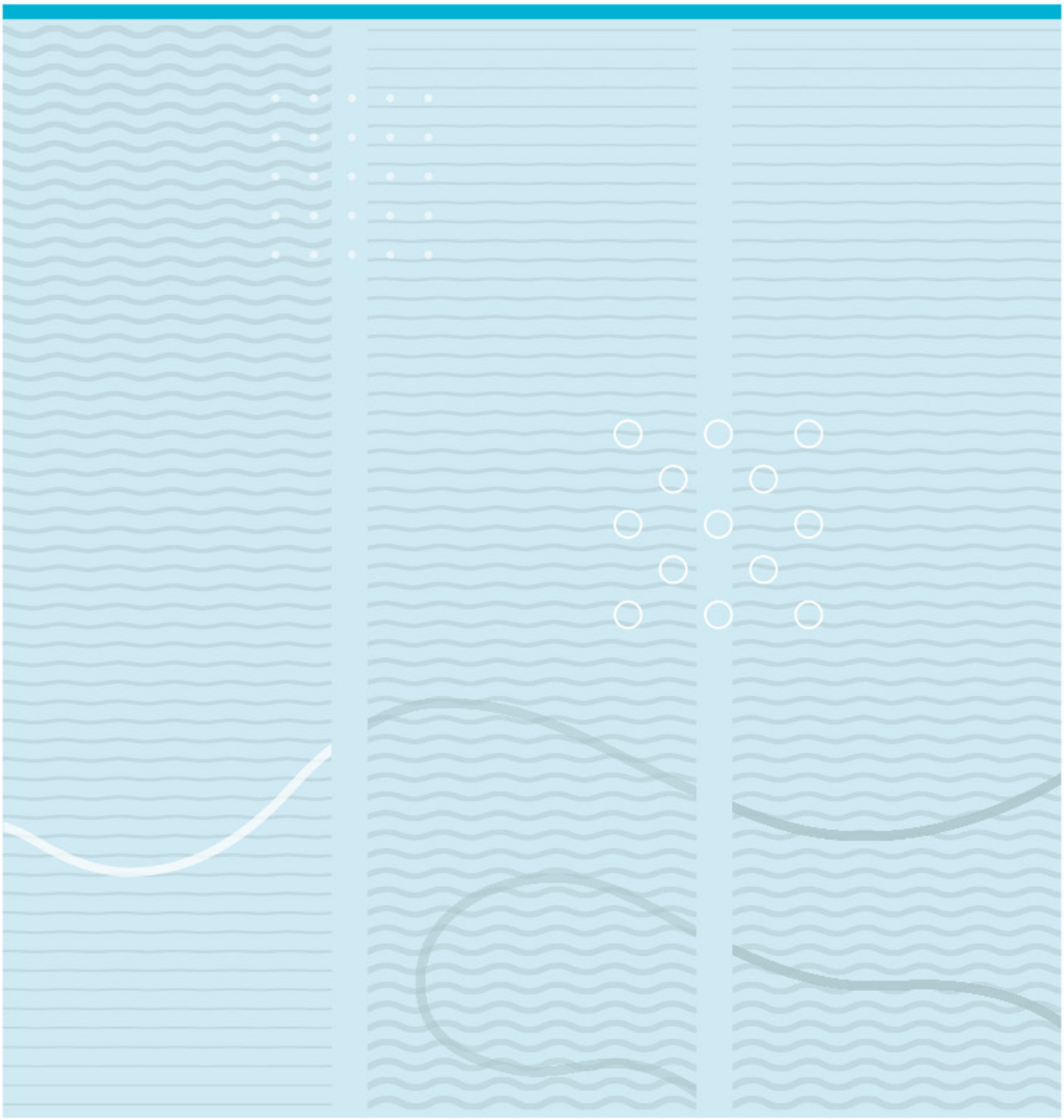
University of South-Eastern Norway
Faculty of Health and Social Sciences

–

Master's Thesis
Study programme: 5153 General Practice Optometry
Spring 2020

Jenna Aro

Optical coherence tomography vs fundus photography in detecting macular edema in subjects with type 2 diabetes



University of South-Eastern Norway
Faculty of Health and Social Sciences
Department of Optometry, Radiography and Lightning Design
PO Box 235
NO-3603 Kongsberg, Norway

http://www.usn.no

© 2020 Jenna Aro

This thesis is worth 30 study points

Summary

Introduction

The screening of diabetic retinopathy has been relied on fundus photography but since it is 2-dimensional, it is difficult to identify diabetic macular edema (DME), which is the most feared ocular complication related to diabetes. Optical coherence tomography (OCT) has been shown to be a useful tool in detecting and monitoring DME.

The main objective of this study was to screen people with type 2 diabetes and find out how many patients have current diabetic macular edema and to compare different screening equipment by means of fundus photography and OCT when evaluating macular edema.

Method

The sample of this study consisted of people with type 2 diabetes who participated in the larger cross-sectional study "Diabetes, vision and ocular health" at University of South-Eastern Norway. Participants were examined in National Centre for Optics, Vision and Eye Care at University of South-Eastern Norway in Kongsberg between August 2018 and February 2019. OCT images (HD-OCT Cirrus 5000, Carl Zeiss Meditec, Germany) and fundus photos focused on macula (Kowa nonmyd 7, Kowa Europe GmBH, Germany) were obtained on the same day. The collected OCT images and fundus photos were evaluated on different days to avoid bias. Presence of DME in fundus photography was based on definitions of Multi-Ethnic Study of Atherosclerosis (MESA) and in OCT on retinal thickness and findings in macular cube 200X200. The evaluated area was in correspondence with the ETDRS (Early Treatment Diabetic Retinopathy Study group) grid 1-3-6 in both fundus photo and in OCT image.

Results

A total of 74 subjects with type 2 diabetes (mean [SD] age 65.28 [9.79] years, 35 women, 39 men) were included in the study. Based on optical coherence tomography (n=123 eyes), DME was found in 10 (8.1%) eyes of total 8 (11.4%) subjects. With monocular fundus photography (n=136 eyes), DME was detected from 8 (5.9%) eyes of total 6 (8.6%) subjects. Clinically significant macular edema was found in 4 eyes (3 subjects). Some images, both OCT and photos, were excluded due to insufficient image quality or the macular conditions interfering with the evaluation of the macula.

112 eyes had both gradable fundus photo and OCT image and were included the analysis when comparing imaging methods. The inter-rater reliability between fundus photography and OCT was calculated by using Cohen´s Kappa in SPSS. Computed kappa was 0.596 which indicates moderate agreement.

Conclusion

The prevalence of DME in this sample seems to be in correspondence with global estimations in the literature. This was a cross-sectional study of a diabetic population, and the number of eyes with DME were low. To draw any statistical conclusions about which imaging techniques of OCT and fundus photography that are most reliable to detect DME, further testing including more subjects is warranted. However, the results indicate that OCT detects more cases with edema, and both diffuse and early stage of edema seemed to be harder to define from the photos

Keywords

Type 2 diabetes, diabetic macula edema, optical coherence tomography, fundus photography, screening

Contents

Optical coherence tomography vs fundus photography in detecting macular edema in subjects with type 2 diabetes....1

Summary....2

Contents....4

Foreword....6

1 Introduction....7

1.1 Diabetes mellitus....7

1.2 Prevalence of diabetes....7

1.3 Ocular complications in diabetes....8

1.3.1 Diabetic retinopathy....8

1.3.2 Diabetic macular edema....11

1.4 Screening of diabetic retinopathy....15

1.4.1 Grading of DME from fundus photography....16

1.4.2 Optical coherence tomography....17

1.5 Visual function....18

2 Methods....19

2.1 Research questions and significance....19

2.1.1 Primary goal....19

2.1.2 Secondary goal....19

2.1.3 Significance....19

2.2 Study design....20

2.3 Recruitment....20

2.4 Inclusion criteria....21

2.5 Exclusion criteria....21

2.6 Measurements....21

2.6.1 Fundus photography....22

2.6.2 Optical coherence tomography....25

2.6.3 Visual function and symptoms....27

2.6.4 Visual acuity....28

2.7 Analysis and statistical issues....28

2.8 Ethical considerations....28

3 Results 29
3.1 Prevalence of DME 30
3.2 OCT vs fundus photography 32
3.3 Subjects with diabetes related findings 33
3.4 Macular thicknesses measured with OCT 33
3.5 Comparison of subjects with and without DME 34
3.5.1 Visual function in subjects with DME 36
4 Discussion 40
5 Conclusions 47
References 49
List of tables and figures 54

Foreword

I sincerely want to express my gratitude to everyone who was part of the “Diabetes, vision and ocular health” -project. A special thank you to Tove Lise Morisbakk and Vibeke Sundling for advice, guidance and support throughout this thesis. I also want to thank all my fellow students for this incredible journey.

Kongsberg 30.4.2020

Jenna Aro

1 Introduction

Diabetic macular edema (DME) is a severe ocular complication in diabetes and it can occur at any stage of diabetic retinopathy (DR). Screening for DR includes fundus photography, but also the use of optical coherence tomography (OCT) has been discussed as an important imaging technique. According to international guidelines OCT is not included as a standard instrumentation for DR screening, but this imaging technique is listed as one of the ancillary tests at high resource settings (The International Council of Ophthalmology, 2017). In this cross-sectional study, the two different imaging modalities, OCT and fundus photography, were compared in detecting DME in subjects with type 2 diabetes.

1.1 Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder where body fails to process the glucose properly. There are three main types of diabetes and they all are characterized by high blood sugar level. In type 1 diabetes, pancreas does not produce enough insulin. The primary problem in type 2 diabetes is that insulin is produced but the body does not respond to it normally and glucose is prevented to transfer from blood into cells. This condition is called insulin resistance. People with type 2 diabetes may develop also a lack of insulin when disease progresses. Unhealthy lifestyle is the major risk factor for type 2 diabetes. The third form is gestational diabetes which occurs during pregnancy and often resolves after delivery (Flaxel et al., 2019.) Only subjects with type 2 diabetes were included in this study.

1.2 Prevalence of diabetes

Prevalence of diabetes has been increasing rapidly in the past years and it has become universal health burden. Unfortunately, similar development is expected to continue in the future. According to estimation, about 592 million people will suffer from diabetes in 2035, when the estimated number of people with diabetes in 2013 was about 382 million (Guariguata et al., 2014.) Approximately 90% of all diabetics have type 2 diabetes (International Diabetes Federation, 2020). Type 2 diabetes is the most commonly diagnosed in adults, but the frequency of type 2 diabetes in the pediatric age group has been increasing in many countries (Flaxel et al., 2019; International Diabetes Federation, 2020).

1.3 Ocular complications in diabetes

Diabetic retinopathy (DR) is a common ocular complication related to diabetes and one of the leading causes of visual impairment and blindness among people of working age in industrialized countries (Kilstad et al., 2012; Porta & Bandello, 2002; Stefánsson et al., 2000). Estimates of prevalence of DR and DME vary. According to comprehensive meta-analysis (Yau et al., 2012) the overall prevalence of any degree of DR was 34.6 % worldwide. Total 35 studies and 22 896 people with diabetes were included in this meta-analysis. The prevalence for DME was 6.81 % and for proliferative diabetic retinopathy (PDR) 6.96 %. 10.2 % had vision threatening diabetic retinopathy (Yau et al., 2012.) Lee et al. found the prevalence of DME in type 2 diabetes to vary between 1.4-12.8% among the population-based studies. Differences between studies may be partly explained by methodology how DME was determined and great variation of duration of disease between the sampled populations (Lee, Wong, & Sabanayagam, 2015.)

Prevalence of DR increases with duration of disease and while life expectancy increases, there will be more and more people suffering from DR (Guariguata et al., 2014; Porta & Bandello, 2002). People with diabetes have also increased risk for other eye problems. Diabetes is associated with many ocular conditions both anterior and posterior eye. Risks of two main types of glaucoma, neovascular and primary, is higher in people with diabetes. Also, cataract seems to emerge at younger age and progression is more rapid. People with diabetes may suffer corneal problems, like corneal erosion and ulcers and corneal sensitivity is often reduced (Browning & Rotberg, 2010, p. 325; Hasan, 2010, p. 347-348; Jeganathan, Wang, & Wong, 2008.)

1.3.1 Diabetic retinopathy

People with type 1 diabetes have more systemic symptoms at onset when it is easier to discover. In type 2 diabetes symptoms occur more gradually because the insulin secretion does not cease totally like in type 1 (The Finnish Medical Society Duodecim, 2018.) Due to that type 2 diabetes can be latent for years, and many patients with type 2 diabetes already have DR when DM is diagnosed (Porta & Bandello, 2002). The most important risk factor for DR is duration of disease which is why DR is more common in people with type 1 diabetes than with type 2. The control of diabetes is essential. Tight glucose control may prevent the development of DR or at least delay it or slow the progression. Other risk factors are e.g. hypertension, hyperlipidaemia, smoking and obesity (Bowling, Kanski, Nischal, & Pearson, 2016, p. 521; Porta & Bandello, 2002.)

It has been long known that hyperglycemia has an important role in pathogenesis of retinal microvascular destruction. In the beginning, high glucose causes dilatation in blood vessels and changes in the blood flow. It is considered that these changes happen in consequence of metabolic autoregulation to increase retinal metabolism. Another early change in DR is an apoptosis of pericytes. The function of pericytes is to contribute support for capillaries. The loss of support eventually leads to localized outpouching of capillary walls, producing small aneurysms. Basement membrane thickening and endothelial cell loss have also been found to occur during pathogenesis of DR. Together with the pericyte loss, they have impact on the impairment of the blood-retinal barrier. As endothelial cell and pericyte loss progresses, it finally results in ischemia. Retinal hypoxia in turn leads to upregulation of VEGF (vascular endothelial growth factor) which is considered to increase vascular permeability. The VEGF is significantly related to the progression of proliferative diabetic retinopathy (PDR) and DME (W. Wang, Lo, & Wang, 2018.)

According to recent evidence, DR is not only a vascular but also neurodegenerative disease. Hyperglycemia gives rise to an apoptosis of retinal neurons and micro-, and microglial cells as well. Retinal neurodegeneration occurs in very early stage and it may cause disturbance in color vision and contrast sensitivity before any clinical signs of DR in the retina (Bhagat, Grigorian, Tutela, & Zarbin, 2009; Flaxel et al., 2019; W. Wang et al., 2018.) A connection between a chronic low-grade inflammation and pathogenesis of DR has also been detected widely (W. Wang et al., 2018).

1.3.1.1 Diabetes related retinal findings

Microaneurysms are saccular protrusions in capillaries and they often are the earliest sign of DR. In fundus examination microaneurysms are seen as small, circular red dots (Bowling et al., 2016, p. 521.) The formation of microaneurysms is associated with pericyte loss which weakens the structure of capillary walls (W. Wang et al., 2018).

Retinal haemorrhages can be dot or blot shaped or sometimes flame shaped depending on which retinal layer they occur. Haemorrhages in nerve fibre layer (NFL) appear flame shaped and dot/ blot haemorrhages typically are located in the deeper layers; below the NFL and down to the outer plexiform layer. It may be difficult to differentiate tiny dot haemorrhages from microaneurysms (Bowling et al., 2016, p. 521-522; Scanlon, Wilkinson, Aldington & Matthews 2009, p. 30, 33, 100.)

Exudates (“hard” exudates) consist of lipoprotein and lipid-filled macrophages and are located typically in the outer plexiform layer. They are strongly associated with edema. In fundus examination exudates are seen as well-defined, yellowish deposits which may appear as spots, clumps or ring-shaped pattern around leaking vessels (Bowling et al., 2016, p. 522; Scanlon et al., 2009, p. 33-34.)

Cotton wool spots (“soft” exudates) consist of accumulation of neuronal debris and result from local ischaemia. These whitish/greyish patches are located in nerve fiber layer and unlike hard exudates, edges are very indistinct (Bowling et al., 2016, p. 526; Scanlon et al., 2009, p. 34, 101-102.)

Intra-retinal microvascular abnormalities (IRMA`s) are abnormalities of retinal blood vessels. They appear as branching or dilation of existing capillaries within ischaemic retina. IRMA is sometimes difficult to distinguish from neovascularization (NV). Compared to NV IRMAs are larger in caliber and are located deeper in the retina which is why their edges are blurrier. Unlike NV, IRMA does not leak. This can be verified with fluorescein angiography (Bowling et al., 2016, p. 527; C. S. Lee et al., 2015.) It is typical that IRMA is located near cotton-wool spots (CWS). IRMA and CWS are both signs of low blood circulation in the nearby area (Scanlon et al., 2009, p. 35.)

Venous abnormalities (beading, looping, dilatation) reflect increasing ischaemia in retina and predict progression to proliferative diabetic retinopathy. Venous beading is a localized increase of the vein caliber. Venous looping is concerned when vein deviates from its normal path forming a precipitous curve. Venous reduplication is dilation in pre-existent channel or formation of a new channel parallel to the original vein (Bowling et al., 2016, p. 527; Scanlon et al., 2009, p. 36, 38.)

When the retina becomes more ischaemic, new vessels may emerge on the optic disc or elsewhere in retina. *Neovascularization* often appear as fine tufts. New vessels are very fragile and bleed easily. The new vessels can leak into vitreous causing a *vitreous haemorrhage*. When it is located in sub-hyaloid space it is also called *pre-retinal haemorrhage* (Scanlon et al., 2009, p. 40-41.)

1.3.1.2 Grading of diabetic retinopathy

Though the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale is recognized as a gold standard for grading of DR, in everyday practice it was found to be impractical and difficult. In 2002, international panel of specialists developed a simplified severity scale for DR *(Table 1)* which is based upon the findings of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the ETDRS (Wilkinson et al., 2003.)

Table 1 Diabetic Retinopathy Severity Scale

Proposed Disease Severity Level	Findings Observable on Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild non-proliferative diabetic retinopathy	Microaneurysms only
Moderate non-proliferative diabetic retinopathy	More than just microaneurysms but less than severe non-proliferative diabetic retinopathy
Severe non-proliferative diabetic retinopathy	Any of the following: more than 20 intra-retinal haemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; prominent intra-retinal microvascular abnormalities in 1+ quadrant *and no* signs of proliferative retinopathy
Proliferative diabetic retinopathy	One or more of the following: neovascularization, vitreous/pre-retinal haemorrhage

(Wilkinson et al., 2003)

1.3.2 Diabetic macular edema

It is estimated that around 21 million people worldwide suffer from diabetic macular edema (DME) (Arthur et al., 2019; Yau et al., 2012). DME is the most feared eye complication and the major cause for vision loss among people with diabetes. It is characterized by thickening of the central part of the retina, macula and can occur at any stage of DR but the prevalence increases together with the increasing severity of DR (Browning, 2010, p.142; Virgili et al., 2015; W. Wang et al., 2018.)

As previously prescribed, the pathogenesis of DR and DME is multifactorial. The exact mechanism of breakdown of blood-retinal barrier (BRB) it is not fully understood but it is known several factors precede the breakdown which triggers sub- and intra-retinal fluid accumulation leading to retinal thickening (Bhagat et al., 2009.)

There are different subtypes of diabetic maculopathies. Focal leakage of microaneurysms can lead to *focal* DME. Circinate rings or clumps of hard exudates often surround the clusters of microaneurysms in focal edema (Bowling et al., 2016, p. 524.)

The *diffuse* variety of edema is caused by expansive leakage from capillaries which results from generalized breakdown of the BRB. In the beginning, the fluid is located between the inner nuclear and outer plexiform layers and later proceeding in inner plexiform and nerve fiber layers. Presence of scattered small retinal haemorrhages and aneurysms is typical in diffuse edema but unlike in focal subtype, hard exudates are not usually seen which makes diffuse edema more difficult to detect in photos (Bowling et al., 2016, p. 524; Scanlon et al., 2009, p. 154.) Diffuse edema has been reported to be less common than focal edema. DME can also be mixed form which makes classification difficult (D. Browning, Stewart, & Lee, 2018.)

Diabetic macular edema is typically divided into focal or diffuse type but when capillary closure causes enlargement of the foveal avascular zone (FAZ), it is called *ischemic* maculopathy. In this form of maculopathy, the control of hypertension plays an important role (Bhagat et al., 2009; Scanlon et al., 2009, p. 74.) The gold standard for identifying ischemic maculopathy is fluorescein angiography (Cennamo, Romano, Nicoletti, Velotti, & Crecchio, 2017). The avascular zone may also be evaluated with OCT-angiography (Henke et al., 2018). In this study, neither of these were not part of the examination process.

Cystoid macular edema (CME) is characterized by extracellular fluid accumulation and cystoid cavity formation in retinal nuclear layers. CME can be seen in diabetic patients, but CME can be associated with variety of other conditions such as age-related macular degeneration, epiretinal membrane, retinal vein occlusion and cataract surgery (Helmy & Atta Allah, 2013.)

When DME is detectable with OCT but cannot be recognized clinically or the definition of CSME (clinically significant macular edema) or CIDME (central-involved diabetic macula edema) is not fulfilled (see description in text below), the term subclinical diabetic macular edema (SCDME) may be used (D. Browning et al., 2018). It has been suggested that people with SCDME should be followed more closely because they have increased risk for developing CSME (Virgili et al., 2015).

Figures of different kind of subtypes of macular edema will be presented in results section (see *Figure 7-11).*

1.3.2.1 Grading of diabetic macular edema

In *Table 2* is presented Diabetic Macular Edema Disease Severity Scale according to Wilkinson et al. (2003). Based on this grading scale, DME will be graded as mild, moderate or severe depending on its location in relation to the center of the macula. This grading scale has been created by same panel of specialists who developed the Diabetic Retinopathy Severity Scale presented earlier in *Table 1*. International Council of Ophthalmology (ICO) guidelines include even more simplified grading of DME. It categorizes DME as follows: no DME, noncentral-involved DME or central-involved DME (The International Council of Ophthalmology, 2017.)

Table 2 Diabetic Macular Edema Disease Severity Scale

Proposed Disease Severity Level	Findings Observable on Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent thickening or hard exudates in posterior pole
If diabetic macular edema is present, it can be categorized as follows:	
Proposed Disease Severity Level	Findings Observable on Dilated Ophthalmoscopy*)
Diabetic macular edema present	- Mild diabetic macular edema: Some retinal thickening in posterior pole but distant from center of the macula - Moderate diabetic macular edema: Retinal thickening or hard exudates approaching the center of the macula but not involving the center of the macula - Severe diabetic macular edema: Retinal thickening or hard exudates involving the center of the macula

***)** Hard exudates are sign of current or previous macular edema. Diabetic macular edema 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

(Wilkinson et al., 2003)

The most severe form of DME is clinically significant macular edema (CSME). Depending on the baseline visual acuity, the risk of moderate visual loss increases about 30% to 50% in patients with clinically significant macula edema (Mackenzie et al., 2011; Virgili et al., 2015.)

Macular edema is clinically significant when at least one of the following criteria is present:

a) Retinal thickening at or within 500 micrometers of the center of the macula.
b) Hard exudates at or within 500 micrometers of the center of the macula with adjacent thickening of the retina
c) One disc area of retinal thickening any part of which is within one disc diameter of the center of the macula (Bhagat et al., 2009; Virgili et al., 2015.)

1.3.2.2 Treatment of diabetic retinopathy and diabetic macular edema

Maintaining the blood glucose, blood pressure and blood cholesterol levels as normal as possible is the first step in treatment of diabetes itself, but also in diabetic eye disease. On early stage, DR does not necessarily require other treatment but must be monitored strictly by an eye specialist in case of progression. The treatment is based on severity and findings (D. Browning et al., 2018; The Finnish Medical Society Duodecim, 2014.) In DME, the treatment must be considered if central vision is threatened (The Finnish Medical Society Duodecim, 2014).

In laser treatment, a beam of high-intensity light is directed into the eye. *Photocoagulation* (focal laser treatment) stops or slows leakage of fluid and blood from abnormal blood vessels in the retina. Focal laser cannot be performed on blood vessels directly under the center of the macula, because laser burns can destroy healthy retinal tissue as well (Bhagat et al., 2009; D. Browning et al., 2018.)

In pan-retinal photocoagulation (scatter laser treatment) the parts of the retina outside the macula are treated with laser and it is indicated especially in proliferative diabetic retinopathy. DME may temporarily precipitate or worsen due to photocoagulation so in less severe cases, when laser treatment is required but not urgent, possible DME should be treated first. Over time, photocoagulation may have positive effect on DME, and vision may be improved (The Finnish Medical Society Duodecim, 2014.)

Focal laser treatment may prevent DME from worsening, but intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is more effective and can decrease edema. The anti-VEGF drugs (e.g. Avastin, Eylea and Lucentis) inhibit the particular protein which stimulates the growth of neovascularization (Bhagat et al., 2009; D. Browning et al., 2018; The Finnish Medical Society Duodecim, 2014.)

Intravitreal steroids have also been found to be an effective treatment for DME, but they may have side-effects. The steroids have been associated with cataract and glaucoma in some patients. The steroids are injected into the vitreous in same way than anti-VEGF drugs. Nowadays, steroids are injected as implants instead of crystalline form, which enables longer effect (Bhagat et al., 2009; D. Browning et al., 2018; W. Wang et al., 2018.)

Pars plana vitrectomy may be considered in patients with VMT, ERM, vitreous haemorrhage, combined traction-rhegmatogenous retinal detachment or traction-induced macular detachment of recent onset (Bhagat et al., 2009; D. Browning et al., 2018; The Finnish Medical Society Duodecim, 2014).

1.4 Screening of diabetic retinopathy

According to Buch et al. (2004), DR was the second most common reason of visual impairment among Scandinavian people younger than 65 years . It is crucial for people with diabetes to have regular eye examinations but approximately only 60% of people with diabetes follow this recommendation. People with type 2 diabetes should have their first comprehensive eye examination instantly when they are diagnosed (Flaxel et al., 2019.)

There are variations in recommendations of screening of DR between countries (Stefánsson et al., 2000). Recommendations for interval of dilated eye examinations have been mainly based on the severity of DR and also, according to some guidelines, on duration of diabetes (D. S. Fong et al., 2004; Stefánsson et al., 2000). According to the ICO guidelines, the screening should at least include measuring of visual acuity and fundus examination which enables classification of DR, like fundus photography (The International Council of Ophthalmology, 2017).

In Finland, screening interval is three years as long as there are no signs of DR. If patient has minor findings outside of fovea, fundus examination must be performed in every second year. In more severe cases, yearly or more often if necessary (The Finnish Medical Society Duodecim, 2014.) According to Norwegian guidelines, also patients with no changes, should be examined in every second year (Norwegian Directorate of Health, 2018).

The optimal time for treatment is before significant visual symptoms occur but a great number of patients who have vision threatening disease, like diabetes, may be asymptomatic. The systematic screening is the only way to ensure that as many of these patients as possible will be reached in time (D. S. Fong et al., 2004; Stefánsson et al., 2000.) With proper screenings of DR and DME, it is possible to decrease and prevent visual impairment and maintain better quality of life. Despite of early diagnose and treatment, vision loss is still possible but e.g. in Iceland, a systematic screening program has been successful; blindness among diabetics has decreased. Screening is also very cost-effective for society (Fong, Aiello, Ferris, & Klein, 2004; Goh et al., 2016; Porta & Bandello, 2002; Stefánsson et al., 2000.)

The screening of DR has relied on fundus photography. Defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group, the gold standard is stereoscopic color fundus photography in 7 standard fields (30°) but it is very time consuming, uncomfortable for the patient and require highly skilled examiner. On that account, most commonly used method is to take 2 or 3-fields. Since fundus photography is 2-dimensional, it is difficult to identify DME, the most feared ocular complication in diabetes and the major cause of vision loss among people with diabetes (Goh et al., 2016; C. S. H. Tan, Chew, Lim, & Sadda, 2016; Vujosevic et al., 2011; Y. T. Wang, Tadarati, Wolfson, Bressler, & Bressler, 2016.)

1.4.1 Grading of DME from fundus photography

Without 3-dimensional view, graders are looking for e.g. hard exudates as a sign of DME. It has been found that hard exudates very likely have an association with retinal thickening (Goh et al., 2016; Strøm, Sander, Larsen, Larsen, & Lund-Andersen, 2002; Virgili et al., 2015.) Unfortunately, this can lead both over- and underestimations as e.g. Mackenzie et al. and Wang et al. found in their studies comparing optical coherence tomography (OCT) and fundus photo (Mackenzie et al., 2011; Y. T. Wang et al., 2016). From a cost-effectiveness point of view it is both important to get patients to treatment early enough and also reduce unnecessary referrals (Goh et al., 2016). There are several different grading systems for maculopathy based on fundus photography. Definitions of DME have slight differences between different systems but common to all is presence of hard exudates. Three different systems are introduced in *Table 3*.

Table 3 Grading systems for maculopathy from fundus photography

	DME	CSME
MESA*	Hard exudate in the presence of aneurysms or blot haemorrhages within 1 disc diameter from the center of the macula or presence of focal photocoagulation scars in the macular area	Macular edema involving or within 500 microns of the foveal center or the presence of focal photocoagulation scars in the macular area
NHANES**	Rings of organized hard exudates, localized areas of color change or the deviation of the normal pathway of the retinal blood vessels in the macular area	Edema involving or within 500 microns of the fovea or presence of ≥ 1 disc size area of edema with at least a portion of it within the macula
ENSP***	Exudate within 1 disc diameter (DD) of the centre of the fovea, or circinate or group of exudates within the macula, or retinal thickening within 1 DD of the centre of the fovea (if stereo available), or any microaneurysm or haemorrhage within 1 DD of the centre of the fovea only if associated with a best VA of (if no stereo) 6/12 or worse	

***)** Multi-Etchnic Study of Atherosclerosis
****)** National Health and Nutrition Examination Survey
*****)** English National Screening Programme

(Mackenzie et al., 2011; Y. T. Wang et al., 2016; Wong et al., 2006)

1.4.2 Optical coherence tomography

OCT technology has improved significantly since it was first introduced. For instance, the capability of Time Domain-OCT is 400 A-scans per second with axial resolution 8-10 microns, spectral-domain OCT (SD-OCT) can perform up to 70 000 A-scans per second and reach axial resolution of 5-7 microns. Higher acquisition speed enhances the resolution and enables even more detailed imaging of the retina (Murakami & Yoshimura, 2013; Sabouri, Kazemnezhad, & Hafezi, 2016.)

OCT is a non-invasive and rapid method to get detailed cross-sectional images from the retina and it is especially good when detecting and monitoring DME. Unlike conventional biomicroscopy, OCT enables objective and quantitative evaluation of DME (Lumbroso & Rispoli, 2015, p. 163; Murakami & Yoshimura, 2013; Virgili et al., 2015.) The Macular Thickness Analysis of Cirrus HD-OCT, which was used in current study, provides retinal thickness values (from ILM to RPE) from all 9 ETDRS subfields (see *Figure 1* in Methods section). The values are compared to a normative data within the built-in software. Color coding gives indications when the thicknesses are outside or within expected values, where green indicates normal thickness value, yellow is considered as borderline and red is outside normal limits (Carl Zeiss Meditec, Inc., 2011.)

It is not possible to diagnose macular edema without a binocular view of the retina. It is also very challenging to determine exact retinal thickness from stereo fundus photographs. It is dependent of both quality of photographs and stereopsis of the examiner. Due to these challenges, thickening has been sometimes underestimated compared to binocular ophthalmoscopy. Strøm et al. (2002) compared subjective (stereo fundus photographs) and objective (OCT) evaluation of DME in their study. They found exact agreement in 84.1% of the cases. When considering how rapid and both patient- and operator-friendly method OCT is, these results support OCT is useful and reliable device for detecting diabetic macula edema. There are also several other studies which support that OCT could be useful in screening of diabetic maculopathy and retinopathy (Mackenzie et al., 2011; G. Tan, Cheung, Wong, & Lamoureux, 2018; Y. T. Wang et al., 2016.)

1.5 Visual function

DME can deteriorate visual function. Patients suffering from DME may report decreased visual acuity (VA) and metamorphopsia but the most optimal time for treatment is actually before significant visual symptoms. Though treatment of diabetes and diabetes-related eye conditions have improved, early diagnose has a very significant role in what kind of the outcome will be (Porta & Bandello, 2002; Stefánsson et al., 2000.) Changes in visual function, e.g. contrast sensitivity, color vision and visual fields, can occur in patients with diabetes before any clinical sign of diabetic retinopathy (Chous, Richer, Gerson, & Kowluru, 2016).

Determination of visual acuity is the most common functional test performed in every day clinical practice. It is considered as kind of a gold standard for vision testing but it is really inadequate to reflect visual function. Functional vision describes how person functions in vision-related situations and how sight impacts on quality of life (Midena & Vujosevic, 2015.)

According to the Diabetic Retinopathy Clinical Research Network, there seems to be only modest correlation between VA and center point thickness of the macula measured with OCT. Macular thickness is only one of the several factors affecting on VA. Many people with normal macular thickness may have reduced vision and also many people with edema may have good visual acuity (Aiello, 2007.) However, relationship between macular thickness and visual acuity seems to vary between different studies and also more significant correlations have been found (Alkuraya, Kangave, & Abu El-Asrar, 2005; Hannouche et al., 2012).

2 Methods

2.1 Research questions and significance

2.1.1 Primary goal

The main objective of the study was to screen people with type 2 diabetes and find out how many subjects have current diabetic macula edema and also to compare different screening equipment by means of fundus photography and OCT when evaluating macular edema.

The main objective was based on the following research questions:

1. How many people with type 2 diabetes have diabetic macular edema measured with OCT?

2. How many people with type 2 diabetes have diabetic macula edema measured with monocular macula centered fundus photo?

3. How many people with type 2 diabetes have diabetic macular changes with or without DME?

4. Is there any difference in the prevalence of subjects with macular edema when comparing two imaging methods, OCT and fundus photography?

2.1.2 Secondary goal

The secondary objective was to investigate and describe visual function and in subjects with DME.

The secondary objective was based on the following research question:

1. In subjects with DME, is the visual function measured with Amsler and visual acuity test chart affected?

2.1.3 Significance

Optometrists meet a wide range of patients in their daily work and have a great opportunity to assess patients with diabetes. The main emphasis of this study was to measure the prevalence of

DME, and to compare monocular macula-centered fundus photo with OCT when evaluating DME. In clinical guidelines for screening for DR, fundus photography is still the gold standard. The comparison done in this study will add information if OCT could be a more useful tool in screening of DME. Secondary purpose was to investigate and describe visual function and subjective symptoms among patients with DME. This study will add information that is useful for the optometrist who can take part of the screening and follow-up of people with diabetes in the future. Nowadays, many private optometric clinics have applicable facilities for screening since fundus cameras and OCT have become more common in past few years and optometrists´ clinical skills have improved due to higher education. The study by Lundmark and Luraas (2017) supports this. Agreement between referrals and medical reports was nearly 80% (Lundmark & Luraas, 2017). Co-operation between optometrists and ophthalmologists should definitely be improved in the future. Optometrists could ease the increasing workload of ophthalmologists by participating the screening of DR and e.g. following up mild cases of DR.

2.2 Study design

This is a cross-sectional study which is part of a larger study "Diabetes, Vision and Ocular Health" at University of South-Eastern Norway (USN).

Study sample consisted of Norwegian subjects over 18 years diagnosed with type 2 diabetes.

2.3 Recruitment

Subjects were recruited through different routes. Patients diagnosed with type 2 diabetes who came to an eye examination at National Centre for Optics, Vision and Eye Care at University of South-Eastern Norway in Kongsberg were invited to attend to the study. Members of the Norwegian Diabetes Association in the counties Buskerud, Telemark and Vestfold were sent a written invitation and there were also held four lectures in these counties. Optometric practices in Buskerud, Telemark and Vestfold were also asked to recruit their patients who have type 2 diabetes. Practices were contacted both by e-mail and telephone by members in the research group. In addition, posters with contact information were sent to the optometric practices, and posters were hung up in all general practitioners` clinics in Kongsberg.

2.4 Inclusion criteria

Test subjects were recruited and examined consecutively. Both women and men over 18 years, who have diagnosed with type 2 diabetes and who provided an informed consent were included into the study. Subjects had also to be able to come to Kongsberg for testing.

2.5 Exclusion criteria

1. Participant was excluded from the study if he or she was so mentally or physically restricted that co-operation and examination was too difficult.

2. Insufficient quality of measurements e.g. bad quality fundus photos or OCT images were excluded when analyzing data.

3. Eyes with other retinal conditions, e.g. epiretinal membrane (ERM) and age-related macular degeneration (AMD), which may interfere the evaluation of DME and have influence on visual function, were excluded from analysis.

2.6 Measurements

All participants were examined at the National Centre for Optics, Vision and Eye Care at University of South-Eastern Norway in Kongsberg. All participants underwent a standard optometric examination and ocular and medical history was collected. In addition to this, fundus photo and ocular coherence tomography of the macula area were taken. All 5 optometrists who collected data were trained observers and were following the same, predefined testing protocol.

All tests were obtained on a same day. The routine eye examination followed the recommended clinical guidelines of Norwegian Association of Optometry (Norwegian Association of Optometry, 2017). The examination procedure included also dry eye- and visual function testing and in addition standardized questionnaires about vision and quality of life. Images of the retina were obtained with fundus photography and optical coherence tomography. Participants were dilated with Tropicamide (0.5%) before fundus examination if there was no contraindication for dilation, like e.g. narrow anterior chamber angle**.** The subjects went through a thorough examination which lasted 3.5 hours included 30 minutes break. Only the measurements that are relevant for this study will be

described in this thesis.

2.6.1 Fundus photography

The fundus was photographed with a digital, Kowa nonmyd 7 fundus camera (Kowa Europe GmBH, Germany), focused on the macula. These macula centered photos (45 degrees field of view) were analyzed on a high-resolution screen Eizo CX 240 24.1 with 100% magnification (1 pixel in photo = 1 pixel in screen). All the images were checked also with red free filter. On first analysis, photos were categorized in two groups; DR changes or no DR changes in macular area. All the images with any diabetes related findings (microaneurysms, hard exudates, dot or blot bleedings, cotton wool spots, neovascularization, venous abnormalities) between the major temporal superior and inferior arcades went through more detailed analysis. Eyes with any signs of retinopathy were also included further analysis even though macula looked clear. All the inadequate quality photos were excluded based on the grading scale presented in *Table 4.*

Table 4 Exclusion/inclusion criteria of fundus photo

	Exposure	Sharpness	Overall quality	Other condition
EXCLUDE	Apparent over/under exposure	Blood vessels in the macula blurry	Structures or some of structures in macula ungradable even with red-free filter	Some other macular condition *
INCLUDE	Good exposure, even brightness	Blood vessels in the macula clear and sharp	Structures in macula clear and gradable in normal mode and red-free filter	No other condition in macular area

*) E.g. AMD, ERM, VMT, macular hole and laser scars that might interfere with the evaluation of DME

Images with changes went through more detailed observation subsequently. Early Treatment Diabetic Retinopathy Study group has defined 9 regions which are located in rings with diameters 1, 3 and 6 mm. The innermost 1mm is called central retinal subfield. The 3mm and the 6 mm rings are divided into 4 quadrants; superior, inferior, nasal and temporal (Sabouri et al., 2016.) Subfields are presented in *Figure 1.* A tool corresponding with ETDRS grid 1-3-6 was placed on top of the photo (see *Figure 2*). The area of 6 mm was chosen so that it matched with the area measured with OCT.

Calculation of the size of the grid-tool was based on the fact that foveola which corresponds 1 degree is 0.35 mm (Bron, Tripathi, Tripathi, & Wolff, 1997, p. 220; Remington, 2005, p. 84). Based on that 3 degrees is 1.05mm, 9 degrees is 3.15mm and 18 degrees 6.3mm which is close to the 1, 3

and 6 mm in ETDRS grid.

To make the grid correct size on top the photo, there was an extra circle corresponding 15 degrees in the grid tool. From the center of optic nerve head to foveola it is 15 degrees (Garway-Heath, Poinoosawmy, Fitzke, & Hitchings, 2000). The grid was enlarged so 15 degrees circle reached from foveola to the center of optic head. After enlarging, the grid was replaced over the center of the macula.

3

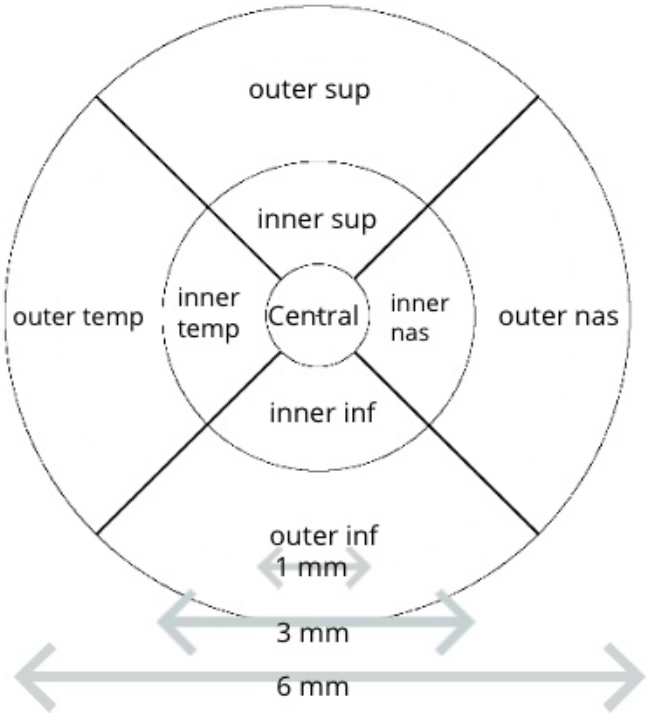


Figure 1 ETDRS zones (right eye)

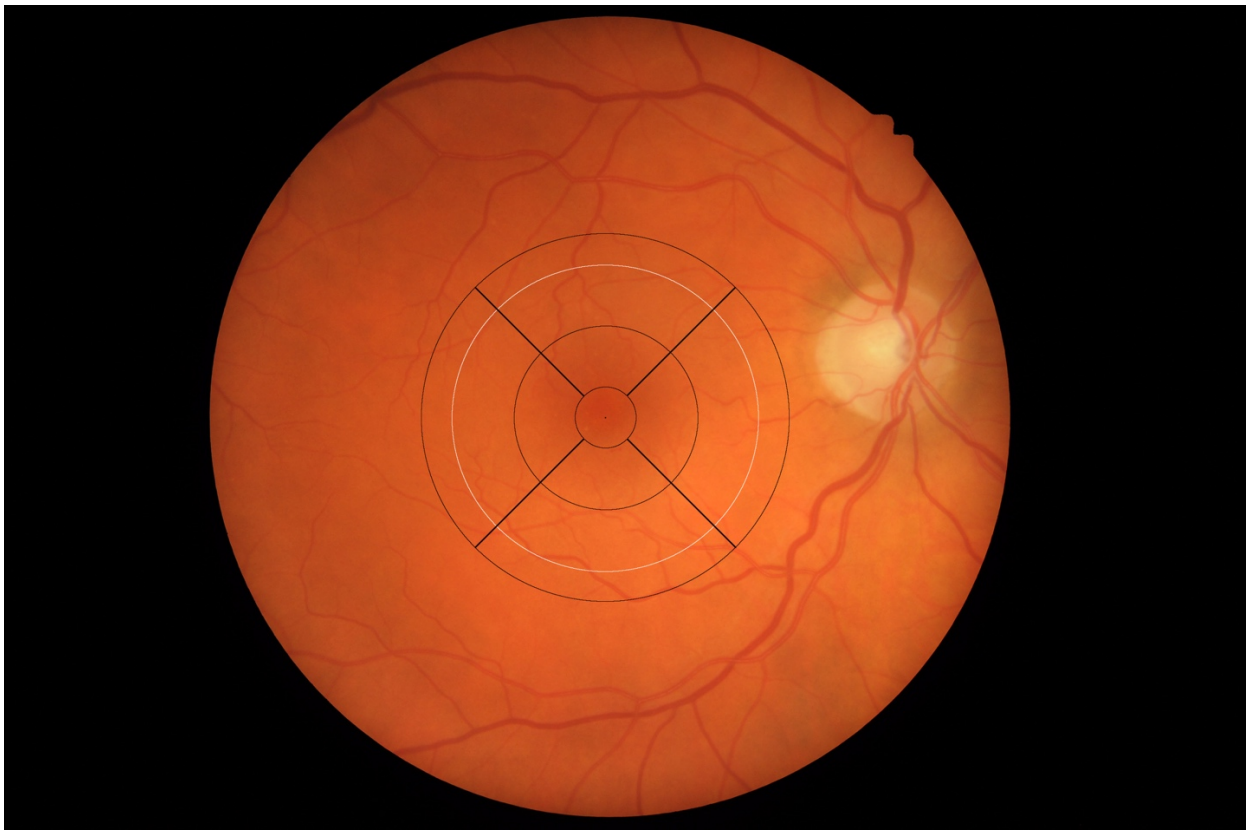


Figure 2 The grid-tool positioned centrally in the fundus photo. The white circle is indicating a diameter of 15 degrees, and the black pattern is ETDRS grid with 1, 3, and 6 mm circles.

The grid size and subfields were verified before analysis that they were consistent with the grid in OCT by comparing the position of the circles with the visible retinal capillaries. Findings in each 9 retinal subfields were then recorded and grading of any DME was made. The classification of DME was based on Multi-Ethnic Study of Atherosclerosis (MESA) definitions (See *Table 3).*

It was crucial to confirm that the area under examination was exactly the same in both the photos and in the OCT images to avoid bias. By means of identifying the zones and findings it is also possible to compare certain subfields to see if findings between these two imaging methods correlate.

The presence of DR was detected from these same macula centered photos (45 degrees field of view) and in addition papilla centered photos were examined to cover wider area from the retina. For example, according to Finnish guidelines, at least two images with 45 degrees field of view must be used in screening of DR (The Finnish Medical Society Duodecim, 2014). DR was not graded, only recorded present or absent. DR was determined as present if any diabetic related signs as described earlier were visible.

2.6.2 Optical coherence tomography

The macular area was measured with HD-OCT Cirrus 5000 (Carl Zeiss Meditec, Germany) and the macular cube 200 X 200 protocol was used. It produces a cube of data through 6mm X 6 mm grid by acquiring 200 horizontal scans each composed of 200 A-scans, except for the central vertical and horizontal scans that are composed of 1000 A-scans each (Al Kharousi, Wali & Azeem, 2013).
All the OCT images were quality checked and categorized in two groups in the same way as the fundus photos; DR changes or no DR changes in macular area. Thickness measurements for all 9 subfields of the ETDRS-grid were noted. Centration and segmentation lines were checked in each scan to confirm the quality. OCT devices automatically detect and delineate the retinal boundaries, but sometimes the software might identify them incorrectly. For instance, advanced retinal condition might cause loss of structure and error in segmentation lines (Lumbroso & Rispoli, 2015, p. 3-4.) If failure in segmentation was only in certain subfield, only those subfields were excluded from the thickness analysis. E.g. if an artefact interfered segmentation in one subfield in outer segment, only that subfield was excluded but both the CST and other thickness values in other subfields were recorded. If the signal strength was less than score 5 (of a maximum of 10), the OCT-

scan was excluded. The grading scale for image quality of OCT images is shown in *Table 5.*

Table 5 The grading of OCT images

	Signal strength	Centration	Segmentation	Other condition
EXCLUDE	Less than 5 of maximum 10	Fovea decentered	Error in segmentation lines	Some other macular condition *
INCLUDE	5 or more of maximum 10	Fovea centered	No error in segmentation lines	No other condition in macular area

*) E.g. AMD, ERM, VMT, macular hole, laser scars, which may affect on macular thickness and disturb evaluation of DME.

Retinal thickness values from ILM (internal limiting membrane) to RPE (retinal pigment epithelium) were recorded from each of the 9 subfields and all the images were scanned through carefully for qualitative findings. Images with any changes indicating an edema were re-analysed later more accurately and grading of DME was made. The location of findings (cysts, diffuse edema, local edema and exudates) were recorded by ETDRS-zones (see *Figure 1)* as for the fundus photos (1, 3, and 6 mm).

Findings that may have influence on the macular thickness were recorded because those had to be excluded from analyses. For example, retinal thickening may occur due to traction from an epiretinal membrane (ERM) (Murakami & Yoshimura, 2013). An example how ERM is affecting on retinal thickness is seen in *Figure 3.* ERM is seen as a thin, hyper-reflective layer in OCT (white arrow). The foveal depression is missing, and retinal thickness has increased in 8 of 9 subfields.

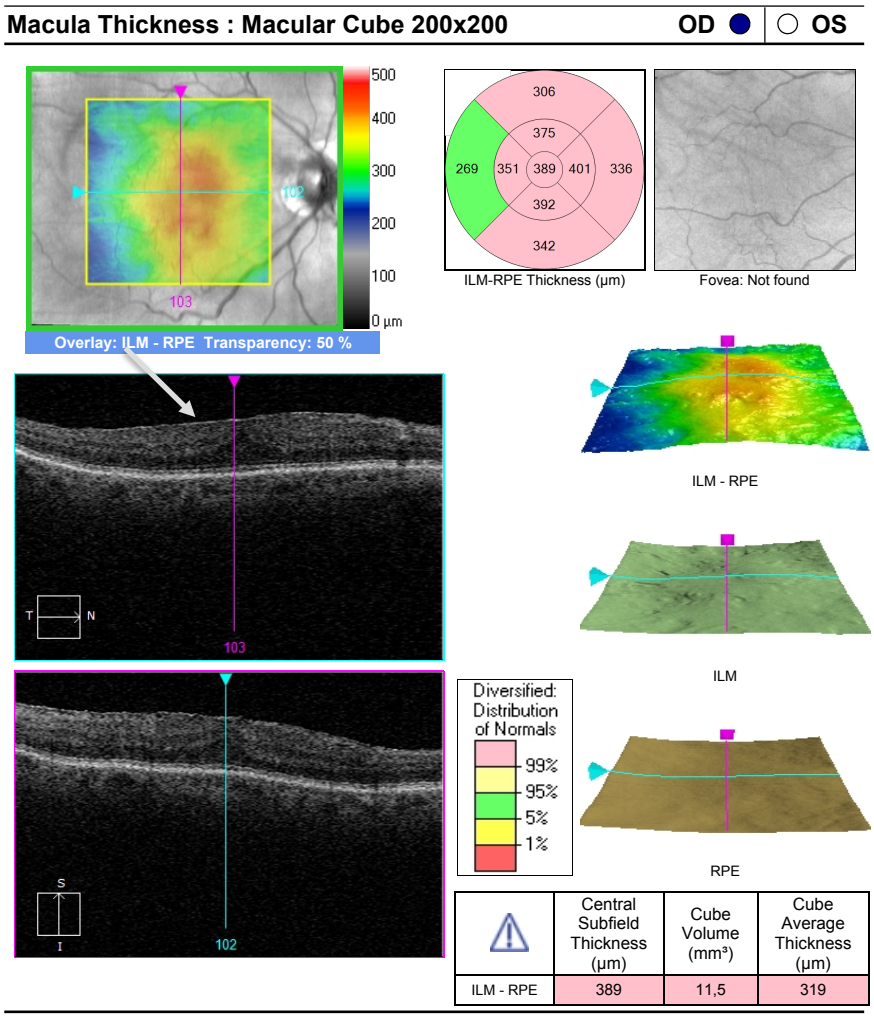


Figure 3 The report shows a Macular Cube 200X200 OCT-scan of a subject with ERM that was excluded from the study. The middle figure, top row (ETDRS-zones), shows that only 1 of 9 subfields is within normal thicknesses (green color). The white arrow indicates the location of the ERM located superficially to the NFL.

2.6.3 Visual function and symptoms

2.6.3.1 Amsler chart

The Amsler chart test was performed monocularly with near correction. Testing distance was 30 cm. Primarily the standard grid was used but if subject was unable to see central white dot, the scotoma chart with additional diagonal lines was used instead. The subject´s eye movements were monitored continuously during testing to assure correct fixation, and the following questions were asked:

Can you see the white dot in the center?

While still focusing on the white dot, can you see all four corners and walls in the big square?

While looking at the white dot, notice the lines. Are there any missing pieces or holes?

Are the lines straight or wavy?

Are all the small squares the same size?

(Bowling et al., 2016, p. 585-586.)

The result was registered as normal or abnormal. Abnormal cases were further categorized as metamorphopsia and visual field loss. Location was not specified in the current study since this was meant for screening, not localizing specific defects.

2.6.4 Visual acuity

Distance and near best corrected visual acuity (BCVA) were measured monocularly and binocularly. The result was recorded in logMAR. BCVA was measured before installation of diagnostic drops. If visual acuity was equal or less than 0.2, it was tested also with pinhole. The refraction was retested when there was an improvement with pinhole to assure correct measurements.

2.7 Analysis and statistical issues

Quantifiable data was transferred and organized in Excel with an anonymous ID-number of each participant. Descriptive analysis of data comprised measures of central tendency (means), measures of spread (standard deviations and ranges) and proportions. Differences between groups were compared by using Welch´s t-test. Statistical significance was set at a level of $p<0,05$. Inter-rater reliability analysis (Cohen`s Kappa) was used to evaluate the agreement between imaging methods when detecting DME. Statistical analysis was performed by IBM SPSS v.26.

2.8 Ethical considerations

The approval for the study was approved by the Regional Committees for Medical and Health Research Ethics (“REK-Sørøst sak 2018/804 Diabetes syn og øyehelse”). The anonymity of the participants is strictly protected. Collected data was properly anonymized. Any names or birth dates were not used but all the participants were created an anonymous ID-number. Collected data was first recorded in a booklet each subject had. Booklets were organized and saved in fire proof safety locker at the University of South-Eastern Norway. All measurements and images were stored in the databases of each instrument. Patient history and the results of routine eye examination and functional tests were saved in patient journal system called Headoptics (ProOptics AS, Norway).

All subjects were informed and explained carefully what kind of measurements will be done and how long it takes. Before any examination started, the purpose of the study was explained, and all participants and observers read and signed a written consent form, which contained all the relevant information about the study and contact information.

All of the procedures were non-invasive and safe and did not cause any pain to the patient. A good and as comfortable position as possible was arranged in every examination. Each participant went through several measurements and visit took about 3,5 hours including a break (30 minutes). If participants needed to have break or they did not feel well, testing was terminated for the time needed or new appointment was scheduled for another day. The participant had right to retreat from the study any time without giving a reason.

If any suspect conditions or pathologies were found, participants were informed about the situation and an appropriate follow up was planned. Participants were referred for further examinations to an optometrist or an ophthalmologist if necessary.

To make sure to get high quality measurements, all subjects were dilated with 0.5% Tropicamide (Chauvin). Before insertion, participant was asked if there has been any allergic reactions or other complications with diagnostic drugs or other medicines. Participants were told beforehand that drops will cause stinging sensation, but it lasts only for some seconds. They were also told that dilation of pupils might cause light sensitivity and blurry vision and normally the pupil size will normalize in a few hours. The participants were recommended to bring sunglasses with them.
The acute angle block is very rare but possible side-effect when using diagnostic drops. To minimize the risk, participants who had narrow anterior chamber angle (Van Herick 1) were not dilated. All participants were informed about side-effects beforehand. In case that some side effects occur after leaving the clinic, they were given written instructions whom to contact.

3 Results

Totally 75 subjects with type 2 diabetes were enrolled in the study. One subject was excluded from all analyses due that all images, both OCT and fundus photos, were inadequate. Mean [SD] age of included 74 patients was 65.28 [9.79] years and 39 (52.7%) were men and 35 (47.3%) women. Duration of diabetes varied between 0-30 years, and with a mean of 10.26 years. 55 (74.3%)

subjects used oral medication for diabetes and 13 subjects (17.6%) had injections. Many subjects had combined treatment and 14 subjects (18.9%) reported having only lifestyle intervention. 13 (17.6%) subjects reported lifestyle intervention as the part of the treatment. The glucose level was self-reported by 64 subjects. The mean [SD] long term glucose level was 6.69 [0.93] Mmol/l. Demographic data is displayed more detailed in *Table 6.*

Table 6 Demographic data

Subjects (n = 74)		
Gender, No. (%)	Men 39 (52.7%)	Women 35 (47.3%)
Age (n=74)	Mean [SD]	Range
	65.28 [9.79]	43-82
Age	Men (n=39)	Women (n=35)
	Mean [SD]	Mean [SD]
	66.54 [10.11]	63.89 [9.36]
Duration of diabetes	Mean [SD]	Range
(n=74)	10.26 [6.67]	0-30
	Men 11.51 [7.05]	Women 8.86 [6.05]
Treatment type*)	Only lifestyle	14 (18.9%)
	Oral medication	55 (74.3%)
	Insulin injections	13 (17.6%)
Glucose level) (n=64)**	Mean [SD]	Range
Mmol/l (%)	6.69 [0.93]	4.1-9.3

*) Some patients had combined treatment, **) Long term glucose level, self-reported

3.1 Prevalence of DME

Total 136 eyes of total 70 subjects met the inclusion criteria and were included when analyzing macular edema measured with monocular macula centered fundus photo. This means that 4 subjects were excluded due to inadequate quality of photos and/or other retinal condition, and in 4 subjects only one eye had appropriate image for grading. When analyzing macular edema measured with OCT, total 123 eyes of total 69 subjects were included to the analysis. In total 9 OCT images and 9 fundus photos were excluded because of inadequate quality and 15 OCT images and 3 fundus photos due to other retinal condition which interfered grading of edema. The number of excluded eyes and reasons for exclusion are presented in *Figure 4.* Other conditions included age-

related macular degeneration (n=6), epiretinal membrane (n=6), macular hole (n=2), vitreous macular traction (n=1) and scarring due to laser treatment (n=2). Macular holes appeared in the presence of the ERM. The number of excluded eyes due to other condition was greater in OCT because some of the fundus photos were still gradable despite of mild ERM or drusens.

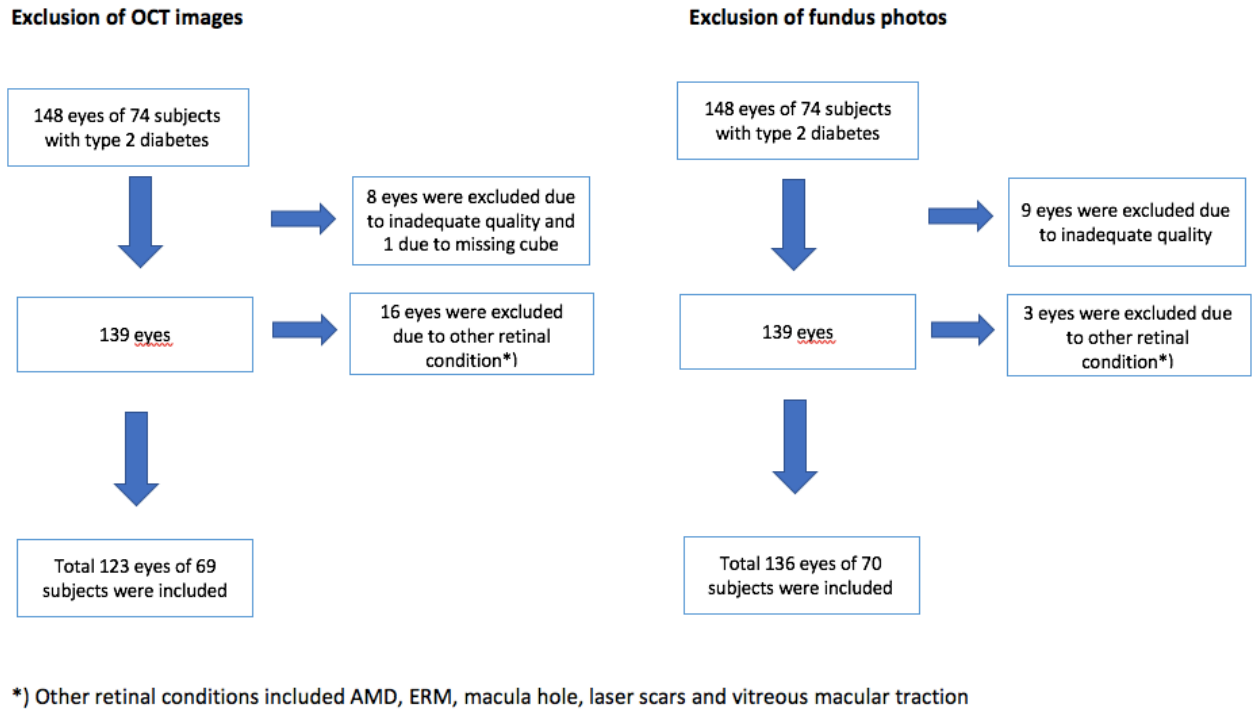


Figure 4 Exclusion of OCT images and fundus photos

Prevalence of DME based on OCT was greater than on fundus photography. Measured with OCT, DME was found in 10 eyes (8.1% of 123 eyes) of total 8 subjects (11.6% of 69 subjects) and with fundus photography in 8 (5.9% of 136 eyes) eyes of total 6 subjects (8.6% of 70 subjects). All findings are presented in ***Table 7.*** Clinically significant macular edema was found in 4 eyes of 3 different subjects. OCT and photo agreed on the presence of CSME in 3 of those 4 eyes (2 subjects). The fundus photos and the OCT images of these two subjects are presented later in the results (see *Figure 7-10).* For the one subject who had CSME in one eye in OCT, methods were not comparable because OCT and photo were not performed the same day. OCT was taken a few weeks later than fundus photo.

3.2 OCT vs fundus photography

There were three participants whose fundus photos and OCT images were not taken in a same day, so they were excluded when analyzing the difference between imaging methods. Eyes without either appropriate OCT image or fundus photo, were also excluded when comparing methods. In total 112 eyes were included in this comparison. One subject had DME in photo according to MESA definitions but in OCT, DME was not visible. In one case, edema was found only in one eye in OCT, though according to photos edema was in both eyes when following MESA definitions. The fundus photo of this subject is presented in *Figure 5.* In 6 eyes (5.4%) there were disagreement between fundus photography and OCT. The inter-rater reliability between photo and OCT was calculated by using Cohen´s Kappa. Computed kappa was 0.596 which indicates moderate agreement and is close to the limit of substantial agreement which is 0.61 (Statistics How To, 2020).

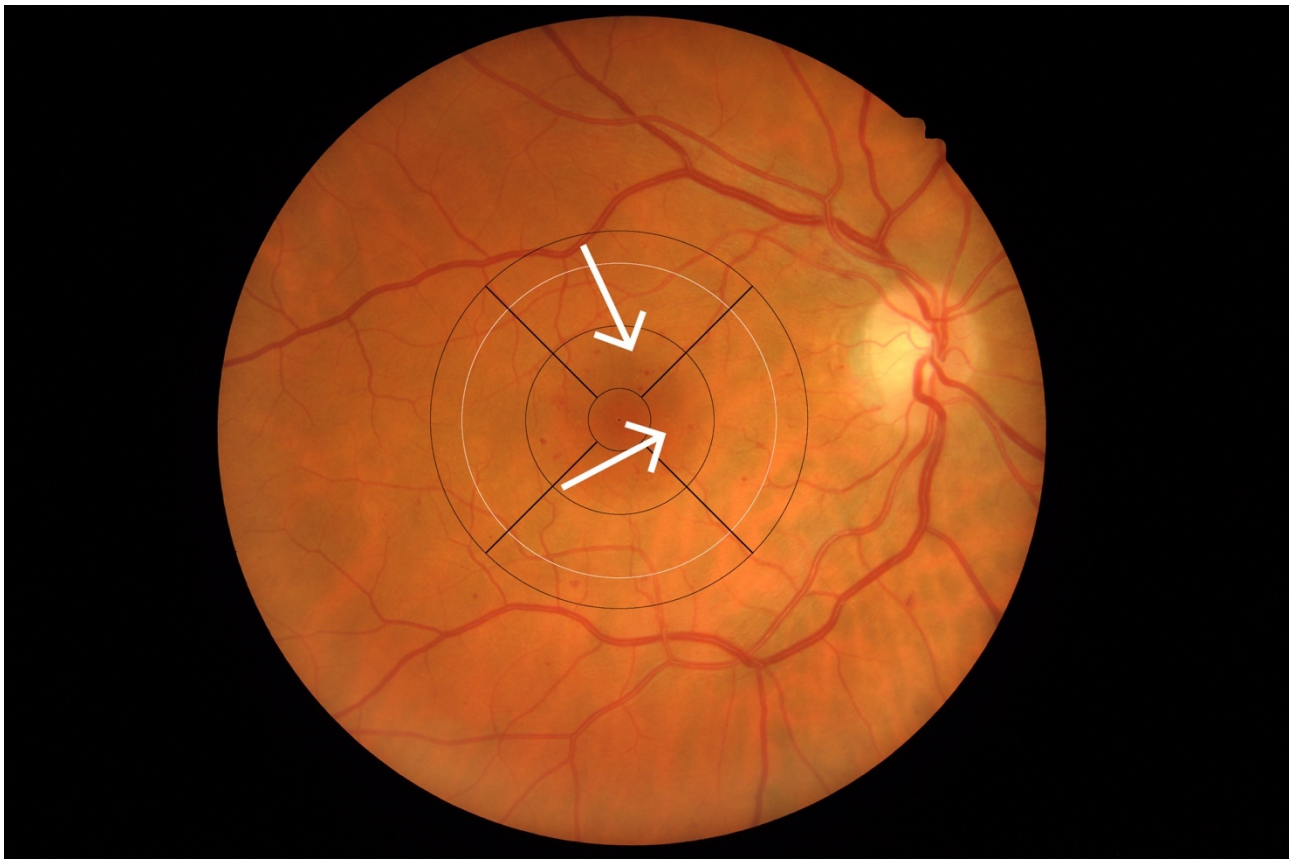


Figure 5 Macula-centered fundus photo in which the MESA definition («hard exudates in the presence of aneurysms or blot haemorrhages within 1 disc diameter from the center of the macula») is fullfilled, but according to OCT, there were no visible signs of edema and retinal thickness was within normal limits in all subfields. White arrows indicate the locations of exudates, dot bleedings and aneurysms. This participant had edema in other eye, which was visible in both OCT and photo.

3.3 Subjects with diabetes related findings

Total 15 subjects (20.1%) of included 74 had some diabetes related changes with or without edema within the 6mm ETDRS grid based on OCT and/or photo. The number of subjects with any DR within 45 degrees field of view and any macular findings (DME or DR) was the same, but not all subjects with any DR had changes in the macular area (within 6mm). This is explained by difference in methods. The presence of DR was determined only from retinal photography when macular findings were detected from photo and/or OCT. So due to these reasons, the prevalence of any DR may be slightly underestimated.

Of the total 74 subjects, 6 subjects had ungradable fundus photos from both eyes and were excluded when evaluating the presence of any DR within the whole macula- and papilla-centered fundus images (45 degrees field of view each). 15 subjects (22.1%) of total included 68 subjects had some stage of DR at least in one eye. Four of included subjects had gradable photos only from one eye. Two of those four subjects had DR in graded eye. There is a chance that other two had DR in the other eye which was excluded due to inadequate quality.

3.4 Macular thicknesses measured with OCT

In Cirrus HD-OCT, threshold for central-involved DME (within 1mm subfield) in women is 290 microns and 305 microns in men. The CST value greater or equal to these threshold values is defined as edema (Wells et al., 2015.) Though DME was detected from 10 eyes with OCT, in only 3 eyes CST was more than threshold (290 µm in women, 305 µm in men). Two eyes with edema had borderline value (over 295 but less than 305 µm) in central subfield. One of them is presented in *Figure* 6. Only in one eye with borderline CST, edema was not present. In ***Table 8*** are presented the CST values of the subjects with DME and also which subtypes of edemas were identified in this sample. Diffuse was the most common and it was found in total 6 eyes. Two eyes had focal edema and cysts were found from two eyes.

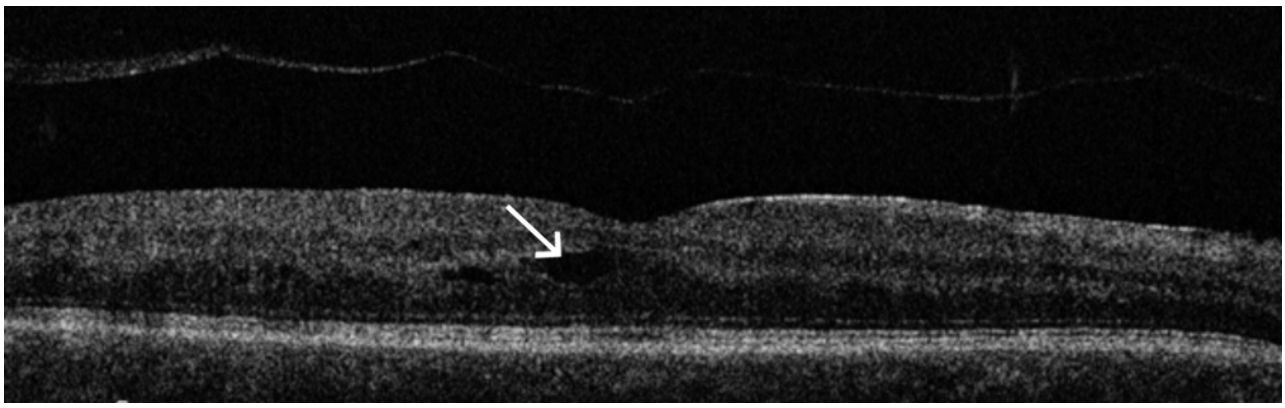


Figure 6 OCT of the subject with edema in central subfield (see the white arrow). Central thickness was 303 µm, which is considered as borderline value in Cirrus HD-OCT. In other subfields, thicknesses were within normal limits.

3.5 Comparison of subjects with and without DME

Due to the unequal sample sizes, Welch´s t-test was used when comparing duration of diabetes and glucose levels between the groups of subjects with and without DME. The duration of diabetes was similar for subjects with DME and subjects with no DME (mean 10.13 years [SD 8.06] and 9.93 [5.85]), respectively. Mean duration was slightly higher (12.00 years [SD 6.66]) in subjects with any diabetes related findings in macula with or without edema. The glucose levels were also similar between subjects with DME and subjects with no DME (6.2 [0.91] and 6.7[0.89] mmol/L). There was no statistically significant difference in duration of diabetes (p= 0.791) or glucose levels (p= 0.163) between subjects with DME and subjects with no DME.

For comparison of the visual function between the groups of subjects with and without DME, only the right eye was chosen for the group without DME and the affected eye for the group with DME, since the two eyes in the same subject are not independent. 2 subjects had edema in both eyes. For them, one eye was chosen by tossing a coin. Welch´s t-test was used also in this comparison, since the number of subjects with DME was so low compared to the group without DME. There was a slight difference in mean BCVA between groups with edema and no edema. The mean [SD] BCVA at distance was -0.07 [0.11] in subjects with no DME (n=51) and -0.03 [0.10] in subjects with DME (n=8). The mean [SD] BCVA at near was 0.03 [0.11] in eyes with no DME (n=52) and 0.07 [0.12] in eyes with DME (n=8). BCVA in eyes with DME was slightly worse both at distance and near than in eyes without DME but difference was not statistically significant either in distance VA (p= 0.27) or near 0.368. The results are presented in ***Table 7***.

Table 7 Results

DME in OCT	8 subjects		10 eyes
(n= 69 subjects, 123 eyes)	(11.6%)		(8.1%)
DME in photo	6 subjects		8 eyes
(n=70 subjects, 136 eyes)	(8.6%)		(5.9%)
CSME (	3 subjects		4 eyes
n=69 subjects, 123 eyes)	(4.3%)		(3.3%)
Changes in the macula* (n=74, 143 eyes)	23 eyes (16.1%)		15 subjects (20.1%)
Prevalence DME	Disagreement in 6		Cohen`s kappa
OCT vs photo	eyes (5.4%)		0.596
(n=69, 112 eyes)	CI 1.2-9.5%)		
Diabetic retinopathy (n=68, 135 eyes)	15 subjects (22.1%)		22 eyes (16.3%)
CST** (µm)	Mean [SD]		Range
(n=69, 123 eyes)	266 [21.51]		216-341
CST women (µm)	Mean [SD]	Threshold for DME	Eyes >290
(n=31, 60 eyes)	260 [19.16]	290	n = 0
CST men (µm)	Mean [SD]	Threshold for DME	Eyes>305
(n= 32, 63 eyes)	272 [22.08]	305	n = 3
CST eyes w/ DME in OCT (µm)	Mean [SD]	Range	
n=8, 10 eyes)	300 [24.81]	267-341	
CST w/o DME in OCT (µm)	Mean [SD]	Range	
n=61, 113eyes)	263 [18.41]	216-296	
Duration of diabetes (years)	Mean [SD]	Range	
Subjects w/ DME (n=8)	10.13 [8.06]	0-20	
Duration of diabetes (years)	Mean [SD)	Range	
Subjects w/o DME (n=45)	9.93 [5.85]	0-30	
Duration of diabetes (years)	Mean [SD]	Range	
Subjects w/ macular findings (n=15)	12.00 [6.663]	0-20	
Glucose level (HbA1c, %) ***)	Mean [SD]	Range	
Subjects w/ DME (n=8)	6.2 [0.91]	5.4-7.5	
Glucose level ***)	Mean [SD]	Range	
Subjects w/o DME (n=38)	6.7 [0.89]	4.1-9.3	
BCVA distance w/DME	Mean [SD]	Range	
(n=8 subjects)	-0.03 [0.11]	-0.2-0.14	
BCVA distance w/o DME	Mean [SD]	Range	
(n= 51 subjects)	-0.07 [0.10]	-0.2-0.44	
BCVA near	Mean [SD]	Range	
subjects w/DME (n=8)	0.07 [0.12]	-0.1-0.24	
BCVA near	Mean [SD]	Range	
Subjects w/o DME (n=52)	0.03 [0.11]	-0.2-0.42	

w/o = without, w = with ***)** Any diabetes related changes (exudates, aneurysms, bleedings, NV, IRMA, venous abnormalities) within the area of 6mm ETDRS grid with or without edema. ****)** Central subfield thickness within 1mm diameter, measured in micron. *****)** Long-time glucose level was self-reported (HbA1c, %)

3.5.1 Visual function in subjects with DME

8 subjects (10 eyes) had DME detected with OCT. More detailed features about those subjects are displayed in *Table 8* . One subject with DME measured with OCT has been excluded from this comparison since OCT imaging was performed a few weeks after other examinations. 2 of these 7 subjects had edema in both eyes and CSME was found in 3 eyes of total 2 subjects. The third one with CSME in this study sample was the excluded subject from comparison analysis. The majority of subjects with DME were men (n=5).

3 of 7 subjects with DME did not reported any symptoms. Two reported only blurry vision, one variable vision and one complained both variable and double vision and floaters. Subjects who did not report any symptoms, neither had any remarkable cataract changes in contrast with other 4 who all had some stage of cataract graded with LOCS III. None of the subjects with DME reported any changes in Amsler chart.

Subjects who had edema only in one eye had generally slightly reduced BCVA both distance and near in the affected eye compared to the other eye. Subject number 4 had diffuse, CSME in both eyes but still excellent BCVA (logMAR); -0.2 OU at distance and 0.0 OU at near. Despite of good visual acuity, this subject experienced the most symptoms. The fundus photo and OCT image of this subject are seen in *Figure 7 and Figure 8.* The visual acuity was affected the most in subject 7 who had focal, CSME in one eye. This subject did not report any symptoms which may be because other eye was healthy. The fundus photo and OCT image of this subject are seen in *Figure 9 and Figure 10.*

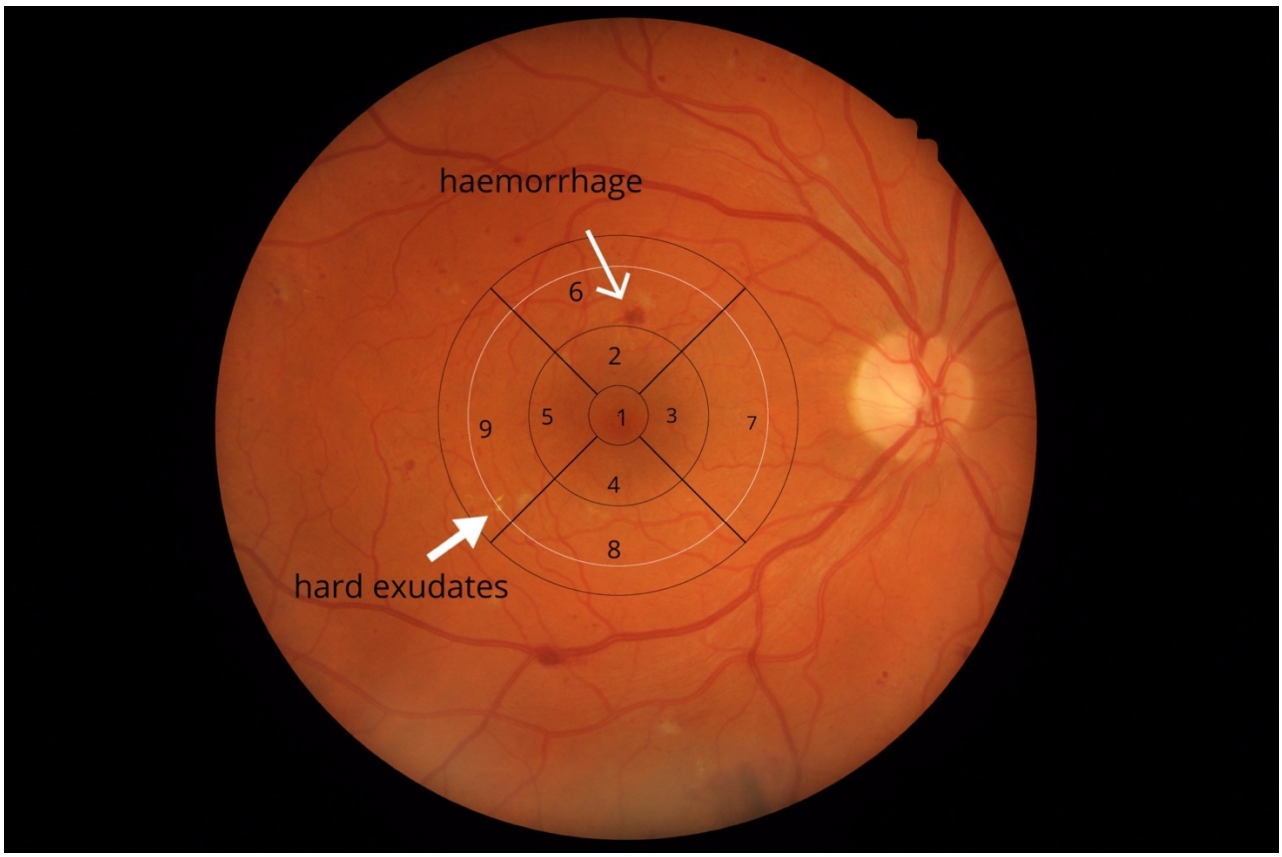


Figure 7 Macula-centered fundus photo of the subject with diffuse DME. Hard exudates (thick arrow) were present in 5 subfields (1, 2, 6, 8 and 9) and large haemorrhage is seen in outer superior (6), near inner superior subfield (2). In one subfield (7) any diabetes related findings were not visible in fundus photo and in addition, subfields 3,4, and 5 appear very clear in this figure. Some aneurysms were identified with magnification and red-free filter in those subfields. This is subject number 4 presented in table 8.

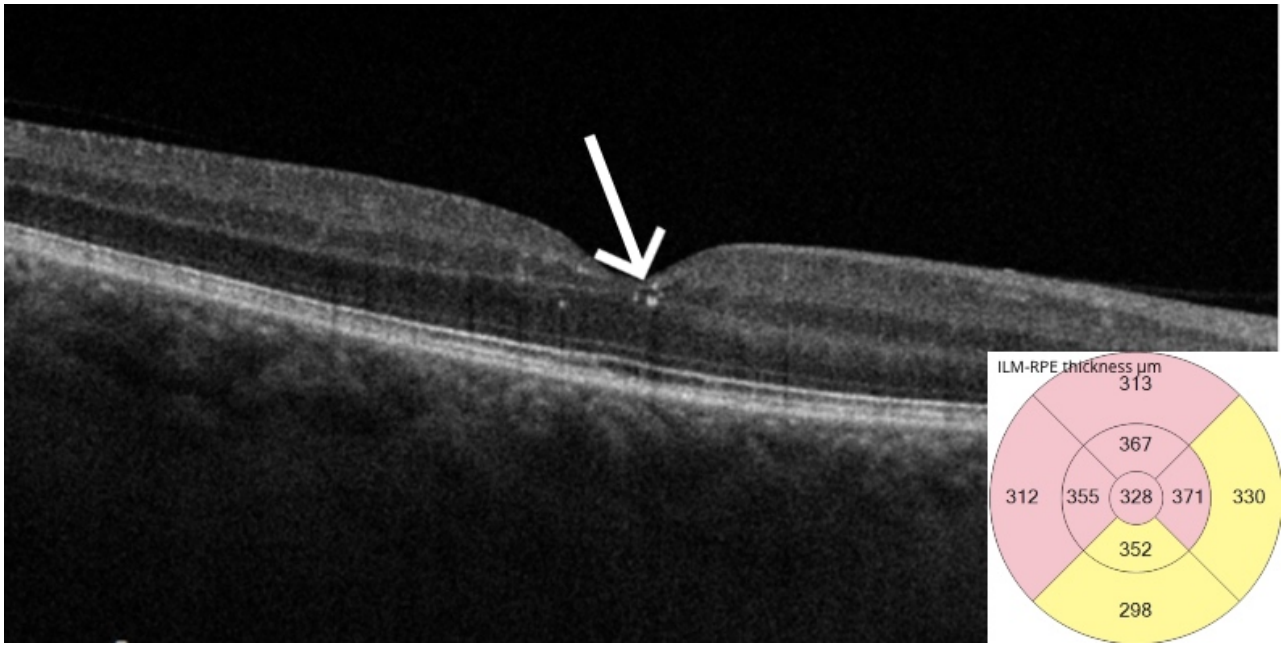


Figure 8 OCT of the same subject (figure 7) with a diffuse DME. Hard exudates (white arrow) are present centrally. The retinal thickness values from ILM to RPE are seen in the ETDRS-figure (to the right in figure) and it shows that all of the subfields are outside normal limits (green). In 3 subfields (yellow) retinal thickness is on borderline. Other 6 subfields are outside of normal limits (red).

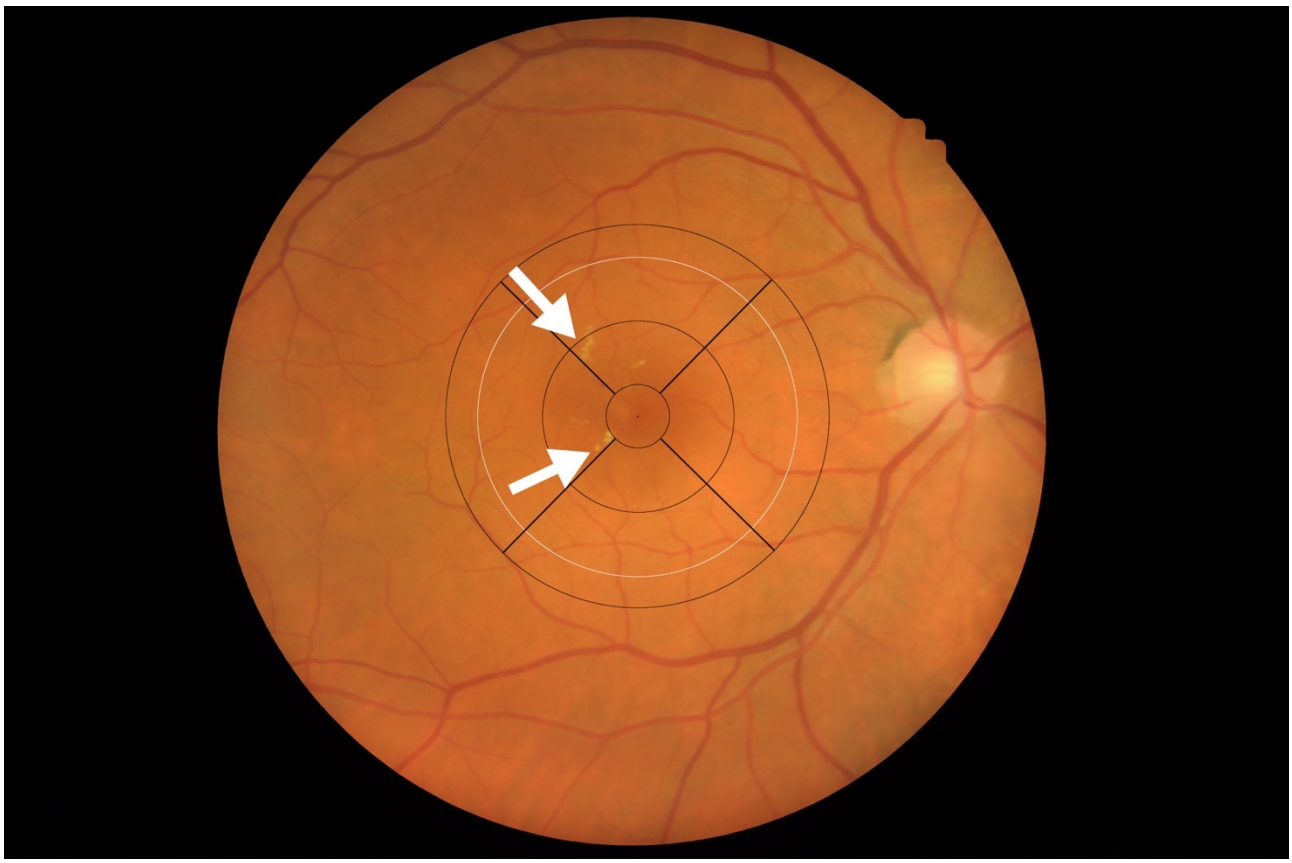


Figure 9 Macula-centered fundus photo of a subject with focal DME. White arrows point out the clumps of hard exudates. This is subject number 7 presented in table 8.

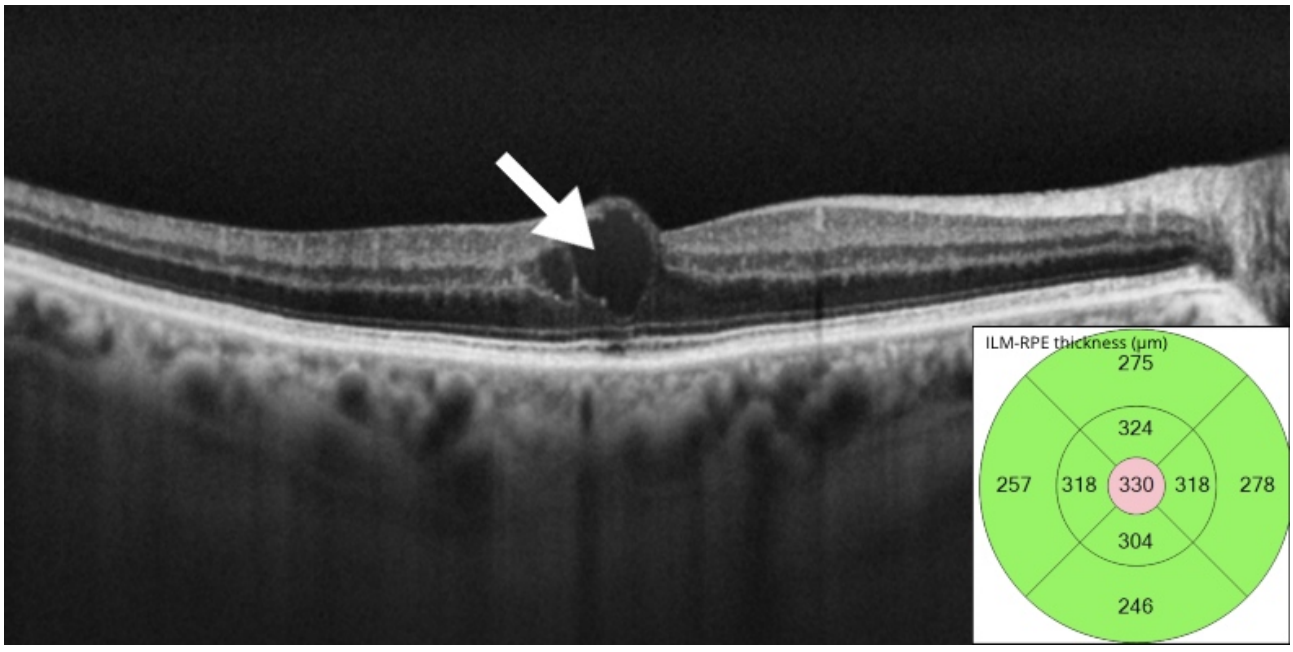


Figure 10 OCT of the same subject (figure 9) with focal DME in the central subfield. White arrow shows the location of the edema. Retinal thickness values from ILM to RPE from all 9 subfields (ETDRS) are seen in the figure to the right. The central subfield thickness is 330 µm and red color indicates that thickness is outside of normal limits.

Without OCT, 4 eyes with DME would not have been detected. In one eye with edema, CST was on borderline and exudates and cysts were found in central subfield. Despite of DME, CST was still within normal limits in 5 eyes. Thickening of the macula occurred in other subfields inside the 6mm ETDRS grid. Those cases could be classified also as subclinical diabetic macular edema (SDME). In *Figure 11* is an example about the subject who has diffuse edema in outer temporal subfield. In addition, thickness values were suspicious in several other subfields.

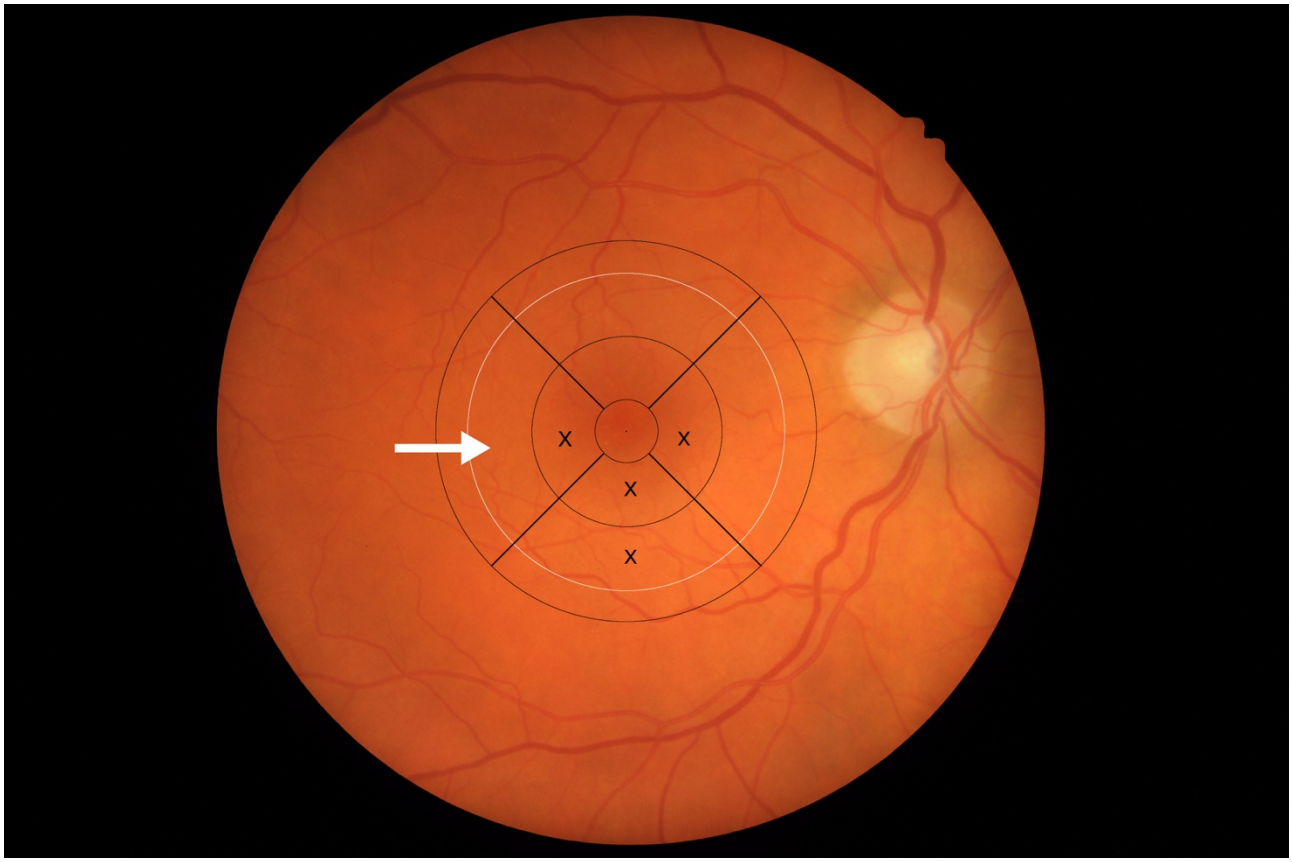


Figure 11 Macula-centered fundus photo of the subject with diffuse/subclinical DME. The white arrow indicates location of the edema. Subfields with borderline thicknesses are marked with «X». Very close observation with red-free filter and magnification revealed some minimal findings (aneurysms and tiny dot bleedings). In this figure these findings are not visible.

There were 2 false positives in photos as mentioned earlier. MESA definitions were fulfilled but OCT revealed no retinal thickening. Hard exudates with bleedings in macular area were present in photo so they were graded as edemas. Whether hard exudates indicate resolved edema or edema is just developing. Both these subjects did have many diabetes-related changes in the macular area and one of them also had edema in other eye. The latter subject was presented earlier in *Figure 5*.

Table 8 Detailed descriptions of the subjects with DME measured with OCT

	Type of edema OD/OS	CST (µm) OD/OS	DME detected with FP	Symptoms	BVCA Distance OD/OS	BCVA Near OD/OS	Amsler OD/OS
Subject 1	Diffuse/-	289/ 284	No gradable image	Blurry vision	0.06/ (0.00)	0.02/ (-0.04)	normal/ (normal)
Subject 2	-/Cysts	296/ 303	no	no	(-0.08)/ -0.08	(0.12)/ 0.02	(normal)/ normal
Subject 3	Diffuse/ diffuse	289/ 290	No/ no	Variable vision	0.00/ 0.00	0.1/ 0.2	normal/ normal
Subject 4	Diffuse/ diffuse	322/ 341	Yes/ yes	Variable vision, double vision floaters	-0.2/ -0.2	0.00/ 0.00	normal/ normal
Subject 5	Focal/-	268/ 268	Yes	Blurry vision	-0.1/ -0.1	-0.1/ -0.1	normal/ (normal)
Subject 6	-/Diffuse, cysts	250/ 267	yes	no	-0.04/ -0.04	0.1/ 0.02	(normal)/ normal
Subject 7	Focal/-	330/ 267	yes	no	0.14/ 0.02	0.24/ -0.1	normal/ (normal)

4 Discussion

The main purpose of this study was to compare retinal photography and OCT when detecting DME to see, could OCT be a useful tool in screening of people with diabetes. The prevalence of DME based on OCT was 11.6% and based on fundus photography 8.6%. The prevalence of DME in this study sample seems to be in concordance with estimations that are reported in the literature. According to the meta-analysis of Yau et al. (2012) the overall age-standardized prevalence of DME was 6.8%. The duration of disease seems to have a significant role. If duration of diabetes was less than 10 years, the prevalence of DME was found to be 3.07% in patients type 2 diabetes. The prevalence increased up to 11.94% with the duration of 10 to 20 years. If duration was over 20

years, the prevalence of DME was as high as 16.47% in patients with type 2 diabetes (Yau et al., 2012.) R. Lee et al. (2015) found the prevalence of DME in type 2 diabetes to vary between 1.4-12.8%. In the review of studies by Williams et al. (2014) the prevalence of CSME varied from 2% up to near 10% in patients with diabetes. In this study sample, the prevalence of CSME was 4.3%.

Total 112 eyes met the inclusion criteria and were included the analysis when comparing imaging methods. Fundus photography and OCT disagreed in 5.4 % of eyes. The inter-rater reliability (Cohen`s kappa) between fundus photography and OCT was 0.596 which indicates moderate agreement and is close to the limit of substantial agreement, 0.61 (Statistics How To, 2020). 2 eyes of total 2 subjects had DME in photo according to MESA definitions, but OCT did not reveal any retinal thickening. Without OCT, 4 eyes with edema would not have been detected. The latter indicates that by means of OCT is possible to find early stage of edemas which cannot be recognized yet clinically. These subclinical diabetic macular edemas are important to find because they have increased risk for developing CSME and need to monitored closely (Virgili et al., 2015). The earlier the edema is identified and treated, the better is prognosis (Porta & Bandello, 2002; Stefánsson et al., 2000).

It is known that race, gender and age affect macular thickness (Sabouri et al., 2016). According to some reports, differences between different OCT devices can be even 50-70 microns regarding retinal thickness in normal individuals, thus comparison of thicknesses between different instruments are not recommended. SD-OCT seem to give significantly higher thicknesses than stratus OCT, which uses an older technology (time-domain OCT). Different kind of anterior-posterior boundaries of the retina is one explanation for these differences (Grover, Murthy, Brar, & Chalam, 2010; Legarreta et.al, 2008; Menke, Dabov, & Sturm, 2009; Sabouri et al., 2016.) For instance, Cirrus HD-OCT, which was used in this study, includes the retinal pigment epithelium in the total thickness but in stratus OCT, the outermost retinal boundary for macular thickness measurements is the inner/outer segment junction (Adhi, Aziz, Muhammad, Adhi, & Li, 2012).

Wang et al. defined the presence of DME in OCT in their study as greater or equal to the threshold values. The values were different between different OCT devices they used and also between men and women (Y. T. Wang et al., 2016.) In this study, in addition to CST, other subfield thicknesses were recorded and evaluated. All images were scanned through carefully for qualitative findings,

and thus not only the thicknesses (quantitative measures) were evaluated. Only 3 eyes of total 10 eyes with DME, had CST over the threshold. 3 eyes were in borderline and 2 of them had edema both being clinically significant. 5 eyes with DME had CST in normal limits and DME would not have been recognized without careful evaluation of scans. Thus, this indicates that a thorough evaluation of each scan, not only evaluating thickness measurements, must be recommended in a clinical setting if OCT is included in DR screening.

Strength of this study is that all the measurements were obtained on same day and with same devices. For example, in the study of Mackenzie et al. (2011) OCT image and fundus photo were taken on separate visits. Wang et al. excluded all the subjects whose OCT image and fundus photo were not performed on a same visit, but OCT images were taken with either Spectral-Domain OCT or Time-Domain OCT, though they had taken into consideration different threshold values between devices (Y. T. Wang et al., 2016.)

Due to technical issues with OCT, 4 participants were scheduled another appointment for OCT measurements. Fundus photo with Kowa was retaken only from one of them so 6 eyes (3 subjects) were excluded from the analysis when the two methods were compared. Changes can occur in short term and one of these excluded cases is a good example. OCT revealed local edema in right eye on a second visit. Based on fundus photo on first visit edema was suspected in outer temporal subfield but central part looked clear. In OCT, there was also local edema in central subfield. Optomap, which is not a part of the current study, was also taken from all participants and in this case on both visits. When going through these images, it revealed that condition had changed during three weeks between appointments. Tiny dot bleeding in the macular area had progressed significantly. This emphasize the importance to do the imaging the same day if any comparison of imaging techniques should be done.

Because of low number of subjects with DME, any statistical conclusions cannot be made but results were similar than in other previous studies. Using only retinal photography in screening can lead both under- and overestimations of the presence of DME (Mackenzie et al., 2011; Y. T. Wang et al., 2016). From the patient's point of view, especially the first one, underestimation, is worrying. The treatment might delay essentially which can lead visual impairment. In turn, false positives may cause unnecessary concern to the patient and extra costs to the society. Visual impairment is

sometimes inevitable but all the vision that can be retained is crucial for person's quality of life. Patients with more severe DR have been reported to have reduced levels of emotional, physical and social wellbeing and poorer quality of life (Goh et al., 2016; The International Council of Ophthalmology, 2017.)

DME can occur at any stage of DR (Arthur et al., 2019; W. Wang et al., 2018). For instance, the subject with focal edema presented in the results section *Figure 9* did not have many diabetes related changes elsewhere in the 45 degrees field of view.

Focal edema has been reported more common than diffuse edema (D. Browning et al., 2018). In this study, diffuse subtype was the most common and was found in total 6 eyes. One the eyes with diffuse edema, had also some cysts. Only in two eyes (1 subject) diffuse edema was clinically significant and other eyes with diffuse edema could also be classified as subclinical edemas. Focal edema was identified from 3 eyes.

Yau at al. (2012) found no substantial difference in the prevalence of DME between males and females in their meta-analysis. In this study, 5 of total 8 subjects with DME were men. Because of low number of subjects, any statistical conclusions about the gender distribution cannot be drawn, but male sex has been considered to be a risk factor for DME severity and men with DR are more likely to develop an edema than women. Due to this, strict monitoring seems to be even more crucial for men (Arthur et al., 2019; Harrison et al., 2011.) The study of Arthur et al. (2019) found that in men with CSME, the central macular thickness is significantly greater than in women. Similar findings have been reported also earlier when Chalam et al. found 16 microns greater central thickness in men compared to women in diabetic subjects without DR or with mild DR (Chalam et al., 2012).

Secondary purpose was to investigate and describe visual function and subjective symptoms among patients with DME. Some subjects with DME reported symptoms, but those subjects also had cataract changes which can also be reason for symptoms, especially for blurry vision. The subject with CSME in both eyes still had very good VA but reported several symptoms. Another subject with CSME and also reduced VA in one eye did not report any symptoms. It is possible that the better

eye compensated for some of this reduced visual function. Other asymptomatic subjects did not have central-involved DME and edema was still very mild and could be classified as SCDME.

In this study sample VA was slightly worse in eyes with DME than in eyes with no DME, but since DME group was so small, any statistical conclusions cannot be made. Though VA was generally worse in subjects with DME, in most cases it was still excellent or only slightly reduced. This supports the findings of The Diabetic Retinopathy Clinical Research Network. They found a modest correlation between visual acuity and OCT-measured macular center point thickness but also pointed out that people with macular edema may have good visual acuity (Aiello, 2007.) Also according to review of Murakami & Yoshimura (2013), there is a modest correlation between central retinal thickness and VA. Relationship between macular thickness and visual acuity seems to vary between different studies and also more significant correlations have been found (Alkuraya et al., 2005; Hannouche et al., 2012). It is useful to measure retinal thickness, for instance, when monitoring the efficiency of the treatment. However, the retinal thickness is only one of the several factors contributing to visual acuity (Aiello, 2007; Deák et al., 2010; Hannouche et al., 2012.)

The features of macular edema correlate with VA according to some studies. VA has been found to be better in diffuse edema than in other subtypes (Alkuraya et al., 2005; Yamamoto, Yamamoto, Hayashi, & Takeuchi, 2001.) When comparing 2 subjects of this study, who both had central-involved edema and similar CST, the subject with diffuse edema had excellent VA, -0.02 (logMAR) in both eyes despite of edema, but in subject with focal edema VA was slightly reduced, 0.14, compared to the other eye (VA 0.02) with no DME. There was no other condition which would have explained the reduced VA but difference in OCT pattern may be one explanation.

The prevalence of DR increases progressively with duration of disease (Porta & Bandello, 2002). The estimated prevalence rate for any degree of DR is 34.6 % worldwide (Flaxel et al., 2019; Yau et al., 2012). In this study sample, the prevalence of DR was a bit lower than global estimates, 22.1%. 20.1% had diabetes related findings in macular area. The prevalence of DR may be slightly underestimated because all the subjects who had gradable photos at least from one eye were included. It is possible they had DR in another eye even though graded eye was healthy. Also, the number of subjects with DR and macular findings was the same but all subjects with DR did not have changes in macula. This is explained by difference in methods and the size of retinal area

evaluated. The presence of DR was determined only from fundus photo (n=68) when macular findings were detected from photo and/or OCT (n=74). This suggests that OCT might have detected some findings which were not visible in fundus photo. In addition, it is possible that some subjects with retinopathy had gradable OCT scans, but fundus photos were inadequate and were excluded.

The global prevalence of diabetes increased from 4.7 % to 8.5% between 1980 and 2014 and unfortunately same trend has continued (Fenner, Wong, Lam, Tan, & Cheung, 2018). This means also more people suffering from diabetic retinopathy and other diabetic related eye problems. In addition, population age structure is changing and there will be all the time more elderly people (Statistics Finland, 2019). The duration of diabetes is one of the risk factors for DR, but aging causes also several other eye conditions. This poses challenges for the society and more resources are needed in order to manage the increasing number of patients. Optometrists could have a significant role when it comes to screening and follow-up of people with diabetes. The clinical skills of optometrists have improved due to education and many private optometric practices have relevant imaging devices for examining e.g. people with diabetes. According to ICO guidelines, screening examination should ideally include refracted visual acuity in addition to retinal imaging and complete ophthalmic examination (The International Council of Ophthalmology, 2017). Unfortunately, the resources of screening are often minimal and only habitual visual acuity is measured when examiners are not optometrists or ophthalmologists. Optometrists could also refract the patients and ensure when reduced visual acuity is actual and not just caused by uncorrected refractive error. By participating in the screening and following up early stage of DR, optometrists would ease the increasing workload of ophthalmologists. It would be also more efficient use of resources. In many countries, optometrists and other professionals can screen patients with DR and other ocular disease (Virgili et al., 2015). According also to ICO guidelines, patients with no apparent or mild non-proliferative retinopathy do not require re-examination by an ophthalmologist (The International Council of Ophthalmology, 2017).

It is challenging to determine exact retinal thickness from stereo fundus photos and thickening is easily underestimated (Strøm et al., 2002). Together with the fundus photography, OCT would provide even more efficient and accurate screening of DR and DME. Performing and evaluating monocular fundus photos and OCT images is more rapid compared to stereoscopic fundus photos. OCT is also an objective method and measures exact retinal thickness and enables easier

monitoring of the condition (Lumbroso & Rispoli, 2015, p. 163; Virgili et al., 2015.) Ophthalmologists can for example evaluate the efficacy of the treatment and make a decision about treatment without seeing and examining every patient personally which saves resources. There are studies which support that OCT could be a useful tool when assessing people with diabetes since it could improve the accuracy of DME detection (Mackenzie et al., 2011; G. Tan et al., 2018; Y. T. Wang et al., 2016). Mackenzie et al. and Wang et al. found that the presence of DME can be under- or overestimated based on monocular fundus photo (Mackenzie et al., 2011; Y. T. Wang et al., 2016). Findings were similar in this current study even though the study sample was small.

One benefit of OCT is that it can enable earlier diagnose. Especially diffuse type of edema is difficult to detect without 3-dimensional view since hard exudates as a landmark of edema are usually not seen (Bowling et al., 2016, p. 524; Scanlon et. al 2009, p. 154). Not to mention SCDME which is impossible to find without OCT. As stated, the ideal time for treatment is before symptoms occur or they are minor (Porta & Bandello, 2002; Stefánsson et al., 2000). Since many patients with DME may not have any symptoms, screening has a significant role in preventing visual impairment and it is justified that OCT should be part of the screening examination.

Since the number of people with diabetes is increasing all the time more efficient screening programs are required to insure early diagnose and treatment to the patients. In addition, it is important to avoid unnecessary referrals to save resources. Not all patients need for immediate referral or treatment so clear guidelines are essential if OCT will be included in screening of people with diabetes in the future.

However, this study had some limitations. Due to the small sample size, the number of eyes with DME was low and results need further consolidation by larger sample before any statistical conclusions can be drawn. Another limitation was that the same person who graded the fundus photos and the OCT images, participated in the conduct of examinations. There is a chance that grader unconsciously remembered some of the subjects. In addition, the same person graded images from both modalities. As the number of eyes with findings was low, there is a chance that the grader remembered findings from other imaging modality though grading was performed at different time points for fundus photos and OCT images to minimize the impact. Ideally, different

graders, who have not taken part of the examinations of the subjects, would have graded the fundus photos and OCT images to avoid bias.

Future studies could focus on other newer imaging modalities, like ultra-wide field (UWF) color fundus photography and autofluorescence (AF) imaging, when detecting DME and DR. Optomap imaging (Model California, Optos Plc, Dunfermline, UK) was part of the larger study "Diabetes, Vision and Ocular Health" at University of South-Eastern Norway (USN) and in addition to color fundus photo, AF imaging was implemented to all participants. The Optos is a scanning laser ophthalmoscope that enables retinal imaging up to 200 degrees in a single image, even without pupil dilation (Fenner et al., 2018). It is demanded several conventional fundus photos to cover as wide field, which is more challenging and time consuming (C. S. H. Tan et al., 2016). Peripheral lesions have been connected with retinal ischemia, the progression of DR and development of proliferative DR (Fenner et al., 2018) and further, correlations between peripheral ischemia and the presence of DME have been reported in the literature (Patel, Messner, Teitelbaum, Michel, & Hariprasad, 2013; Wessel et al., 2012). In turn, increased AF has been connected with DME (C. S. H. Tan et al., 2016). For instance, UWF and conventional fundus photography could be compared in detection of DR and in addition, investigate AF in detection of DME, to see could these imaging modalities be useful tools in screening of people with diabetes in the future.

5 Conclusions

In this study more eyes with DME were detected with OCT than with fundus photography. Cases not detected with fundus photography were diffuse and/or in very early stages. All the clinically significant edemas were detected with both imaging methods.

The prevalence of DME in this sample seems to be in correspondence with global estimation in the literature. This was a cross-sectional study of a diabetic population, and the number of eyes with DME were low. To draw any statistical conclusions about which imaging techniques of OCT and fundus photography that are most reliable to detect DME, further testing including more subjects is warranted. However, the results indicate that OCT detects more cases with edema, and both diffuse and early stage of edema seemed to be harder to define from the photos.

Visual acuity was slightly worse in subjects with DME compared to subjects without DME. The difference was not statistically significant, and since the number of subjects with DME were low, further testing is warranted to draw any conclusion considering the visual function in these subjects.

References

Adhi, M., Aziz, S., Muhammad, K., Adhi, M. I., & Li, T. (2012). Macular Thickness by Age and Gender in Healthy Eyes Using Spectral Domain Optical Coherence Tomography (Macular Thickness by Age and Gender Using SD-OCT). *PLoS ONE, 7*(5), e37638. doi:10.1371/journal.pone.0037638

Aiello, L. P. (2007). Relationship between Optical Coherence Tomography–Measured Central Retinal Thickness and Visual Acuity in Diabetic Macular Edema. *114*(3). doi:10.1016/j.ophtha.2006.06.052

Al Kharousi, N., Wali, U. K., Azeem, S. (2013). Current applications in Optical Coherence Tomography in Opthalmology. In Kawasaki M. (Ed.) *Optical Coherence Tomography.* (6) Retrieved from https://www.intechopen.com/books/optical-coherence-tomography/current-applications-of-optical-coherence-tomography-in-ophthalmology

Alkuraya, H., Kangave, D., & Abu El-Asrar, A. (2005). The correlation between optical coherence tomographic features and severity of retinopathy, macular thickness and visual acuity in diabetic macular edema. *International Ophthalmology, 26*(3), 93-99. doi:10.1007/s10792-006-9007-8

Arthur, B. E., Young, E. S., Elsner, A. A., Baskaran, S. K., Papay, J. J., Muller, P. M., . . . Cuadros, A. J. (2019). Central Macular Thickness in Diabetic Patients: A Sex-based Analysis. *Optometry and Vision Science, 96*(4), 266-275. doi:10.1097/OPX.0000000000001363

Bhagat, N., Grigorian, R. A., Tutela, A., & Zarbin, M. A. (2009). Diabetic Macular Edema: Pathogenesis and Treatment. *Survey of Ophthalmology, 54*(1), 1-32. doi:10.1016/j.survophthal.2008.10.001

Bowling, B., Kanski, J. J., Nischal, K. K., & Pearson, A. (2016). *Kanski's clinical ophthalmology : a systematic approach* (8th ed. ed.). Amsterdam: Elsevier.

Bron, A. J., Tripathi, R. C., Tripathi, B. J., & Wolff, E. (1997). *Wolff's anatomy of the eye and orbit* (8th ed. Anthony J. Bron, Ramesh C. Tripathi, Brenda J. Tripathi. ed.). London: Chapman & Hall.

Browning D.J. (2010). Diabetic Macular edema. In D.J. Browning (Ed.), *Diabetic retinopathy: Evidence-Based Management* (142). New York, NY: Springer

Browning D. J. & Rotberg M. H. (2010). The Relationship of Diabetic Retinopathy and Glaucoma. In D.J. Browning (Ed.), *Diabetic retinopathy: Evidence-Based Management* (325). New York, NY: Springer

Browning, D., Stewart, M., & Lee, C. (2018). Diabetic macular edema: Evidence-based management.(Review Article). *Indian Journal of Ophthalmology, 66*(12), 1736. doi:10.4103/ijo.IJO_1240_18

Buch, H., Vinding, T., La Cour, M., Appleyard, M., Jensen, G. B., & Vesti Nielsen, N. (2004). Prevalence and causes of visual impairment and blindness among 9980 Scandinavian adults: The Copenhagen City Eye Study. *Ophthalmology, 111*(1), 53-61. doi:10.1016/j.ophtha.2003.05.010

Carl Zeiss Meditec, Inc. (2011). Cirrus HD-OCT: How to read the Cirrus reports. Retrieved from https://www.zeiss.co.uk/content/dam/Meditec/gb/Chris/OCT%20Business%20Builder/PDF%27s/1.pdf

Cennamo, G., Romano, M. R., Nicoletti, G., Velotti, N., & Crecchio, G. (2017). Optical coherence tomography angiography versus fluorescein angiography in the diagnosis of ischaemic diabetic maculopathy. *Acta Ophthalmologica, 95*(1), e36-e42. doi:10.1111/aos.13159

Chalam, K. V., Bressler, S. B., Edwards, A. R., Berger, B. B., Bressler, N. M., Glassman, A. R., . . . Orr, P. R. (2012). Retinal thickness in people with diabetes and minimal or no diabetic retinopathy: Heidelberg Spectralis optical coherence tomography. *Investigative ophthalmology & visual science, 53*(13), 8154-8161. doi:10.1167/iovs.12-10290

Chous, A. P., Richer, S. P., Gerson, J. D., & Kowluru, R. A. (2016). The Diabetes Visual Function Supplement Study (DiVFuSS). *British Journal of Ophthalmology, 100*(2), 227. doi:10.1136/bjophthalmol-2014-306534

Deák, G. G., Bolz, M., Ritter, M., Prager, S., Benesch, T., & Schmidt-Erfurth, U. (2010). A systematic correlation between morphology and functional alterations in diabetic macular edema. *Investigative ophthalmology & visual science, 51*(12), 6710-6714. doi:10.1167/iovs.09-5064

Fenner, B., Wong, R., Lam, W.-C., Tan, G., & Cheung, G. (2018). Advances in Retinal Imaging and Applications in Diabetic Retinopathy Screening: A Review. In (pp. 333-346). Cheshire.

Flaxel, C. J., Adelman, R. A., Bailey, S. T., Fawzi, A., Lim, J. I., Vemulakonda, G. A., & Ying, G.-S. (2019). Diabetic Retinopathy Preferred Practice Pattern®. *Ophthalmology*. doi:10.1016/j.ophtha.2019.09.025

Fong, D., Aiello, L., Ferris, F., & Klein, R. (2004). Diabetic Retinopathy. *Diabetes Care, 27*(10), 2540-2553.

Fong, D. S., Aiello, L., Gardener, T. W., King, G. L., Blankenship, G., Cavallerano, J. D., . . . Klein, R. (2004). Retinopathy in diabetes.(Position Statement). *Diabetes Care, 27*(1), S84.

Garway-Heath, D. F., Poinoosawmy, D., Fitzke, F. W., & Hitchings, R. A. (2000). Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology, 107*(10), 1809-1815. doi:10.1016/S0161-6420(00)00284-0

Goh, J. K. H., Cheung, C. Y., Sim, S. S., Tan, P. C., Tan, G. S. W., & Wong, T. Y. (2016). Retinal Imaging Techniques for Diabetic Retinopathy Screening. *Journal of Diabetes Science and Technology, 10*(2), 282-294. doi:10.1177/1932296816629491

Grover, S., Murthy, R. K., Brar, V. S., & Chalam, K. V. (2010). Comparison of retinal thickness in normal eyes using Stratus and Spectralis optical coherence tomography. *Investigative ophthalmology & visual science, 51*(5), 2644. doi:10.1167/iovs.09-4774

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice, 103*(2), 137-149. doi:10.1016/j.diabres.2013.11.002

Hannouche, R. Z., Avila, M. P. d., Isaac, D. L. C., Silva, R. S. C. E., Rassi, A. R., & Hannouche, R. Z. (2012). Correlation between central subfield thickness, visual acuity and structural changes in diabetic macular edema. *Arquivos brasileiros de oftalmologia, 75*(3), 183-187. doi:10.1590/S0004-27492012000300007

Harrison, W. W., Bearse, M. A., Schneck, M. E., Wolff, B. E., Jewell, N. P., Barez, S., . . . Adams, A. J. (2011). Prediction, by retinal location, of the onset of diabetic edema in patients with nonproliferative diabetic retinopathy. *Investigative ophthalmology & visual science, 52*(9), 6825. doi:10.1167/iovs.11-7533

Hasan S. A. (2010). The Cornea in Diabetes Mellitus. In D.J. Browning (Ed.), *Diabetic retinopathy: Evidence-Based Management* (347-348). New York, NY: Springer

Helmy, Y., & Atta Allah, H. (2013). Optical coherence tomography classification of diabetic cystoid macular edema. *Clinical Ophthalmology, 2013*(default), 1731-1737.

Henke, S., Papapostolou, I., Heimes, B., Lommatzsch, A., Pauleikhoff, D., Spital, G., & Henke, S. (2018). [OCT-Angiography in diabetic maculopathy : Comparison between microaneurysms and the foveal avascular zone with flourescein angiography]. *Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft, 115*(11), 941-947. doi:10.1007/s00347-017-0605-9

Internetional Diabetes Federation. (2020). Type 2 diabetes. Retrieved from https://www.idf.org/aboutdiabetes/type-2-diabetes.html

Jeganathan, V., Wang, J., & Wong, T. (2008). Ocular associations of diabetes other than diabetic retinopathy. In *Diabetes Care* (Vol. 31, pp. 1905-1912).

Kilstad, H. N., Sjølie, A. K., Gøransson, L., Hapnes, R., Henschien, H. J., Alsbirk, K. E., . . . Bergrem, H. (2012). Prevalence of diabetic retinopathy in Norway: report from a screening study. *Acta Ophthalmologica, 90*(7), 609-612. doi:10.1111/j.1755-3768.2011.02160.x

Lee, C. S., Lee, A. Y., Sim, D. A., Keane, P. A., Mehta, H., Zarranz-Ventura, J., . . . Tufail, A. (2015). Reevaluating the Definition of Intraretinal Microvascular Abnormalities and Neovascularization Elsewhere in Diabetic Retinopathy Using Optical Coherence Tomography and Fluorescein Angiography. *American Journal of Ophthalmology, 159*(1), 101-110.e101. doi:10.1016/j.ajo.2014.09.041

Lee, R., Wong, T., & Sabanayagam, C. (2015). Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis., 2*(1). doi:10.1186/s40662-015-0026-2

Legarreta JE, Gregori G, Punjabi OS, Knighton RW, Lalwani GA, Puliafito CA. Macular thickness Measurements in normal eyes using spectral domain optical coherence tomography. Ophtalmic Surg Lasers Imaging. 2008;39(4 suppl): S43-9. Doi: 10.3928/15428877-20080715-02

Lumbroso, B., & Rispoli, M. (2015). *Practical handbook of OCT : (retina, choroid, glaucoma)* (2nd ed. ed.). New Delhi: The health sciences publishers.

Lundmark, P. O., & Luraas, K. (2017). Survey of referrals and medical reports in optometric practices in Norway: Midterm findings from a 3-year prospective internet-based study. *Clinical Optometry, 9*, 97-103. doi:10.2147/OPTO.S136510

Mackenzie, S., Schmermer, C., Charnley, A., Sim, D., Vikas Tah, M., Dumskyj, S., . . . Myer, L. (2011). SDOCT Imaging to Identify Macular Pathology in Patients Diagnosed with Diabetic Maculopathy by a Digital Photographic Retinal Screening Programme (OCT Diabetic Macular Screening). *PLoS ONE, 6*(5), e14811. doi:10.1371/journal.pone.0014811

Menke, M., Dabov, S., & Sturm, V. (2009). Comparison of Three Different Optical Coherence Tomography Models for Total Macular Thickness Measurements in Healthy Controls. *Ophthalmologica, 223*(6), 352-356. doi:10.1159/000226600

Midena, E., & Vujosevic, S. (2015). Diagnosing and monitoring diabetic macular edema: structural and functional tests. *The International Journal of Clinical Ophthalmology and Visual Sciences, 35*(5), 623-628. doi:10.1007/s10792-012-9566-9

Murakami, T., & Yoshimura, N. (2013). Structural Changes in Individual Retinal Layers in Diabetic Macular Edema. *Journal of Diabetes Research, 2013*. doi:10.1155/2013/920713

Norwegian Association of Optometry. (2017). Clinical Guidelines. Retrieved from http://www.optikerne.no/pages/kliniskeretningslinjer/

Norwegian Directorate of Health. (2018). Retinopathy and regular retinal examination in diabetes. Retrieved from https://www.helsedirektoratet.no/retningslinjer/diabetes/retinopati-og-regelmessig-netthinneundersokelse-ved-diabetes

Patel, R. D., Messner, L. V., Teitelbaum, B., Michel, K. A., & Hariprasad, S. M. (2013). Characterization of Ischemic Index Using Ultra-widefield Fluorescein Angiography in Patients With Focal and Diffuse Recalcitrant Diabetic Macular Edema. *American Journal of Ophthalmology, 155*(6), 1038-1044.e1032. doi:10.1016/j.ajo.2013.01.007

Porta, M., & Bandello, F. (2002). Diabetic retinopathy - A clinical update. In *Diabetologia* (Vol. 45, pp. 1617-1634).

Remington, L. A. (2005). *Clinical anatomy of the visual system* (2nd ed. ed.). St. Louis, Mo: Elsevier Butterworth Heinemann.

Sabouri, M., Kazemnezhad, E., & Hafezi, V. (2016). Assessment of Macular Thickness in Healthy Eyes Using Cirrus HD-OCT: A Cross-Sectional Study. *Medical Hypothesis, Discovery & Innovation Ophthalmology Journal, 5*(3), 104-111.

Scanlon, P. H., Wilkinson, C. P., Aldington, S. J., Matthews, D. R. (2009). *A Practical Manual of Diabetic Retinopathy Management.* Chichester: Wiley-Blackwell.

Statistics Finland. (2019). Population structure. Retrieved from: http://tilastokeskus.fi/til/vaerak/2019/vaerak_2019_2020-03-24_tie_001_en.html

Statistics How To. (2020). Cohen´s Kappa Statistic. Retrieved from https://www.statisticshowto.com/cohens-kappa-statistic/

Stefánsson, E., Bek, T., Porta, M., Larsen, N., Kristinsson, J. K., & Agardh, E. (2000). Screening and prevention of diabetic blindness. *Acta Ophthalmologica Scandinavica, 78*(4), 374-385. doi:10.1034/j.1600-0420.2000.078004374.x

Strøm, C., Sander, B., Larsen, N., Larsen, M., & Lund-Andersen, H. (2002). Diabetic macular edema assessed with optical coherence tomography and stereo fundus photography. *Investigative Ophthalmology and Visual Science, 43*(1), 241-245.

Tan, C. S. H., Chew, M. C. Y., Lim, L. W. Y., & Sadda, S. R. (2016). Advances in retinal imaging for diabetic retinopathy and diabetic macular edema. *Indian Journal of Ophthalmology, 64*(1), 76-83. doi:10.4103/0301-4738.178145

Tan, G., Cheung, C., Wong, T., & Lamoureux, E. (2018). Telemedicine screening with Optical coherence tomography can improve the detection of diabetic macular edema in a primary care cohort with diabetes. *Invest. Ophthalmol. Vis. Sci., 59*(9).

The Finnish Medical Society Duodecim. (2014). Diabetic retinopathy: Current Care Guidelines. Retrieved from https://www.kaypahoito.fi/hoi50043#K1

The Finnish Medical Society Duodecim. (2018). Type 2 diabetes: Current Care Guidelines. Retrieved from https://www.kaypahoito.fi/hoi50056#K1

The International Council of Ophthalmology. (2017). ICO Guidelines for Diabetic Eye Care. Retrieved from http://www.icoph.org/downloads/ICOGuidelinesforDiabeticEyeCare.pdf

Virgili, G., Menchini, F., Casazza, G., Hogg, R., Das, R., Wang, X., & Michelessi, M. (2015). Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. In *Cochrane Database Syst Rev.* (Vol. 1).

Vujosevic, S., Casciano, M., Pilotto, E., Boccassini, B., Varano, M., & Midena, E. (2011). Diabetic macular edema: fundus autofluorescence and functional correlations. *Investigative ophthalmology & visual science, 52*(1), 442. doi:10.1167/iovs.10-5588

Wang, W., Lo, A. C. Y., & Wang, W. (2018). Diabetic Retinopathy: Pathophysiology and Treatments. *International journal of molecular sciences, 19*(6). doi:10.3390/ijms19061816

Wang, Y. T., Tadarati, M., Wolfson, Y., Bressler, S. B., & Bressler, N. M. (2016). Comparison of Prevalence of Diabetic Macular Edema Based on Monocular Fundus Photography vs Optical Coherence Tomography. *JAMA ophthalmology, 134*(2), 222-228. doi:10.1001/jamaophthalmol.2015.5332

Wells, J. A., Glassman, A. R., Ayala, A. R., Jampol, L. M., Aiello, L. P., Antoszyk, A. N., . . . Yilmaz, T. (2015). Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *The New England journal of medicine, 372*(13), 1193-1203. doi:10.1056/NEJMoa1414264

Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. Retina 2012;32:785-91. doi: 10.1097/IAE.0b013e3182278b64.

Wilkinson, C. P., Ferris, F. L., Klein, R. E., Lee, P. P., Agardh, C. D., Davis, M., . . . Verdaguer, J. T. (2003). Proposed international clinical diabetic retinopathy and diabetic macular edema

disease severity scales. *Ophthalmology, 110*(9), 1677-1682. doi:10.1016/S0161-6420(03)00475-5

Williams, R., Airey, M., Baxter, H., Forrester, J., Kennedy-Martin, T., & Girach, A. (2004). Epidemiology of diabetic retinopathy and macular oedema: a systematic review. *Eye, 18*(10), 963-983. doi:10.1038/sj.eye.6701476

Wong, T. Y., Klein, R., Islam, F. M. A., Cotch, M. F., Folsom, A. R., Klein, B. E. K., . . . Shea, S. (2006). Diabetic Retinopathy in a Multi-ethnic Cohort in the United States. *American Journal of Ophthalmology, 141*(3), 446-455.e441. doi:10.1016/j.ajo.2005.08.063

Yamamoto, S., Yamamoto, T., Hayashi, M., & Takeuchi, S. (2001). Morphological and functional analyses of diabetic macular edema by optical coherence tomography and multifocal electroretinograms. *Graefe's Archive for Clinical and Experimental Ophthalmology, 239*(2), 96-101. doi:10.1007/s004170000238

Yau, J., Rogers, S., Kawasaki, R., Lamoureux, E., Kowalski, J., Bek, T., . . . For The Meta - Analysis For Eye Disease Study, G. (2012). Global Prevalence and Major Risk Factors of Diabetic Retinopathy. *35*(3), ementaryData.pdf-564. doi:10.2337/dc11-1909

List of tables and figures

Table 1 Diabetic Retinopathy Severity Scale 11
Table 2 Diabetic Macular Edema Disease Severity Scale 13
Table 3 Grading systems for maculopathy from retinal photography 17
Table 4 Exclusion/inclusion criteria of retinal imaging 22
Table 5 The grading of OCT images 26
Table 6 Demographic data 30
Table 7 Results 34
Table 8 Detailed descriptions of the subjects with DME measured with OCT 40

Figure 1 ETDRS zones (right eye) 24
Figure 2 The grid-tool positioned centrally in the fundus photo. 24
Figure 3 The report shows a Macular Cube 200X200 OCT-scan of a subject with ERM 27
Figure 4 Exclusion of OCT images and fundus photos 31
Figure 5 Macula-centered fundus photo in which the MESA definition is fullfilled 32
Figure 6 OCT of the subject with edema in central subfield 34
Figure 7 Macula-centered fundus photo of the subject with diffuse DME 37
Figure 8 OCT of the same subject (figure 7) with diffuse DME 37
Figure 9 Macula-centered fundus photo of a subject with focal DME 38
Figure 10 OCT of the same subject (figure 9) with focal DME in the central subfield. 38
Figure 11 Macula-centered fundus photo of the subject with diffuse/subclinical DME. 39