2 images using weighted Cohens kappa, was for the right eye κ= 0.29 (95% CI: [0.0-0.57]) and for left eye κ= 0.36 (95% CI: [-0,25-0.97]). The images were equally graded in 48.4% for the right eye and in 50% for the left eye when grading with KOWA VK-2, and within one degree of DR the agreement was 74.2% for the right eye and 73.3% for the left eye.

When using the KOWA VK-2 grading results and compare these with the DR results from the central 45-degree Optomap images, the exact DR agreement were for the right eye 79.0% and for the left eye 75.9%, and within one degree of DR grading the agreement for the right eye were 83.9% and for the left eye 86.2%.

Table 14: Intra grader agreement for ten participants

N= 10	**KOWA VK-2 (n, %)**		**45-degree Optomap (n, %)**		**UWF Optomap (n, %)**	
	OD	**OS**	**OD**	**OS**	**OD**	**OS**
Equally graded	7 (70%)	7 (70%)	7 (70%)	7 (70%)	7 (70%)	8 (80%)

N= Number of images regraded, n= number of images equally graded, (%) and in percent.

Intragrader agreement for grading retinopathy using left eye for KOWA VK-2, 45-degree field Optomap and UWF Optomap images using weighted Cohens kappa was respectively κ= 0.79 (95% CI: [0.51–1.0]), κ= 0.75 (95% CI: [0.78-0.78]) and κ= 0.84 (95% CI: [0.84-0.84]).

5.0 Discussion

5.1 Prevalence

The 89 participants with DMT2 included in this study. A total of 65 (73.0%) of the participants had signs of DR. The prevalence found is much higher compared to the prevalence of DR found in other larger studies in Norway (24%) and in Europe (25%). The ICDO guidelines states that 1 in 3 will develop DR (Wong et al., 2018).

In many cases it is difficult to differentiate drusen and hard exudates, which may lead to a false increase in DR grading. Some of the participants in this study had both drusen and hard exudates. A study by Yongpeng et al. (2022) looks at the relationship between DR and AMD, and confirms that the prevalence of dry AMD in DM patients with DR was increased, as well as DR being a risk factor for dry AMD. Some of the images from the KOWA VK-2 have an unusual high number of hard exudates, and reflexes from vitreous when capturing the KOWA-VK-2 image could have been falsely counted as hard exudates. KOWA VK-2 images have a clearer image than Optomap due to higher resolution, and a study by R. Khan et al. (2021) show that especially very small and white lesions are more easily detected in KOWA

VK-2 images, leading to a higher count of small lesions when using KOWA VK-2 than Optomap images.

One of the risk factors for the prevalence of DR is duration of diabetes (Ana et al., 2021). In the samples from this study the mean duration (self-reported) of diabetes is 10.3 years (95% CI: [8.8-11.3]), indicating that many of these participants are likely to have DR. No subjects were excluded from participating in the study.

It also became clear that it was easier to detect DR when looking at images with maximum increased enhancements, up to 150% zoom, different filters, and enough time to carefully examine each picture. Due to the high number of DR found in this study, one has to keep in mind that the number of participants with DR could be too high.

5.2 Image Quality

The data analysed in this study, was a part of a larger study (DVOH). When using Optomap, the images of peripheral retina were captured without eye-steering, and therefore none of the images have the full 200° field. Image 1 is an example of an image captured. In this study, all the findings have been counted in the peripheral retina as long as a part of the peripheral retina was visible, even if the area was less than ¼ of the total UWF area. When critically looking at the investigated area there are some images where the graded area is less than ¼ of the possible gradable area. This is especially true for the inferior nasal area where respectively the right eye has 56 (62.9%) and the left eye has 49 (55.1%) of the images with this smaller area (Table 6). If more of the retina had been visible, the proportions of retinopathy would have been counted over equally large areas. This may result in an underestimation of possible findings, especially inferior. Ideally, images with eye-steering could have been captured to avoid this, but it was not possible to change this in this particular study, since the data was already collected. When the participant is already dilated and sits in the right position, the images with eye-steering consisting of four images put together as one would probably not take longer than two minutes to capture. The participants will still be sitting in the same position without moving their head and look at the green fixation target while the four images are captured.

The image quality of the central retinas was better than the peripheral. The central areas are nearly equally large and there is a low number of images that are not gradable. KOWA VK-2 images had 1.7% of the images not gradable and the 45-degree Optomap had 0.6% of the images not gradable. Findings counted from the KOWA VK-2 images and the 45-degree Optomap images are gradable and reliable.

5.3 Frequency of Diabetic Retinal Findings in the Peripheral Retina

When investigating only the peripheral retina, respectively 36 (40.4%) of the right eyes and 45 (50,1%) of the left eyes have any DR. When increasing the area from WF to UWF in this study using the left eye, 15 (16.9%) of the participants have an increased degree of DR.

When investigating the findings, for the right eye the mean number of images with microaneurysms (sd) were 9.0 (4.2), for haemorrhages were 8.3 (2.2), and for the left eye the mean number of images with microaneurysms were 12.3 (4.3), haemorrhages were 12.5 (2.7). Of all the findings microaneurysms and haemorrhages were significantly most frequently found in the peripheral retina (p-value <0.001) compared to the other findings.

When counting the number of microaneurysms and haemorrhages for the left eye in this study the number of microaneurysms increases with 250 (30.6%) from the WF to the UWF area, and the number of haemorrhages increases with 384 (61.2%). This is not directly comparative to other studies since both the lesions and the area investigated are different. Other studies have counted the number of lesions and combined the number of haemorrhages and microaneurysms and elongated the EDTRS fields to the periphery. A study by P. S. M. D. Silva et al. (2013) found 52% more H/Ma, 26% more IRMA and 4% more Vb in the UWF area compared to EDTRS seven-field. A study by Nanegrungsunk, Patikulsila og Sadda (2022) found that 40% of the lesions were outside the EDTRS seven-field, and a study by P. S. M. D. Silva et al. (2017) found 49.8% more H/Ma when investigating UWF compared to EDTRS seven-field. All these studies find more lesions when including the UWF area which are in concordance with the current study.

As stated, P. S. Silva, A. J. Dela Cruz, et al. (2015) found that PPL is associated with an increase of DR worsening over four years independent of baseline diabetic retinopathy severity score. In this study 13 (14.6%) of the participants have predominantly peripheral lesions, and one (1.2%) participant has only peripheral lesions. The retinal lesions causing discrepancies were in this study microaneurysms and haemorrhages as found in the study by P. S. M. D. Silva et al. (2013) and Dennis M. et al. (2022). Another study by (Aiello et al., 2019) found 41% of the eyes to have PPL.

The only participant in this study with PPL were 55 years old and has a self-reported duration of diabetes for 10 years. The mean age of the participants with PPL were 61.9 years (95% CI: [56.8-67.1]), and they have a mean self-reported duration of DMT2 of 10.4 years (95%CI: [4.9-15.8]). The early onset and the duration of DMT2 agrees with other studies that have investigated PPL. Cherian et al. (2022) found that the distribution of were associated with young age of DM onset (<40 years), long duration of DM (>10 years), and the number of PPL increased with the severity of DR. They found PPL also to be a marker for coronary artery disease.

5.4 Differences in DR in the Peripheral Retina when Comparing the Four Retinal Quadrants

According to the findings no peripheral quadrant is significantly more likely to have DR than another quadrant p= 0.883 for right eye and p= 0.942 for the left eye. In this sample peripheral DR is likely to occur in any quadrant.

The peripheral lesions are evenly distributed in the four quadrants, with the SN showing the greatest number of findings and IN quadrant showing the least number of findings for both eyes. Bearing in mind that the IN area has the least number of gradable images. As of now, there seems to be no other studies that have compared DR in the same peripheral quadrants used in this study. However, a study by X. Li et al. (2020) analysed for the distribution of DR. They found that manifest lesions of DR were common in the nasal field besides the posterior

pole in Chinese patients, while a study by P. S. M. D. Silva et al. (2013) found that all lesions were more frequently found in the temporal peripheral retina.

When looking at the PPL, this study found PPL to be evenly distributed in the peripheral retina. PPL were most frequent found in the SN quadrant (11.2%) followed by ST (9.0%), IT (6.7%) and IN (3.4%) quadrant. Bearing in mind that in this study the SN area most frequent have a larger area to be graded (Table 6). A study by Verma et al. (2020) discovered that PPL could be observed in 37% of eyes with DR in an Indian population. They investigated the frequency of a PPL distribution, which showed that for any grade of DR severity the temporal fields had the greatest PPL frequency (69.9%), followed in order by the superior (42.6%), inferior (34.4%) and nasal (30.1%) fields. In addition, they found that PPL had no correlation with the severity of DR. These two studies are not completely comparable since area investigated is not equal, but both studies find the temporal part of the retina to have most peripheral lesions. Another reason for the small amount of PPL in the IN quadrant in this study is the higher amount of non-gradable images found in this area.

5.5 The Differences in DR in the Peripheral Retina, on Retinal Optomap Images Compared to DR Graded on Central 45-Degrees Retinal Images (Optomap and KOWA VK-2)

When looking at the DR found in the central 45-degrees images and compare them with the peripheral finding when using Optomap, the results from this study found a linear relationship between the DR found in the peripheral retina and in the central 45-degree retina ($p= 0.003$ with 45-degree Optomap image and $p= 0.007$ with KOWA VK-2 image). When using a linear model, this study found the linearity to be better when using Optomap to investigate both the central 45-degree and the peripheral retina. The figures from both studies (Figure 8 and 10) show that proliferative DR is least common to find, followed by severe DR, mild DR, moderate DR, and most frequent is no DR.

Looking at the left eye 32 (36.0%) of the participants have an increased DR severity when using UWF Optomap compared to central 45-degrees Optomap images. 10 (31.5%) of the participants went from no DR to mild DR, 7 (21.9%) from mild to moderate DR, 14 (43.8%)

from no DR to moderate DR, and 1 (3.1%) from moderate to severe DR (Table 11). When comparing the results from KOWA VK-2 and UWF Optomap, this study found 35 (39.3%) more participants having an increased degree of DR. These two studies find about the same increased DR severity from central 45-degree to the peripheral retina, 3 (3.4%) more participants when using KOWA VK-2. This study shows that moderate NPDR are more frequent found in images from KOWA VK-2 than in 45-degree Optomap images.

When using Optomap to investigate the severity of DR, there was an increased severity of DR when including the mid-peripheral retina in 22 (24.7%) of the participants, and when including the UWF 15 (16.9%) more participants have an increased level of DR. The results when comparing KOWA VK-2 with WF Optomap showed an increase in severity in 26 (29.2%) of the participants and when including the UWF another 12 (13.5%) participants showed an increase in DR severity. Other studies have compared the EDTRS seven-field area with the UWF area and also found an increase severity of DR similar to this study bearing in mind that the areas are different. A study by P. S. M. D. Silva et al. (2017) illustrated that UWF imaging was able to detect a more severe H/Ma count in 12.7% of eyes compared to a ERDRS seven field photograph, a study by Liam D. Price, Stephanie Au og N. Victor Chong (2015) found an increased the DR severity grade in 15% of the eyes, and Aiello et al. (2019) found an increase of DR severity in 12.5% of the eyes. Also a study by Nanegrungsunk et al. (2022) showed that 9%–15% of UWF colour fundus photo led to detection of a more severe DR level than was seen on ETDRS seven-field image. DR found in the mid-peripheral and peripheral retina will be missed when only investigating the 45-degree field.

When comparing the mean DR for the central retina and the UWF retina, the Wilcoxons rank sum test is significant p= 2.47e-7 (45-degree Optomap) and p= 0.005 (KOWA VK-2) indicating that the mean DR are significant different in the central 45-degree retina and UWF retina.

Also, the number of participants with any DR increased with the area investigated. 25 (28.1%) more participants have DR when increasing the area from central 45-degrees to the UWF when using Optomap, and 17 (19.1%) more participants have DR when increasing the area from KOWA VK-2 to the UWF area. This is showing that UWF images detect more participants with DR than the central 45-degrees imaging technologies, and this is in concordance with the literature.

Studies have also used FA to discover a relationship between findings in central and peripheral retina. Mastropasqua et al. (2019) investigated the microvasculature in DR, since it has been suggested that DR-related damage may begin around the macula and that the central sector would be expected to have the best predictive sensitivity for DR. Their study demonstrated progressive impairment of retinal and choriocapillaris flow features both in central and peripheral retina at advancing DR severity, with high correlation between central and peripheral retina. Results from a study by Sim et al. (2014), where UWF FA images were obtained, also observed relationships between ischemia and vascular leakage in the macula and periphery.

5.6 Diabetic Retinopathy Severity Agreement

When using kappa statistics to compare the grade of DR found by UWF Optomap images and KOWA VK-2 images, weighted kappa is κ= 0.46 indicates that there is a moderate agreement between the results. The weighted kappa when using UWF Optomap compared with the central 45-degrees image is κ= 0.75 giving an overall good agreement between the results. The moderate agreement when using KOWA VK-2 is due to the differences in grading between the two methods. Some participants have more severe DR when using KOWA VK-2 image and some have less severe DR when using KOWA VK-2 image compared to the Optomap image, even when more participants (3.4%) are graded with DR when using KOWA VK-2 compared to 45-degree Optomap.

The results by Optomap with weighted kappa κ= 0.75 correspond to the study mentioned earlier by P. S. M. D. Silva et al. (2017) counting haemorrhages and microaneurysms in EDTRS fields and UWF images. They found that weighted κ statistics for severity of H/Ma for all fields 0.61/0.69 with overall exact agreement in 81.3% of fields, and also here a greater proportion of fields were graded a more severe H/Ma level in UWF images than in the corresponding ETDRS photos.

Other studies have graded the mid-peripheral field by using two instruments and found differences in grading. Paolo S. Silva et al. (2012) compared UWF-100-degree images with

the EDTRS seven field and found an exact DR severity agreement in 84%. A Danish cross-sectional study by Byberg et al. (2019) compared photos using both Optos and a conventional Topcon. The inter-camera agreement was fair for peripheral grading, with Optos identifying more microvascular changes in the periphery. Of the images evaluated by Domalpally et al. (2021), exact agreement was found in 48.8% of eyes between standard seven-field and masked UWF seven-field levels with a weighted κ- value of 0.59 not very different from a study by Aiello et al. (2019) who compared ETDRS seven-field images and UWF masked images and found 48.4% of eyes to have exact agreement with a weighted κ of 0.51. Agreement rates varied with DR severity and were least for early DR, and with the area investigated.

When comparing the results from the KOWA VK-2 images between the two graders, the interrater agreement is fair. The weighted Cohen's kappa is for the right eye κ= 0.29 and for the left eye κ= 0.25. The exact agreement for the right eye is 48.4% and for the left eye 50.0%. Grading within one level of agreement is for the right eye 74.4% and for the left eye 73.3%. This could mean that the interpretation of the KOWA images was difficult, which lead to different results due to grading errors, but also a disagreement in how the two graders interpret findings. The interrater agreement is lower than other studies. A study by Srinivasan et al. (2022) showed an exact agreement between two observers in 84.8% of the images. A review by Nanegrungsunk et al. (2022) evaluated the agreement in DR severity grading between ETDRS seven-standard field images and UWF colour images in several studies: the perfect agreement was between 48.4%–84% and agreement within one-level was 88%–100%. In this study both graders had completed the VIOLA program, and still the interobserver reliability is not very high. When comparing the degree of DR for the same 31 KOWA VK-2 images graded by the senior with the central 45-degree Optomap images graded by the author, the interrater agreement is good with an exact agreement in 79.0% for the right eye and 75.9% for the left eye. This may indicate that some of the results from the KOWA VK-2 images have been incorrectly interpreted, but to make any conclusions, it would be necessary to grade the same Optomap images.

A study by Sundling, Gulbrandsen og Straand (2013) concluded that Norwegian optometrists does not meet the required screening standard when evaluating retinal images of diabetic retinopathy. Showing that more praxis is needed among optometrists for them to be reliable

graders. For a higher degree of perfect agreement for the current study, a pilot study where the two graders compared the grading of 10-20 pictures before starting this study probably had increased the inter observer reliability.

The intrarater agreement is higher, images from 10 participants have been re-graded. When using the left eye weighted kappa is κ= 0.79 for KOWA VK-2 images, κ= 0.75 for 45-degree Optomap images and κ= 0.84 for UWF Optomap. This means an exact agreement in 70% and 80% of the images which is a good agreement, and a very good agreement when comparing the UWF Optomap image.

5.7 Strength of the Study

This study is a single centre study representing the South-Eastern Norwegian population. All the participants have gone through the same procedures and the images are captured by the same instruments for all participants.

Before the data collection started, detailed written procedures and protocols were produced and evaluated. The written procedures and protocols made sure that the investigators followed the same procedures and used the same grading tools.

The information about the participants were blinded for the image graders. Duration of DM, HbA1c level and type of treatment are self-reported. These data were not used to answer the research questions but included as visuals for the discussion.

This study has a power of 0.8. A total of 89 participants from the DHVO project were included in the study, and a total of 179 images were captured. 147 images had signs of DR and 31 images did not have any signs of DR. With power calculations wanting a power of the study to be 0.9, this study needed 34 images in each group. However, these criteria were not fulfilled. With a power of 0.8 the study needed 25 images in each group, and this requirement was fulfilled.

Other strengths with this study, is that the grading has been done under controlled conditions. Both graders have done the grading in the same room with the same illumination and on the same high resolution calibrated colour screen.

5.8 Limitation of the Study

The images were not controlled for other diseases or conditions that might impact the grading of DR, such as age-related macular degeneration, cataract, ptose, high blood pressure or medication.

During the analysis of the images, missing and misdiagnosed lesions may have occurred. Dot haemorrhages might be small and difficult to distinguish from microaneurysms, and larger microaneurysms might have been mistaken from haemorrhages. Some studies count microaneurysms and haemorrhages as one lesion. In the peripheral retina it was difficult to distinguish microaneurysms from dot haemorrhages even with the help of high magnification, red free filter, and maximum enhancement. Dot haemorrhages cannot always be differentiated from microaneurysms as they are similar in appearance but vary in size (Wong et al., 2018). Artefacts as reflexes from vitreous, dust on the camera lens, and findings from other underlying diseases like high blood pressure, have altered the real number of the findings. In this study all findings have been counted as long as they seemed to be a result from complication due to DMT2.

Ptose and heavy eyelids may have covered the pupils in some participants and made the fundus image less gradable, also cataract can make the fundus image more unclear.

All the images are captured with automated eye alignment without using the steering-function. The steering function move the fixation target allowing the images to be larger in the nasal, inferior, temporal, and superior direction. The images evaluated has therefore a smaller peripheral area than it potentially could have, and peripheral DR may have been missed and underestimated as previously mentioned, due to this.

A pilot study were the images that were difficult to grade had been re-graded and discussed with a senior optometrist would probably have increased the intra- and inter observer reliability in this study.

5.9 Future and further research and advice

5.9.1 The role of the optometrist and the future

Optometrists today are a part of the first-line vision and eye health services. Retinal imaging has been a key tool in the diagnosis, evaluation, management, and documentation of DR for many decades, and imaging technologies have evolved rapidly. In the modern world the role of documentation becomes more and more important. Instruments are producing images with higher resolution and contrast with less time, effort, and invasiveness, and UWF fundus imaging allows us to accurately classify retinal diseases and improve the quality of clinical evaluation. This again allows us to compare images of the same eye acquired in different moments to help monitoring DR.

The optometrist should be aware of the possibility that a minority of the most peripheral lesions may not be entirely visualized using Optomap. Retinal UWF imaging might be considered a first line diagnostic modality to determine the level of DR and DME, in the context of a full ophthalmological eye examination, and not a substitute for a comprehensive eye examination that evaluates the entire eye. In-person examinations are clearly necessary when photographic quality is inadequate, as well as to follow up detected abnormalities. An in-person comprehensive eye examination should be performed at least initially and at intervals thereafter as recommended by an eye care professional (Paolo S. Silva et al., 2012).

In the future, optometrist with suitable expertise and instruments should be able to screen and follow up the DM patients with an annual eye examination or more often as appropriate (Wong et al., 2018). This allows the optometrist to make the GP or the instance that has the overall responsibility for the patients' medical follow-up, aware of the results by sending a report and referring to an ophthalmologist for treatment when appropriate.

Kato et al. (2021) found the use of UWF retinal imaging with remote reading by experts to be very useful in areas where qualified eye care professionals are not available. It may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used preferentially for more complex cases and treatment. During the COVID-19 pandemic, a

remote screening system ensured compulsory social distancing and reduce the number of ophthalmic visits, which became a safe system for patients and clinicians.

By examining the relationship of ischemia between the macula and periphery, UWF fluorescein angiography (FA) images provide an insight into the relationships between diabetic vascular complications in the retinal periphery and central macula. Sim et al. (2014) found that there was a relationship between ischemia in the centre and in the peripheral retina, but not in all patients.

P. S. Silva et al. (2022) found that approximately 70% of non-perfusion in diabetic eyes is located outside the posterior pole. Increased non-perfusion is associated with the presence of FA-PPL, suggesting UWF-FA may better predict future DR worsening than UWF- colour alone. A study by Marcus et al. (2022) found that only fluorescein angiography (FA) PPL was associated with a greater risk of DR worsening over four years, while the PPL found by colour fundus photos was not, and his results support use of UWF-FA for future DR investigations to determine prognosis more accurately in NPDR eyes.

5.9.2 Further research and advice

It would have been interesting to see the results from a future study with a larger sample size to gain a better statistical power. Such a study should be done with the steering function to gain a larger peripheral field of view and the results should be compared in groups according to age, gender, duration of diabetes and HbA1c level. In this future study participants with diseases that might affect the retina should be excluded, and a pilot study should be performed to gain better intergrader and intragrader agreements.

Wong et al. (2018) stated that the ICO guidelines were developed for grading DR and provides a basis for countries to develop more specific programs targeted at reducing the risk of vision loss resulting from DR. Lucente et al. (2023) stated that WF and UWF imaging are revolutionary technologies in ophthalmology and should be promptly integrated as an indispensable part of the eye examination for their diagnostic, prognostic, and forensic value. In Norway many Ophthalmologists and Optometrists have access to UWF- imaging, OCT- angiography, UWF- angiography and modern software to assess and manage DR. UWF imaging allows detailed visualization of the retinal periphery, which is particularly impactful

in the diagnosis and management of DR. New severity scales should be adopted based on these imaging technologies. The Norwegian guidelines should therefore be re-evaluated with regards to the new novel techniques to be able to detect diabetic retinopathy at an earlier stage and thus improve the management of DR to avoid blindness.

6.0 Conclusion

This study shows that there is no doubt that wide field imaging tools that have evolved over the last years improve our abilities to detect DR. Visualization of peripheral retina enables eyecare professionals to discover, diagnose, document, and treat ocular pathology that may first be present in the periphery – pathology which may go undetected using traditional fundus cameras. This study showed that nearly half of the participants have peripheral DR. Microaneurysms and haemorrhages are the most frequently found lesions, and predominantly peripheral lesions were found in 13 (14.6%) of the Optomap images. There were no significant differences in DR when comparing the four peripheral retinal quadrants. When including the peripheral retina about one third of the participants have an increased severity level of DR compared to the central 45-degree images.

This study shows that ultra-widefield imaging is a useful tool for Optometrists to detect peripheral DR and thus provide better patient care.

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8.0 List of Tables, Images and Figures

9.0 Appendix

Appendix 1.

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. Du bør ikke kjøre bil før synet er normalisert.

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, (2018/804).

Appendix 2.

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

Appendix 3.

Procedure for analysing KOWA VK-2 images.

High performance digital image system. Kowa VK-2 is a professional digital imaging system to acquire, analyse, and store patient image data. The VK-2 work area includes: an image frame window containing an image and a menu bar at the top of the window, and various toolbars available to provide easy access to the tools used for viewing images.

1. Turn on the PC and the start-up window and the VK-2 application will appear.
2. Double click on the icon “VK-2” to start the application.
3. To open the database, click on Database and Open database list. The ID list allows you to perform a search for patient records by using patient ID and name, or by date. The Database List dialog window displays a list of all patient records sorted by ID number.
4. Enter patient ID in the dialogue box.
5. Click on start search. A list of patients that match the ID are displayed in the list window and sorted by ID.
6. Click on the right patient record to view the fundus image.
7. Click on the Multiple button 

on right side and multiple images from the same patient are displayed on the screen.
8. Click on the image of central fundus with macula in centre on the first examination day according to the journal. If several images are done this day, choose the most gradable image. Use the PREW 

and NEXT 

button to view the images several times for choosing the best image.
9. Click on the Image process button 

to display the image process bar


10. Move the most gradable image and the toolbar to the EIZO screen for examination.
11. First evaluate the image to see if it is gradable or not according to table X. Only gradable images are evaluated.
12. Click the left button on the mouse. Choose Lens size: medium, Magnification: high and Filter: none. Start at the disk and follow the arcades to the end of image, do it clockwise to make sure that the whole image is covered. Count and make a note of all diabetic retinopathy findings om the XL sheet.
13. Use a transparent overlay and place it over macula to make sure that findings are counted in the correct quadrant. First in a the horizontal direction and then in the vertical direction.
14. To evaluate the superior and inferior part of the image, click on zoom button 

to incrace the image size. Click on the point of interest and it will be magnified to twise the size if needed.
15. Click on origin button 

to restore and view original image.
16. Click the green button to view only the red components in the image after finishing the coloured image.
17. Then evaluate the patients left eye. Click on the Multiple button and find the best gradable image of left eye with macula in centre on the first examination day and repeat the procedure.
18. Repeat the same procedure for the next patient.
19. Log out when finished.

Appendix 4.

Procedure for analysing Optomap central 45-degree image.

Optos introduced ultra-widefield retinal imaging to discover, diagnose and document ocular pathology that may first be presented in the periphery. Optomap model California are able to capture more than 80% or 200° of the retina in one image. The work area is including an image of retina and a tool bar at the top of the window allowing help from different tools to evaluate the image. The same functions can be utilized from the mouse controls which is more efficient to use.

1. Turn on the PC and the start-up window and the Optomap application will appear.
2. Double click on the icon “Optomap” on the desktop to start the application.
3. The program starts on the EIZA screen, write in username and password, and tick the Login button.
4. Enter the patient ID in the dialogue box and click on it to open for review.
5. Make sure you choose the patients first examination day.
6. Images of the left and right fundus are presented in the view box.
7. Choose the right eye first, double click on the image and only the right image will fill the screen.
8. Increase the image size by holding the left button on mouse down and move the image towards you. Increase the image until the disk and the area around is about 45 degrees. Move the image by pressing the right button down to allow the posterior pole being in the centre of image.
9. Evaluate if the central posterior pole is gradable or not. Only gradable images are evaluated.
10. Tick on the button beside the Area, and then on the ruler. Make a line from the centre of the disk to the centre of macula. It is 15 degrees from the macula to the centre of the disk. To get 45 degrees take the number on the line and multiplicate it with 3. This is the diameter of the central 45 degrees.
11. Divide the number by 2, this is the radius of the circle, and elongate the line from centre of macula first nasally and then temporally. Make sure macula is in the centre of the line, and make sure the line is straight. Make a new line going from the centre of macula and then up and down, perpendicular to the first line. Make the length of this line equal to the diameter of the circle. This line will have the same length as the first line, and the macula is in the centre of the line.
12. Tick on the Area Ellipse under the Area measurements. An ellipse is turning up, increase the ellipse until it has become a circle. The position the circle covering the two lines. Evaluate the area within the overlay. Findings covering the line are counted if more than 50% of it is within the central area.
13. Tick the Enhance button and increase the contrast to 3.
14. Enlarge the image looked at by using the SmartZoom button. An overlay will appear on the image, and you can change size of the overlay and the magnification and the filter within the overlay. Move the overlay to the area you are examining. Start with the macula area, then the superior nasal part, superior temporal part, inferior temporal part and then inferior nasal part.
15. After evaluating the coloured image. Change the settings by ticking the Blend icon, it allows you to look at the image with a red free filter. Move the mouse towards you while holding the right mouse button and you will view the image in red free colour (100% green).
16. Work from the disk along the arcades with the clock and make sure the whole area is covered. Count the DR findings and note them down in the XL sheet.
17. Click on Reset on toolbar to reset image to original exposure and magnification settings if needed.
18. Repeat the same procedure for the patient left eye.
19. When finishing the patient evaluation click Studies icon to go back to the Patient Study Directory and repeat the same procedure for the next patient.
20. Click on Close button when finishing patient session.
21. When exit use the Log off button.

Appendix 5.

Procedure for analysing Optomap image, grading each quadrant in the mid- peripheral and ultra-wide field area.

1. Turn on the PC, the start-up window and the Optomap application will appear.
2. Double click on the icon “Optomap” on the desktop to start the application.
3. The program starts automatically on the EIZA screen. Write in username and password and click on the Login button.
4. Enter the patient ID in the dialogue box and click on it to open for an examination.
5. Choose the right examination day.
6. Images of the left and right fundus are presented in the view box.
7. Choose the right eye first, double click on the image and only the right image will fill the screen.
8. Use the previous image with the marked central 45 degrees. This image has the largest field of view that include both macula and the disk.
9. Tick on the Blend icon and look at the image with 100% red filer. Locate the ampullas.
10. Tick on the Area Ellipse under the Area measurements and increase the ellipse until it becomes a circle, and it covers the anterior part of the vortex ampullas. Make sure the circle is round, and parallel with the central circle. Now you have the right area to evaluate even if you do not see all the ampullas. Evaluate the area outside the two circles. Findings covering the boarder lines are counted if more than 50% of it is within the central area we are looking at.
11. Tick on the Enhance button and increase the contrast to 3.
12. Start to evaluate the superior temporal area first. Evaluate if the peripheral area is gradable or not. Choose to evaluate the image that is most gradable by flicking between the two images taken the same day. Make sure the two images have the same larger magnification. If the most gradable image is different from the mid-peripheral area already produced, you need to draw the midperipheral ring for this image to make sure that the area you are counting are similar for all patients.
13. Tick the zoom button. Increase the image size by pressing the left button on the mouse down and move the image towards you. Move the image to allow the macula to be positioned in the lower right corner and increase the image size until the image of the periphery fill the screen.
14. We have two images from the same examination day. It is a lot of artefacts on the camera lens, and to avoid counting artefacts you need to flick between the two images by moving the mouse up and down. Do not count findings that is not moving and do this several times while counting retinopathy.
15. Enlarge the image looked at by using the SmartZoom button. An overlay will appear on the image. You can change size by moving one of the corners of the overlay and the magnification and filters within the overlay by moving the mouse.
16. After examining the coloured image. Change the settings by ticking the Blend icon, it allows you to look at the image with a red free filter. Move the mouse towards you while holding the right mouse button and you will view the image with 100% red free filter.
17. Work from the top right corner to the left and move along the arcades with the clock and make sure the whole area is covered.
18. Count all DR findings and note them down in the patient’s sheet.
19. When finishing the superiortemporal quadrant, evaluate the superiornasal quadrant, then the inferiortemporal, and at last the inferior-nasal quadrant. Move the image and place macula in a corner and enlarge the image until the peripheral retina fills the screen.
20. After finishing all the four peripheral quadrants in the right eye, repeat the procedure for the patents left eye. To find the left eye double click on the mouse and both eyes will be visualised on the screen. For evaluating the left eye, double click on the left image. The left eyes image will now fill the screen.
21. When finishing the patient evaluation click Studies icon, or the arrow in the corner to go back to the Patient Study Directory for evaluating the next patient.
22. When finishing evaluating all the peripheral images, then evaluate the mid- peripheral retina, the area inside the circles.

23. Start with the patients' right eye by double click on the right eye. Do the same procedure as with the peripheral part. Start with superiortemporal quadrant, and evaluate which image is most gradable, and choose the image that has the largest field of view with visible retina and vessels.
24. Increase the image until the supertemporal area fills the screen. Increase the enhancement to 3 for best contrast. Flick between the images to avoid counting artefacts. Count findings with 50% red and 50% green filter first, then with 100% green filter.
25. Tick on the SmartZoom button, and the magnification button to increase the magnification within the area you are looking at. Flick between the two images to avoid counting artefacts, use the coloured background and the green free filter inside the Smartzoom area to make the counting easier.
26. Write down DR findings on the patient- sheet for the superiortemporal quadrant. Repeat the procedure for the other three quadrants, and then for the patients left eye.
27. When finishing the patient evaluation click Studies icon to go back to the Patient Study Directory for evaluating the next patient.
28. Click on Close button when finishing patient session.
29. When exit use the Log off button.

Appendix 6:

Registration form. The peripheral diabetic retinopathy in type 2 diabetes: a cross-sectional study

Patients ID:	Date for grading image:	Graded by:
Date, first time examination:	Age at first examination:	Comment:

Grading of image quality:

Gradable image: Yes = 1,2 No = 3	KOWA, 45 degrees	Optomap, central 45 degrees	Optomap, peripheral ST	Optomap, peripheral SN	Optomap, peripheral IT	Optomap, peripheral IN
Right eye						
Left eye						

Gradable image: Yes = 1,2 No = 3	Optomap, mid-peripheral ST	Optomap, mid-peripheral SN	Optomap, mid-peripheral IT	Optomap, mid-peripheral IN
Right eye				
Left eye				

Registration of diabetic retinopathy –

KOWA central 45 degrees, number of findings in each eye

	Right eye	Left eye		Right eye	Left eye
No diabetic retinopathy			Venous beading, ST		
Microaneurysms			Venous beading, SN		
Haemorrhages, ST			Venous beading, IT		
Haemorrhages, SN			Venous beading, IN		
Haemorrhages, IT			Neovascularisation, NVO		
Haemorrhages, IN			Neovascularisation, NVE		
Hard exudates, >1DD			Vitreous haemorrhage		
Hard exudates, CME >1mm			Grading DR: RE: LE:		Image grading: RE: LE
Hard exudates, CME<1mm					
Cotton-wool spots					
IRMA					

Optomap central 45 degrees, number of findings in each eye

	Right eye	Left eye		Right eye	Left eye
No diabetic retinopathy			Venous beading, IT		
Microaneurysms			Venous beading, IN		
Haemorrhages, ST			Neovascularisation, NVO		
Haemorrhages, SN			Neovascularisation, NVE		
Haemorrhages, IT			Vitreous haemorrhage		
Haemorrhages, IN					
Hard exudates, >1DD			Grading DR: RE: LE:		Image grading: RE: LE
Hard exudates, CME >1mm					
Hard exudates, CME<1mm					
Cotton-wool spots					
IRMA					
Venous beading, ST					
Venous beading, SN					

Optomap peripheral, SUPERIOR - Number of findings in each eye

Superior-temporal quadrant	**Comments:**		**Superior-nasal quadrant**	**Comments:**	
	Right eye	**Left eye**		**Right eye**	**Left eye**
Image grading			**Image grading**		
No diabetic retinopathy			**No diabetic retinopathy**		
Microaneurysms			**Microaneurysms**		
Haemorrhages			**Haemorrhages**		
Hard exudates			**Hard exudates**		
Cotton-wool spots			**Cotton-wool spots**		
IRMA			**IRMA**		
Venous beading			**Venous beading**		
Neovascularisation			**Neovascularisation**		
Vitreous haemorrhage			**Vitreous haemorrhage**		

Optomap peripheral, INFERIOR - Number of findings in each eye

Inferior-temporal quadrant	**Comments:**		**Inferior-nasal quadrant**	**Comments:**	
	Right eye	**Left eye**		**Right eye**	**Left eye**
Image grading			**Image grading**		
No diabetic retinopathy			**No diabetic retinopathy**		
Microaneurysms			**Microaneurysms**		
Haemorrhages			**Haemorrhages**		
Hard exudates			**Hard exudates**		
Cotton-wool spots			**Cotton-wool spots**		
IRMA			**IRMA**		
Venous beading			**Venous beading**		
Neovascularisation			**Neovascularisation**		
Vitreous haemorrhage			**Vitreous haemorrhage**		

Grading of DR - PERIPHERAL: RE: _____ LE: _____

Optomap MID-PERIPHERAL, SUPERIOR - Number of findings in each eye

Superior-temporal quadrant	Comments:		Superior-nasal quadrant	Comments:	
	Right eye	Left eye		Right eye	Left eye
Image grading			Image grading		
No diabetic retinopathy			No diabetic retinopathy		
Microaneurysms			Microaneurysms		
Haemorrhages			Haemorrhages		
Hard exudates			Hard exudates		
Cotton-wool spots			Cotton-wool spots		
IRMA			IRMA		
Venous beading			Venous beading		
Neovascularisation			Neovascularisation		
Vitreous haemorrhage			Vitreous haemorrhage		

Optomap MID-PERIPHERAL, INFERIOR - Number of findings in each eye

Inferior-temporal quadrant	Comments:		Inferior-nasal quadrant	Comments:	
	Right eye	Left eye		Right eye	Left eye
Image grading			Image grading		
No diabetic retinopathy			No diabetic retinopathy		
Microaneurysms			Microaneurysms		
Haemorrhages			Haemorrhages		
Hard exudates			Hard exudates		
Cotton-wool spots			Cotton-wool spots		
IRMA			IRMA		
Venous beading			Venous beading		
Neovascularisation			Neovascularisation		
Vitreous haemorrhage			Vitreous haemorrhage		

Grading of DR – MID-PERIPHERAL: RE: _____ LE: _____

Grading of diabetic retinopathy

Classification Diabetic retinopathy	**KOWA Central 45 degrees**	**Optomap Central 45 degrees**	**Optomap Mid-peripheral**	**Optomap Peripheral**
No diabetes retinopathy				
Mild non-proliferativ DR				
Moderate non-proliferativ DR				
Severe non-proliferativ DR				
Proliferativ DR				
Diabetic macula oedema				
No macula oedema				
Non-central macula oedema				
Central macula oedema				