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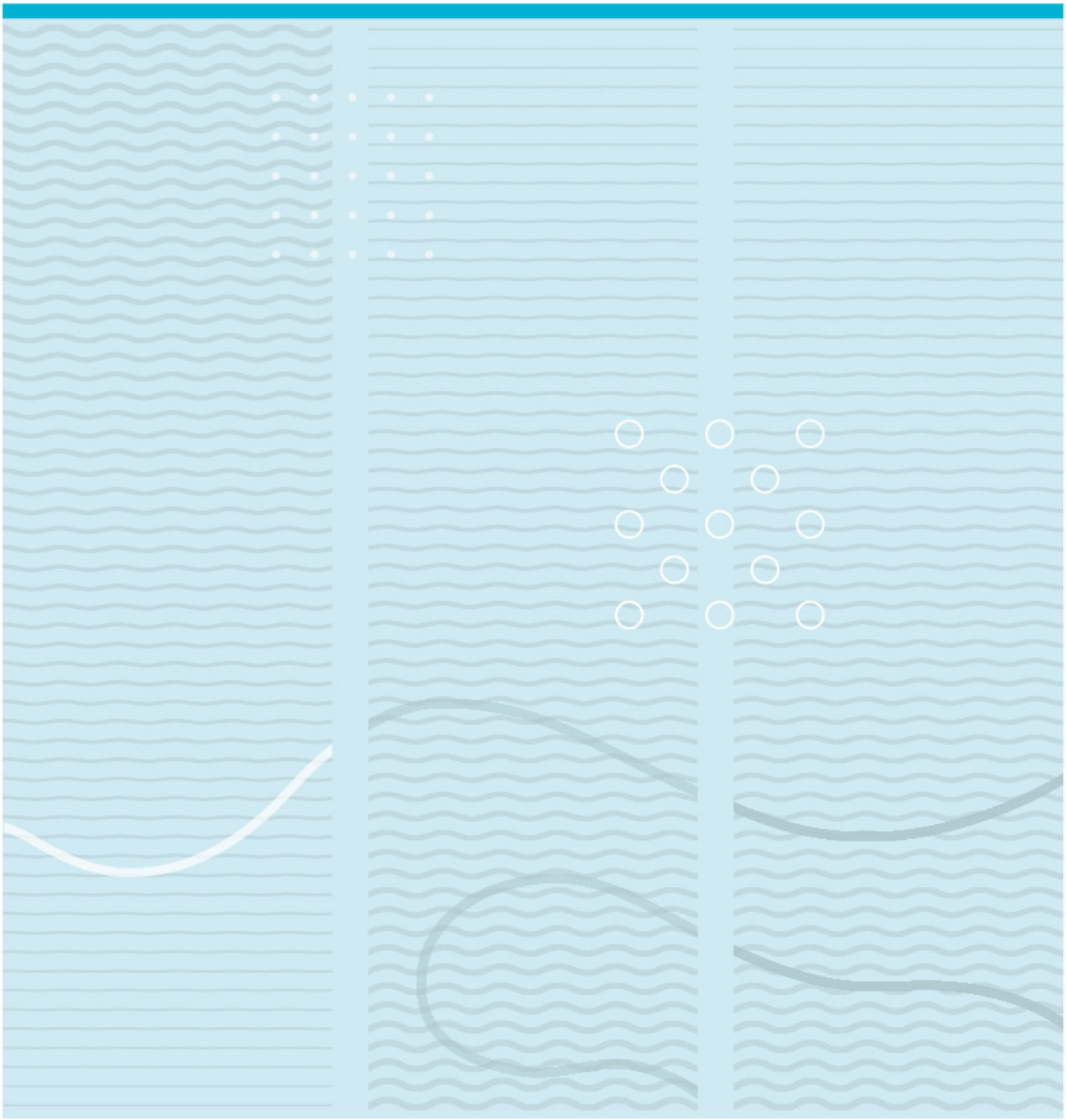
Retinal ganglion cell layer and nerve fiber layer thickness, and central visual function in type 2 diabetic patients, a year from baseline recordings.

Prospective cross-sectional study – results one year from baseline measurements.



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This master thesis is worth 30 study points

Abstract

Is there a reduction in the retinal ganglion cell layer and nerve fiber layer thickness in type 2 diabetic patients, a year from baseline recordings, and does this affect their central visual function?

Aim

Diabetic retinopathy is one of the leading causes of blindness worldwide that can be avoided by systemic control of blood glucose levels in diabetic type 2 subjects. Early detection of retinal changes can help practitioners advise and treat patients to reduce the visual impact of diabetes. This study investigated whether there is a change in retinal ganglion layer thickness and nerve fiber layer thickness in Norwegian diabetic type 2 subjects a year from baseline recordings, indicative of neurodegenerative effects of diabetes, prior to vascular retinopathy findings. The secondary objective is to investigate whether there is a subsequent difference in visual function in these subjects, specifically, contrast sensitivity and visual acuity, a year from baseline recordings.

Method

The study is a prospective cross-sectional study in which 45 Norwegian type 2 diabetic subjects (25 male and 20 female) were tested at the University in South-Eastern Norway; over the age of 18. The test subjects underwent an optometric examination testing their best corrected VA, contrast sensitivity using the MARS CS test, and retinal examination with retinal photographs (KOWA) and had SD-OCT scans (volume scan 200x200 and disc scan 200x200) using the Zeiss Cirrus OCT. The exact same tests were then conducted again one year from baseline and the results are compared to establish if there is a reduction in retinal nerve fiber layer (RNFL) thickness (in microns), in quadrants and the global average, and the ganglion cell and inner plexiform layer (GCIPL) thickness, in sectors and the global average, as well as a change in the visual function of these subjects after one year. Descriptive statistics and paired t-tests were used to compare the changes one year from baseline recordings. The level of significance used was 5% ($p < 0.05$).

Results

The results show that for a type 2 diabetic population (n = 42, mean age = 66 years), the change in GCIPL thickness one year from baseline OD, there is a statistically significant reduction in the mean thickness for sectors 1 and 6 (at a p-level of 0.05). 3 subjects were excluded due to the image quality selection criteria. The average difference in the thicknesses was 0.548 microns thinner one year from baseline, compared to the baseline recordings, ($p = 0.036$). The change in the GCIPL thickness for OS (n=39) for sector 2, 3 and 5 decreased after one year ($p<0.05$). The average difference in the thicknesses was 0.359 microns thinner one year from baseline, compared to the baseline recordings, however, this average change was not statistically significant as $p>0.05$. The RNFL thickness was not significantly different from the one year from baseline results for OD or OS. The results for the visual function show that the VA was not significantly different one year from baseline OD or OS. The CS results are reduced for OU ($p<0.05$), with a 0.0623 log units reduction OD and 0.064 log units reduction OS.

Conclusion

There was a statistically significant reduction in the GCIPL thickness after one year from baseline for some of the sectors, however this change was not very clinically significant. There was no reduction in the RNFL thickness one year from baseline and no reduction in the VA one year from baseline. The CS results were reduced one year from baseline, although the change was minimal. Therefore, the results are not conclusive due to the short time span of the study and small sample size but do highlight the importance of good baseline recordings in order to measure change over time in diabetic patients.

Keywords*:*

Type 2 diabetes, retinal ganglion cell and inner plexiform layer, nerve fiber layer, ocular coherence tomography

Contents

Foreword

The process of writing my master's thesis has been interesting and challenging. I am grateful for the lessons I have learned and the knowledge I have gained. Firstly, I would like to thank my main supervisor, Tove Lise Morisbakk, for her motivation, encouragement and constructive advice throughout the whole process. I would also like to thank the subjects who participated in the study for their engagement and dedication. Finally, I would like to thank my family, friends and most of all my husband for supporting and inspiring me.

Kongsberg - 13.05.2020

Antara Saha Olafsen

List of abbreviations

BRB	Blood-retinal-barrier
C	Cortical cataract
CI	Confidence Interval
CS	contrast sensitivity
DM2	Diabetes mellitus type 2
DR	Diabetic retinopathy
DRN	Diabetic retinal neurodegeneration
DVOH	Diabetes, Vision and Ocular Health study
ERG	Electroretinogram
GCIPL	Ganglion cell and inner plexiform layer
GCL	Ganglion cell Layer
GCC	Ganglion cell complex
IOP	Intraocular pressure
ILM	Inner limiting membrane
IPL	Inner Plexiform Layer
LGB	Lateral geniculate body
LGN	Lateral geniculate nucleus
LOCS III	Lens Opacity Classification System III
Log MAR	Log of the minimum angle of resolution
NC	Nuclear colour
NDR	Non- diabetic retinopathy
NO	Nuclear opacity
OCT	ocular coherence tomography
OD	Oculus Dexterous (right eye)
OS	Oculus Sinister (left eye)
PSC	Posterior subcapsular cataract
RGCL	Retinal ganglion cell layer
RNFL	Retinal nerve fiber layer
SD	standard deviation
SD-OCT	Spectral domain ocular coherence tomography
VA	visual acuity
VEGF	vascular endothelial growth factor

1 Introduction

Diabetes mellitus (DM) is a predominant cause of visual impairment worldwide, and it is estimated that between 90- to 120 000 Norwegians are diagnosed with diabetes, and approximately 28% of them have diabetic retinopathy (Sundling, 2013). Due to the potentially sight threatening consequences of diabetic retinopathy (DR), regular follow-ups and tightly monitored diabetic control is the most effective way to prevent visual impairment. DR is an eye disease that often has few symptoms until the condition is quite advanced (Aamodt & Sundling, 2016). Traditionally DR has been considered a vascular condition, in which retinal changes can be observed as a result of increased permeability of blood vessels in the retina; causing leakage and oedema (Barber, 2015). However, modern research indicates that there may be a neurodegenerative component of DM preceding vascular changes that are seen, though these neurodegenerative changes are more subtle at the cellular level and are not visible with traditional fundoscopy (Wang, 2016).

In this study the neurodegenerative component of DR will be examined as well as the subsequent effect on visual function. It is hypothesised that thinning in the retinal ganglion cell layer (RGCL) and nerve fiber layer (RNFL), which can be measured by ocular coherence tomography (OCT), which can be a good indicator for early neurodegeneration in the retinal tissue in diabetic patients. Currently, in Norwegian healthcare practice, ophthalmologists have the primary responsibility in the follow-up care of these patients. However, due to long waiting times for appointments, some patients do not get the follow up care they need and can drop out of the system. Therefore, caring for these patients should involve optometrists, with the correct equipment and expertise who can screen and follow up diabetic patients as a part of their routine eye examination.

1.1 Retinal anatomy and physiology

The retina is the neuroreceptive tissue layer, covering approximately 2/3 of the posterior inner eye, and is approximately 100 to 250 microns (μm) in thickness, comprised of ten layers (Standring *et al.* 2009). The retinal layers from the innermost to outermost layers of the retina are as follows; internal limiting membrane (ILM), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL) axons, outer nuclear layer (ONL), external limiting membrane (ELM) desmosomes, photoreceptor

inner segments and photoreceptor outer segments and finally, the pigment epithelium (RPE) (Bergmanson, 2013).

1.1.1 Ganglion cell complex (GCC)

The GCC comprises of the nuclei of approximately 1.2 million ganglion cells, the axons of which become the optic nerve fibers (Bergmanson, 2013). The retinal ganglion cells (RGC) start in the inner retina, beginning at the inner plexiform layer (IPL), where they synapse with bipolar and amacrine cells and extend to the lateral geniculate nucleus (LGN) in the midbrain, the cell bodies making up the ganglion cell layer (GCL), the axons of which make up the RNFL (Lakkis, 2013). Collectively, the GCL and the IPL is known as the ganglion cell complex (GCC) or the GCIPL (Lakkis, 2013). The ganglion cells are made up of three different types of bipolar cells which they synapse with. Firstly, midget cells (making up approximately 70% of all ganglion cells) which project to the parvocellular layer in the LGN comprised of "red" and "green" cones necessary for the perception of finer detail, colour and form, secondly, parasol cells (making up approximately 10% of all the ganglion cells) projecting to the magnocellular layer of the LGN and are comprised of rods and cones necessary for movement and depth perception as well as differences in brightness, and thirdly, small bistratified cells which project to the koniocellular (interlaminar) layer of the LGN comprised of short wavelength "blue" cones (Bergmanson, 2013).

1.1.2 Retinal Nerve Fiber Layer (RNFL)

The RNFL is located between the ILM and the GCIPL and is comprised of the axons of the ganglion cell nuclei, the larger of which arise from the magnocellular cells, and are covered by astrocytes and Müller glial cell processes (Bergmanson, 2013). The Beijing Eye Study in 2011, examined the thickness of the RNFL in normal eyes, concluding that RNFL thickness is greater with younger age, shorter axial length, a larger neuroretinal rim and larger optic disk, lower refractive lens power, female gender and flatter anterior cornea (Wang *et al.* 2011). The study also concluded that after the age of 50 years, the age related RNFL thickness decreased by approximately 0.3% per year of life, which coincides with the yearly loss of approximately 0.3% of retinal rods, cones and RPE cells (Wang *et al.* 2011). The number of optic nerve axons decreases with age, a linear regression can be observed annually in terms of RGC loss in patients aged between 55 and 95 years, with a loss of 7205 cells per year (R^2 = 0,50, P = 0.002) in healthy patients (Kerrigan-Baumrind *et al.*

1999). There is also a large variation in the total number of RGCs in patients, and the total number of optic nerve fibers in the normal optic nerve can vary from 600 000 to 1.2 million in normal patients (Kerrigan-Baumrind *et al.* 1999).

1.2 Current classifications of diabetic retinopathy and diagnosis

Diabetes mellitus type 2 is a systemic disease stemming from a combination of both genetic and environmental/lifestyle factors, leading to insulin resistance and impaired insulin secretion; as a result of diminished pancreatic B-cell function, affecting glucose metabolism (Kaku, 2010). This altered glucose metabolism, leads to hyperglycaemia induced metabolic stress, causing DR, which is a result of long-term cumulative damage to the microvasculature of the retina, leading to diagnostic signs such as microaneurysms, retinal haemorrhages, vascular leakage, oedema, exudates and neovascularisation (Marques-Neves, 2015). On a biochemical level, hyperglycaemia induces activation of protein kinase C and increased formation of glycation end products causing oxidative stress, therefore, DR is seen as a neurovascular condition due to the oxidative and metabolic stresses on the sensory neuroretina (Marques-Neves, 2015).

DR severity has been described in several studies, most prominently in the multicenter collaborative clinical trial known as the Early Treatment Diabetic Retinopathy Study (ETDRS), with a grading scale in terms of; no abnormalities, non-proliferative (mild, moderate and severe), proliferative and presence or absence of macular oedema (ETDRS group, 1991). Visual complications can arise at all stages of diabetes retinopathy and can include; transient change of the patients' refractive status, decreased visual acuity, colour vision or contrast sensitivity, often due to cataracts that may be induced by diabetes, vitreal haemorrhages, or macular oedema that could cause metamorphopsia or visual field loss (Sundling, 2013). The ETDRS group developed an international grading system for diabetic retinopathy which is still used today for classification, treatment and follow up of diabetic retinopathy, summarised in table 1 below.

Table 1: Summary of the International diabetes retinopathy classification system:

Severity	Findings
No apparent retinopathy	No abnormalities
Mild NPDR	Only microaneurysms
Moderate NPDR	Microaneurysms/haemorrhages; and other signs (ie. Hard exudates, Cotton wool spots, Mild IRMA), but less than severe
Severe NPDR	4:2:1 rule: more than 20 intraretinal haemorrhages in each of 4 quadrants, venous beading in at least 2 quadrants, IRMA in one quadrant. No signs of proliferative retinopathy
Proliferative diabetic retinopathy (PDR)	Neovascularisation (disk – NVD, iris – NVI, elsewhere – NVE), vitreal haemorrhage or preretinal haemorrhage
Macula oedema (ME)	Retinal thickening outside of the central 500 μm of the fovea
Clinically significant macula oedema (CSME)	Retinal thickening within of the central 500 μm of the fovea

1.3 Mechanism of neurodegenerative effects

In DR, the structural changes arise due to an increased vascular permeability, due to the breakdown of the blood retinal barrier (BRB), which thereby causes leakage of the vessels, leading to oedema (Barber, 2003). Following the breakdown of the BRB, vascular microaneurysms can form, and deposition of exudative lipoproteins (or drusen) can be seen in the retina as well as vascular proliferation mediated by vascular endothelial growth factor (VEGF) causing proliferative diabetic retinopathy (PDR) (Aiello *et al,* 1998). However, in addition to these vascular changes, there is newer evidence to say that there are other neurodegenerative effects that also occur in diabetic patients, prior to vascular diabetic retinopathy (Barber, 2003 & 2015).

These neurodegenerative changes are believed to be the reason for reduced visual function in diabetic patients, preceding vascular changes, some proposed mechanisms behind these changes include; increased neural apoptosis, loss of ganglion cells, changes in glial cell reactivity, activation of microglia, and changed glutamate metabolism (Barber, 2003 & 2015). Increased glutamate accumulation in the extracellular space, oxidative stress, imbalance in the retinal production of neuroprotective factors and inflammation, leads to neurodegeneration, causing a reduction in the thickness of the inner retinal layers, subsequently causing a thinning of the RNFL and GCIPL (Wang, 2016). Animal studies on mice retinas, have shown that damage to GCL are first seen in the dendrites (in the IPL) as a result of mitochondrial splitting, which in turn leads to apoptosis of

the RGC and then phagocytosis of the outer axon which is seen as RNFL thinning (Feng *et al.* 2013). Therefore, early diagnosis of diabetic neurodegeneration can be evaluated in the form of subtle changes in the RNFL and GCIPL thickness measured with an OCT (Barber, 2015).

Current hypotheses for why there is neurodegeneration of the retina in diabetic patients are likely interrelated; the first being that the breakdown of the BRB integrity, leading to the increased vascular permeability and thereby decreased control over the composition of the extracellular retinal fluid leads to oedema which causes neuronal cell loss (Barber, 2003). The second hypothesis is that diabetes effects neural retinal metabolism, causing increased cell apoptosis which subsequently causes a breakdown of the BRB (Barber, 2003). Another key component in the mechanism of neural damage in diabetic patients is through the insulin-response in retinal tissue (Reiter & Gardner, 2003). Insulin is a crucial regulator for metabolic functions, and it is hypothesised that insulin also modulates neural metabolism and synapse activity, as insulin receptors are expressed on vascular cells and neurons which can stimulate neuronal differentiation, growth and development as well as glucose uptake, and therefore the retina is defined as an insulin sensitive tissue (Reiter & Gardner, 2003). Furthermore, insulin control can thereby control glucose levels and reverse or slow retinal neural cell apoptosis and provide trophic support for retinal neurons (Reiter & Gardner, 2003). Therefore, this neurodegenerative effect is likely to be irreversible. Current treatment modalities for DR targets vascular permeability with laser panretinal photocoagulation or anti-VEGF treatments to prevent neovascularisation (Aiello *et al.* 1998).

1.4 Zeiss Cirrus HD-OCT imaging and normative data

Optical coherence tomography (OCT), is an imaging device which is becoming frequently available in optometric practices in Norway, and can be a useful, non-invasive tool that allows high resolution cross-sectional microscopic viewing and documentation of the macula and optic nerve head in diabetic patients. Such measurements allow for the early diagnosis and monitoring of treatment for retinal and neuroretinal diseases. In this study spectral domain OCT (SD-OCT), using the Cirrus HD-OCT 5000 (Carl Zeiss Meditec Inc., Jena, Germany), will be used to examine the posterior pole, specifically, the RNFL and the GCIPL scans (macular cube 200x200 and optic disc 200x200 cube scans), and to investigate whether there are any neurodegenerative effects prior to DR findings. The scanning speed of the Cirrus HD-OCT is 68 000 axial scans per second giving an axial resolution of 5μm in tissue, and 15μm transverse (Cirrus HD-OCT 5000 user manual, 2015).

A normative database is used as a reference within the software of the Cirrus HD-OCT 5000, in which 284 healthy subjects, aged 19 to 84 years, are used to collect normative data for the RNFL thickness, which is available from the user manual released by Carl Zeiss in 2015. This data used to develop the normative database was collected as a part of a multi-center, prospective, non-randomised study, in which the enrolled subjects had no history of any eye disease, refractive error within -12.00D and +8.00D and were screened for eligibility prior to undergo testing. Within the test population, the gender distribution was 134 males and 150 females, and ethnicity; 43% Caucasians, 24% Asians, 18% African, 12% Hispanic, 1% Indian and 2% mixed ethnicity. The results showed that the difference in average RNFL thickness between any of these race groups were within 6μm, and amongst these groups, Caucasians had a thinner average RNFL thickness than the other groups (Zeiss Cirrus HD-OCT user manual, 2015).

The ganglion cell normative database within the Cirrus software provides normative data for the ganglion cell analysis module, which examines the GCL and the IPL together (GCIPL) to develop a thickness map, comparing the results to normal limits. The thickness map was developed using a segmentation algorithm (see figure 1 below), in which the thickness values of the six sectors are expressed, where each sector represents 60 degrees of an elliptical annulus where the central radius is 0.5mm vertically by 0.6mm horizontally and the outer radius is 2.0mm vertically by 2.4mm vertically, as well as an average value of the GCIPL thickness (Zeiss Cirrus HD-OCT manual, 2015).

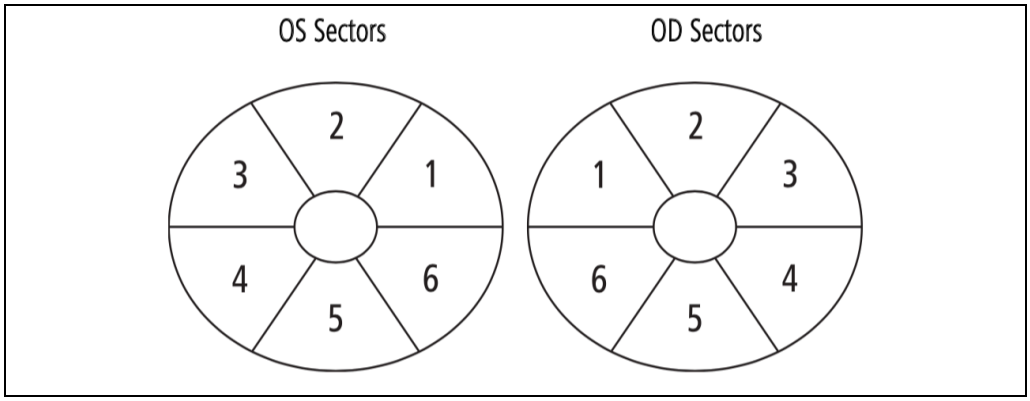


Figure 1: Segmentation divisions used for the Ganglion Cell Analysis with the Zeiss Cirrus HD-OCT 5000 (Zeiss Cirrus HD-OCT manual, 2015).

The average thickness parameters for these segments are summarised in table 2 below, and these values are based on the thickness of the sectors of 282 participants who were measured, and does not consider the differences due to age, ethnicity, refraction or axial length (Zeiss Cirrus HD-OCT manual, 2015).

Table 2: The average parameters for the average GCIPL thickness and for each of the 6 sectors summarised in the Normative database for the Zeiss Cirrus HD-OCT (Zeiss Cirrus HD-OCT manual, 2015).

	Average GCL + IPL Thickness	Sector 1	Sector 2	Sector 3	Sector 4	Sector 5	Sector 6
Mean	84.7	82.9	86.4	86.8	85.3	83.2	83.8
Std	7.1	6.3	7.9	8.3	9.0	7.8	6.5
Min	67.7	68.0	67.0	65.0	62.0	62.0	68.0
Max	104.2	102.0	113.0	112.0	111.0	109.0	106.0

Other studies, using the Zeiss Cirrus HD-OCT, which have looked at changes in the thickness of the RNFL and the GCIPL in glaucoma patients with a healthy control group, have defined normative values as; RNFL thickness: 98.07μm ± 11.4μm and GCIPL thickness as 84.33μm ± 5.63μm, in a population of 40 healthy subjects (Leung *et al.* 2013). In a similar study with a control group population of 225 healthy participants the average RNFL thickness was; 99.3μm ± 8.9μm and GCIPL thickness as 84.6μm ± 5.4μm (Xu *et al.* 2017). The average thickness parameters taken from normative database within the Cirrus software are summarised in figure 2 below, showing a decline in the average RNFL thickness with age (Zeiss Cirrus HD-OCT manual, 2015).

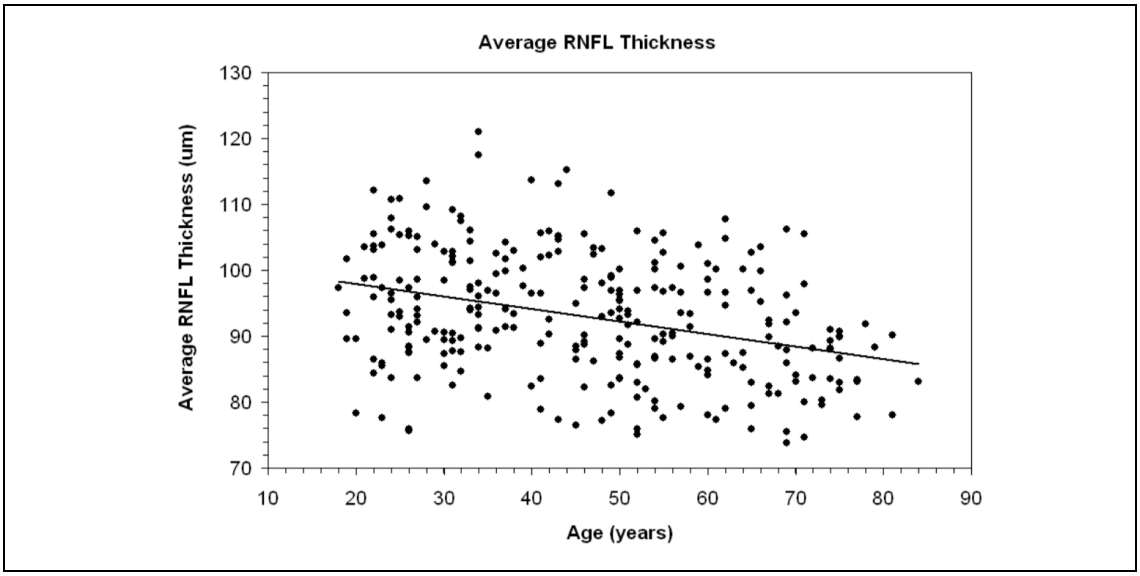


Figure 2: Average RNFL thickness vs. age in the Normative database for the Zeiss Cirrus HD-OCT (Zeiss Cirrus HD-OCT manual, 2015).

1.5 Visual function tests

For testing visual function in relation to neurodegeneration at the retinal level, visual acuity (VA) and contrast sensitivity (CS) measures are used in this study. Both VA and CS can be a numerical measure of increased or decreased function over time. It is hypothesised that ganglion cell layer thickness can affect visual function, leading to decreased visual acuity; as reduced GCL and RNFL thickness is a result of a loss of retinal ganglion cell axons, cell bodies and dendrites (Dijk *et al.* 2011). This loss of neural tissue is likely to decrease the processing capacity of the inner retina and thereby limit transmission of visual information to the brain (Dijk *et al.* 2011, Barber & Baccouche 2017).

The Log MAR scale was used as this is a superior visual acuity measure compared to traditional visual acuity charts such as Snellen, due to increased consistency with test-retest reliability (Laidlaw *et al.* 2003). The log MAR scale, devised by Bailey and Lovie, is an acronym for the log of the minimum angle of resolution, and the values are represented by a decimal number, giving ease for data collection and statistical analysis (Oduntan *et al.* 2009). The MARS contrast sensitivity was developed by the Mars Perceptrix Corporation in 2004 and was used as a visual function test in this study, due to its good repeatability and validity (Dougherty *et al*. 2005). The MARS CS test has a finer scale, which indicates that each letter corresponds to a smaller change

in contrast, with each letter corresponding to a 0.04 change in log units, giving the test a greater specificity than the Pelli-Robson test which has steps of 0.15 log units (Dougherty *et al*. 2005). This greater repeatability and specificity in log units makes the test more consistent in terms of comparability between the initial baseline recordings and the one year from baseline results in the study.

1.6 Former studies

The loss of RNFL thickness in diabetic patients in early stage DR was measured in a cross-sectional study of 158 type 2 diabetic patients using a Topcon 3D OCT-1, and other systemic risk factors such as the duration of diabetes, body mass index (BMI), HbA1c levels and serum lipids were investigated (Shi *et al.* 2018). The study subjects were divided into 3 groups, with no DR (n = 53), mild DR (n = 51) and moderate DR (n = 54). It was concluded that the earliest degeneration in diabetic subjects without retinopathy (n = 53), was RNFL loss, specifically in the superior (124.24 ± 21.69μm, p = 0.004) and inferior (134.55 ± 24.83μm, p = 0.003) quadrants (Shi *et al.* 2018). It was also concluded that strict control of lifestyle factors, weight, serum lipid levels and glycemic control was the most effect strategy for preventing early retinal neurodegeneration in diabetic patients, and that diabetes duration was one of the major risk factors affecting retinal neurodegeneration (Shi *et al.* 2018).

In a study examining retinal thickness and visual function in type 2 diabetic patients without retinopathy, 141 participants without retinopathy and 158 healthy participants were tested and the GCIPL thickness was significantly decreased in the diabetic patients compared to the healthy patients, however, there was little significant difference in the RNFL thickness in both groups (Zhu *et al.* 2015). The diabetic group had on average 6.8% thinner superior macular GCL thickness than the control group (Zhu *et al.* 2015). Contrast sensitivity in these two groups were also tested using the OPTEC 6500 (Stereo Optical), and the results were significantly different between the diabetic patients and the control group, the diabetic group having a reduced CS compared to the control group, however, the BCVA was not significantly different between the two groups (Zhu *et al.* 2015). Thereby concluding that the inner retina appears to be more vulnerable to metabolic stress induced by diabetes than the outer retina which is supplied by the choroid. These alterations in the neuronal structure of the inner retina in diabetic patients presents prior to signs of diabetic retinopathy, thus leading to a thinner GCL and decreased CS compared to the control group (Zhu *et al.* 2015). In another prospective cross-sectional study comparing the visual

function (CS measured using the CSV-1000 CS chart) in 46 diabetic patients (without retinopathy findings) to a control group with 46 healthy patients; both groups with BCVA of the log MAR equivalent VA: 0.00 and the CS was 0.16 log units lower in the diabetic patients compared to the control group (Safi *et al.* 2017). The study therefore concluded that patients with diabetes and no clinical signs of retinopathy had a loss of CS at all spatial frequencies tested, compared to the healthy control group (Safi *et al.* 2017).

When looking at the association between retinal neuronal degeneration and visual function, specifically dark adaptation (using an electroretinogram/ERG) and CS (using OPTC 6500, Stereo Optical), morphological changes in neuroretinal tissue appeared to lead to reduced neurovisual function prior to retinopathy findings in diabetic type 2 patients (Zhu *et al.* 2015). The Chinese study examined 141 diabetic patients without retinopathy and a control group of 158 healthy participants, comparing the thickness of the RNFL and the GCIPL (using a SD-OCT, Optovue RTV-ue 100) (Zhu *et al.* 2015). The average thickness of the RNFL in the control group was 102.0μm ± 12.1μm and in the diabetic group the average thickness was 99.2μm ± 14.7μm, the GCIPL thickness in the control group was 101.6μm ± 10.2μm and in the diabetic group the average thickness was 99.3μm ± 9.5μm (Zhu *et al.* 2015). Compared to the control group, the CS and ERG results of the diabetic group were reduced, thereby indicating that both the thickness of RNFL and GCIPL as well as visual function were affected by diabetes, pre-retinopathy, showing a specific thinning in the superior GCIPL sector by 6.8% (Zhu *et al.* 2015). A Japanese study found similar results when comparing RNFL thicknesses between healthy patients and type 2 diabetic patients without DR (n = 32); the superior sector was significantly decreased with a reduction of 7.3μm (p = 0.02) (Sugimoto *et al.* 2005).

In a comparable study conducted in India, there was a statistically significant reduction in the GCIPL and RNFL thickness (using the Cirrus HD-OCT) when comparing 30 diabetic type 2 patients without DR or mild DR, compared to a control group of 30 participants. The average RNFL in the diabetic group was 86.18μm ± 8.44μm and in the control group the average thickness was 91.79μm ± 4.77μm, with a p value of 0.002 (Borooah *et al.* 2018). The data for the average GCIPL thickness for the diabetic group was 79.95μm ± 4.32μm and in the control group the average thickness was 84.66μm ±3.26μm with a p-value of less than 0.001 (Borooah *et al.* 2018). When comparing the two diabetic groups, the group without DR had an average RNFL thickness of 86.74μm ± 11.18μm and average GCIPL thickness of 80.15μm ± 5.78μm (Borooah *et al.* 2018). In the mild DR group; the average RNFL thickness was 85.62μm ± 11.10μm, and GCIPL average thickness of 79.75μm ± 5.70μm, these values were closely related to the duration of diabetes

and the HbA1c values (Borooah *et al.* 2018). Similarly, statistically significant ($p < 0.001$) conclusions were drawn in a study examining the RNFL thickness in 100 type 2 diabetic patients without DR, compared to 100 healthy participants conducted in Pakistan (Mehboob *et al.* 2019). Progressive reduction of RNFL thickness was observed in healthy patients and in type 2 diabetes patients with and without DR; however, type 2 diabetes was associated with an increased loss of RNFL thickness regardless DR, suggesting that RNFL loss may occur in people with type 2 diabetes without DR progression (Lim *et al.* 2019).

2 Aims

2.1 Research aims and significance in clinical practice

2.1.1 Primary goal and research questions

The central objective of the study is to investigate whether there is a reduction in the GCIPL and RNFL thickness (in microns) in Norwegian type 2 diabetic subjects, a year from baseline recordings, using the spectral-domain OCT (volume scan).

The main objective is based on the following research questions:

1. Is there a measurable change in the retinal ganglion cell complex thickness 1 year from baseline recordings in type 2 diabetic subjects?
2. Is there a measurable change in the nerve fibre layer thickness 1 year from baseline recordings in type 2 diabetic subjects?

2.1.2 Secondary goal and research questions

The secondary objective is to determine whether there is consequential effect on central visual function using conventional clinical methods of measuring visual acuity (Log MAR) and contrast sensitivity (MARS), comparing the visual function at baseline and then again, a year from baseline recordings.

The secondary objective is based on the following research questions:

1. Are there any measurable changes in the visual acuity (using Log MAR) in type 2 diabetic subjects a year from baseline recordings?
2. Are there any measurable contrast sensitivity changes measured with the MARS contrast sensitivity test, in type 2 diabetic subjects after a year from baseline measurements?

2.2 Significance:

A decrease in the thickness of the GCIPL and RNFL thickness could be indicative of a neurodegenerative effect of diabetes type 2, prior to the appearance of microvascular changes apparent in diabetic retinopathy. Despite there being similar studies conducted examining the neurodegenerative effect on diabetes, examining the RNFL and GCIPL thickness changes and

visual function, there are few studies with data from the Nordic region or in Norway. Optometrists in Norway have increasing access to OCT equipment, and can thereby monitor changes in patients over time between visits to the ophthalmologist or prior to. For Norwegian optometrists, a better understanding of this information could strengthen the argument that monitoring by optometrists, with an OCT, they could reduce waiting times for patients to see ophthalmologists. In this way optometrists could monitor the changes in retinal layer thickness and visual function and compare results from baseline recordings and refer patients showing signs of degeneration of the RNFL or GCIPL. An early sign of neurodegeneration in the RNFL and GCIPL in diabetic patients, prior to vascular retinopathy, would provide useful information for ophthalmologists about whether there is a need for neuroprotective treatments to avoid neurodegeneration in the retina, and therefore avoid functional visual loss.

2.3 Hypotheses

2.3.1 Null hypotheses

- There is no reduction in GCIPL and RNFL thickness one year from baseline in type 2 diabetic subjects.
- There is no reduction in the VA one year from baseline in type 2 diabetic subjects.
- There is no reduction in the CS one year from baseline in type 2 diabetic subjects.

2.3.2 Hypotheses

- There is a reduction in thickness of GCIPL and RNFL thickness one year from baseline in type 2 diabetic subjects.
- There is a reduction in the VA one year from baseline in type 2 diabetic subjects.
- There is a reduction in the CS one year from baseline in type 2 diabetic subjects.

3 Methods

3.1 Study design

The study design used was a prospective cross-sectional study in which type 2 diabetic subjects were examined a year from baseline recordings. The analyses were based on the change in the thickness (in microns) of the GCIPL thickness, in the central macula area (using the macular cube scan, 200x200 pixels or 6 x 6mm^2), a year from baseline recordings, and this was examined by measuring the average thickness of the inferior and superior segments, as well as the average thickness change, using the Zeiss Cirrus OCT. The RNFL thickness (using the optic disc cube scan, 200x200), was also examined in terms of thickness at baseline recordings and one year from baseline. The visual function was also evaluated, by measuring the VA and CS at baseline and one year from baseline recordings.

3.2 Study subjects

3.2.1 Recruitment

Type 2 diabetic subjects, male and female, were recruited and first tested in 2018 as a part of a larger study, the Diabetes, Vision and Ocular Health (DVOH) study at the University of South-Eastern Norway. Subjects who are eligible to participate in this study are aged over 18 years old with a type 2 diabetes diagnosis.

Subjects were recruited from the University of South-Eastern Norway optometry clinic if they have type 2 diabetes, and also from optometrists, medical clinics and diabetic associations in the Buskerud, Vestfold and Telemark areas. Subjects were informed about the study through verbal and written consent (see Annex 1). The subjects that agreed to partake in the study, and the test data and measurements were transferred to the data registration booklet (see Annex 2). The identity of the subjects was protected by giving the subjects a randomly assigned ID- number, the list containing the names and ID numbers of the subjects will be destroyed following completion of the study.

In any case of suspect pathology and requirement for treatment of diabetic retinopathy or any other eye disorder seen at the time of testing, the subjects was referred to follow up appointments with the appropriate specialist or ophthalmologist in their local area.

3.2.1.1 Subject samples

The subject sample consisted of 45 diabetic type 2 subjects, both with and without and diabetic retinopathy signs. In the DVOH study; 89 subjects were tested at baseline; of these subjects; 51 subjects were tested a second time, and 45 of these were included in the sample population. This is due to the fact that 6 subjects were excluded due to the exclusion criteria, 4 of the subjects no longer wished to be tested at the one year follow up examination and 34 subjects were not yet tested for a second time.

3.2.1.2 Size of sample

The study sample consisted of 45 subjects; 25 were male, 20 were female.

3.3 Inclusion criteria

Subjects were both male and female type 2 diabetic subjects aged between 18 and 80 years old. The duration of diabetes was recorded, but not a determining factor for being selected in this study.

3.4 Exclusion criteria

Subjects with other eye diseases such as other retinopathy, macular degeneration or neurodegenerative eye conditions, such as glaucoma, were also excluded from this study as this is likely to affect the RNFL and GCIPL thickness. Subjects exceeding a refractive error of -6.00D or over +6.00D were excluded; as higher refractive errors could affect retinal layer thickness.

Other factors that need to be considered are; the image quality to ensure good reliability of the data. The images were tracked for central alignment from the baseline measurements, to ensure that they can be used to make a comparison after one, images which did not have tracking enabled were excluded from the study, to ensure that the images were comparable. All subjects examined also required dilation, allergy to dilating drops (tropicamide 0.1%) or contraindications for dilation, such as a shallow anterior chamber angle or increased IOP, would thereby exclude subjects from being dilated and therefore examined. For this reason, the subjects are examined with a slitlamp microscope prior to dilation, to ensure an open chamber angle, and the pressures

are measured with the I-care tonometer. Subjects who were unable to give written consent also had to be excluded from the study.

For ensuring the image quality and repeatability in this study, selection of images was based on several things, which was arranged into a quality checklist summarised in the table 3 below:

Table 3: Quality checklist for selection of OCT images:

	Evaluation	Description
1	Tracking	Image tracking was used for both the initial baseline image and for the one year follow up image to ensure that the exact same centration was used for both images for optimal repeatability
2	Signal quality	A minimum of 6/10 signal strength was required for each image to be considered an acceptable image quality
3	Centration	The images are centered according to the correct placement of the disk (RNFL images) and the fovea (GCL) images
4	OCT resolution	Clear OCT image resolution so that it is possible to visibly differentiate the retinal layers
5	OCT thickness analysis	Well-defined segmentation lines and clear definitions of the inner and outer limits of the area correctly identified in the measured area

3.5 Numerical analysis and statistical issues

The original data were collected in the data collection booklets and stored by the patient identification number in a manual paper archive, the data were also electronically entered into a Microsoft Office Excel 2019 spreadsheet. The GCIPL and RNFL thickness data were also collected at a later time, using a separate spreadsheet for data entry, as this was not included in the original data collection booklet. The names of the participants were not saved electronically, as their identification numbers were used in the Excel spreadsheets. Following the data collection, the data were then measured, and statistical analysis was conducted using the (IBM) SPSS Statistics version 26 for Mac OSX for the statistical analysis.

A paired t-test was implemented to investigate the research aims to compare the baseline and the one year from baseline results for the thickness of the GCIPL and the RNFL; as well as for the changes in the VA and the CS at baseline and one year from baseline. To determine whether or

not there was a significant change from baseline and one year from baseline; the level of significance used was 5% ($p < 0.05$). The statistical analyses implemented were; descriptive statistics, demographic data, mean values, standard deviation and paired samples t-test, in order to compare the means at baseline and one-year form baseline. All data were controlled as regards to biases; outliers and unrealistic values were compared with the other data but were excluded as missing data.

Parameters considered in the numerical analysis include; the average thickness of the GCIPL was examined in microns for each of the 6 sectors, as well as they average thickness, the RNFL was also examined as the 4 sectors and the average thickness change comparing the results from the baseline measurements and the one year follow-up measurements. The visual acuity of the subjects was examined as a numerical value using the Log Mar scale for each eye. The contrast sensitivity was also examined as a MARS contrast sensitivity value given as a log value for each eye. The presence or absence of diabetic retinopathy findings were summarised as a binary finding, in order to give demographic information of the study group, as well as the age and sex of the participants. The self-reported duration of their type 2 diabetes (or the number of years since they were first diagnosed) was also a demographic factor which is summarised in the results section.

3.6 Ethical considerations

The DVOH study which initiated in 2018, was conducted in agreement with, and approved by the Regional Committee for Medical Research Ethics and Southern Norwegian Regional Health Authority (REK). The subjects received verbal and written information prior to giving their consent in participating in the study (see annex 1). Participants were also informed that they could withdraw from the study at any given time, without needing to provide an explanation.

During the conduction of the study, the subjects underwent a thorough ocular health examination, and subjects requiring further intervention or follow up of an ophthalmologist or other eye health professional, were referred so that they can get further treatment for symptoms or signs uncovered during the examinations. The subjects were informed about each individual test conducted verbally, both at baseline recordings and at the one year follow up appointment once again. The subjects were also informed about the use of the tropicamide, dilatation drops, which would dilate the pupils and therefore could induce some photophobia in the hours

following the tests, the subjects were asked to wear sunglasses for this purpose. The subjects were also asked about allergies prior to the instillation of the drops, and if they had previously had an allergic reaction to dilation drops. Prior to dilation, the subjects were checked for an open anterior chamber angle using the Van Herrick's method and their intraocular pressure was tested to ensure that they were not at risk for angle closure.

The duration of each examination conducted was about 3 hours, which the subjects were informed about prior to the commencement of the examination. Because of the long test duration, some participants became tired and a little less motivated, especially if they were tested in the afternoon. For this reason, the participants were given at least 1-2 breaks, or more if they required, to be able to have something to eat or a cup of coffee or water. The subjects were encouraged to ask questions at any stage of the testing, and they were well informed about what each of the tests entailed. The subjects also could receive a copy of their refraction if they were interested in purchasing spectacles from the refraction conducted.

Due to the sensitive nature of the personal health information collected in the study, the information was recorded in data collection booklets (se annex 2) and stored in a locked filing cabinet during the data collection period. The data were anonymously entered into a data collection spread sheet, and stored electronically, which did not include any personal or identifiable information about the subjects – only the data collected in each section was entered according to the randomly assigned ID number. To ensure privacy of all the research participants, the personal information and data were handled confidentially, only by study supervisors who entered the data into the data collection form. From this data registration form, the data was then analysed anonymously, without any personal information, using the reference number each patient was allocated to conduct the statistical analysis. Thereby making it impossible to identify which patient the data came from. The OCT images examined in each case for measuring the thickness of the GCL and the RNFL examined, would be very similar in appearance and not easy for the examiner to identify the patient based on their scan. At the conclusion of the data collection phase of the DVOH study, the data collection booklets will be destroyed.

3.7 Method overview

Each patient underwent a full ophthalmic examination, due to this study being a part of a larger study, the DVOH study (see appendix 2 for data registration booklet). The total testing time was

approximately 3 hours per subject. The test battery included; a patient history, a questionnaire evaluating their visual function, an Ocular Surface Disease index questionnaire, McMonnies questionnaire for dry eyes, refraction and visual acuity check (using Log MAR), pachymetry, HRR colour vision testing, Amsler test, contrast sensitivity test (using MARS), dry eye examination using the oculus keratograph K5, meibography, OCT – five scans, retinal photography (macula, disc and stereo disc), Optomap scan (with autofluorescence and normal imaging), fundus photography conducted using the KOWA non-mydriatic fundus camera, with stereoscopic disc images, perimetry 10-2 using the Octopus perimeter by Haig-Strait. The images taken with the KOWA non-mydriatic fundus camera were evaluated and graded as having DR or the absence of DR using the ETDRS international grading scale described above in table 1. Following the testing, if the subjects required further referred for management, they would be advised treatment for dry eye conditions, or with any pathologies they would be referred to their ophthalmologist, and a report would be sent to their doctor. However, only the tests relevant for this study will be described and discussed further.

3.7.1 Visual acuity testing method

The distance visual acuity was measured following the refraction of the patient to ensure that the BCVA was measured. For the testing, the same 2 test rooms were used in the clinic to increase repeatability, and the binocular refraction was measured using a manual phoropter as well as a visual acuity chart adjusted to a 6-meter testing distance with the same lighting measures and the same charts were used. The visual acuity and the CS were both measured monocularly while the patient wore the trial frame containing their most updated refraction. The results were recorded as a decimal log value in the data registration booklets and then entered into the data collection spread sheet, data was then extracted and used, comparing the initial baseline measurements and the one year from baseline measurements, entered into a new data collection spreadsheet which was to be used to analyse the data.

3.7.2 Contrast sensitivity testing method

Contrast sensitivity was evaluated using the MARS contrast sensitivity test. The test consists of 48 letters which are 1.75cm high arranged in 8 rows of 6 letters in each row, with contrasts varying from 91% (or - 0.04 log units) to 1.2% (-1.92 log units), with each letter having a value of

0.04 log units (Dougherty *et al*. 2005). This test provides a score measured in log units where the final letter gives a value from which the number of misses prior to the final letter are subtracted after multiplying by 0.04, as recommended in the protocol by the manufacturer (see annex 3 for the MARS score sheet). The test distance used was 50cm, and the patient had a trial frame with their optimal correction (adjusted near addition) for that distance as measured from the refraction. The test was conducted monocularly, therefore an occluder was used to cover one eye at a time, and the scores recorded for the right and left eye respectively, 2 different test plates were used, one for the left and one for the right to ensure that the subjects did not memorise the letters. The plates were held by the examiner and tilted so they were at a right angle to avoid any reflections that may alter the results from the room lighting and to maintain a stable test distance.

The CS test was taken shortly after the refraction and the measuring of the BCVA, as a part of the initial tests, prior to any use of the slitlamp microscope or retinal imaging to ensure that the subjects would not be affected by light in their eyes. The subjects were asked to read all the letters they could read from the top of the chart and then the final values were recorded, subtracted by the letters they did not read correctly, and these responses and scores were recorded on the standard score sheets which were in the data collection booklets.

3.7.3 OCT method

The OCT scans were taken using the Cirrus HD-OCT model 5000 (Carl Zeiss Meditec Inc., Jena, Germany), post dilation with tropicamide to optimise the image quality, that can be affected by smaller pupil size or lens opacities. Of these scans, the 2 scans of interest in this study were the macular cube 200x200 and the disc cube 200x 200 scan. The macular cube scans (see figure 3 below) were used to view the thicknesses for the 6 sectors examined in the GCIPL thicknesses as well as the average thickness examined for each eye. The optic disc 200x200 scans (see figure 4 below) were used for examining the RNFL quadrant thicknesses and the average thickness for each eye. Both scans were performed with tracking and the quality control checklist (described in table 3 above) was used to determine if the images were of good enough resolution to be considered. The scans were taken in a dark room, with the lights turned off. The subjects were informed prior to each scan that they needed to look at the fixation light to ensure a stable image.

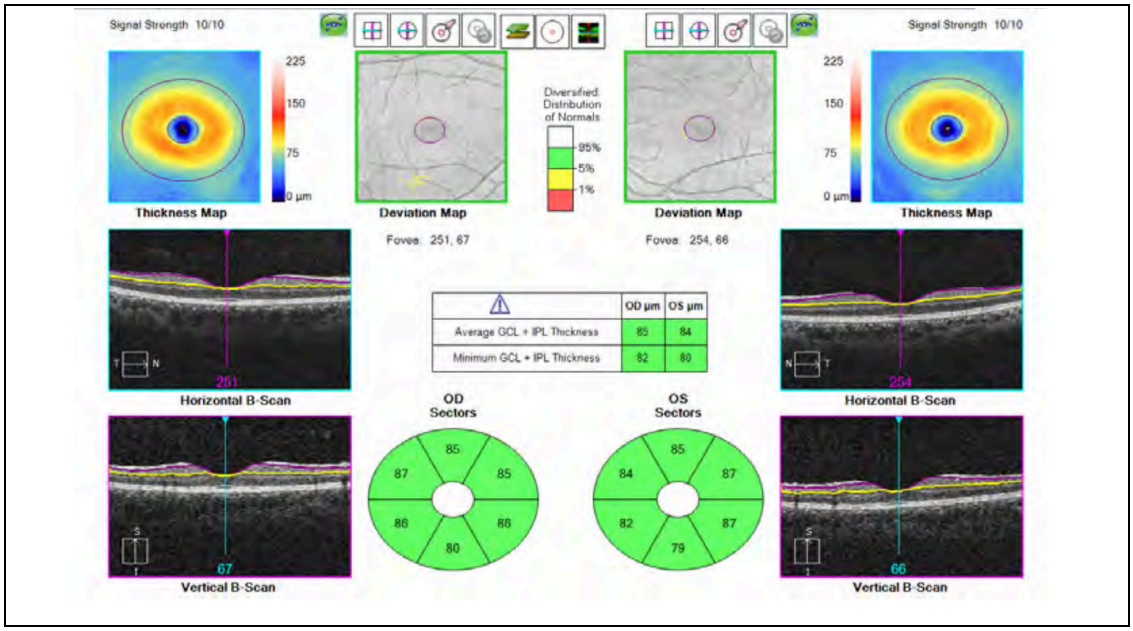


Figure 3: Example of the segmentation divisions used for the Ganglion Cell Analysis overview with the Zeiss Cirrus HD-OCT 5000, showing the sectors for each eye and the average GCIPL thickness maps, taken from the Zeiss Cirrus HD-OCT user manual.

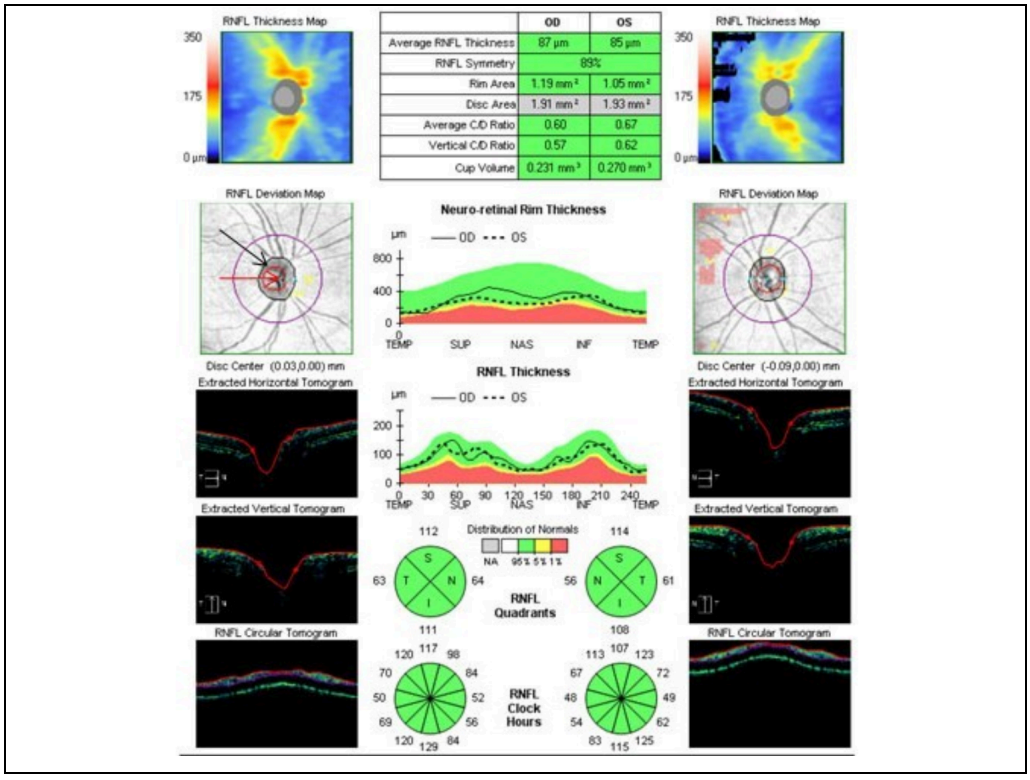


Figure 4: Example of the segmentation divisions used for the Optic Disc 200x200 overview with the Zeiss Cirrus HD-OCT 5000, showing the RNFL quadrants and the average RNFL thickness values.

Tracking of the previous scan was used to ensure that the centration of the image was as close to the previous image as possible, and the image quality of the scans were evaluated at the time of each scan, if the quality was less than 6/10, the scan was taken again. If there were any vitreous floaters or opacities affecting the OCT image scan quality by casting a shadow or interrupting the scan, the images were taken again. Subjects with dry eyes were asked to blink and were given lubricating eye drops in the event of reduced image quality due to poor tear film, as the subjects had a dry eye evaluation prior to the images being captured with the OCT. Images that did not meet the quality requirements (summarised in table 3 above) were not included in this study. The subjects were seated so that the OCT was at a comfortable height, they were encouraged to try and keep their eyes open during the image capture time, and if required the subjects were asked if they required assistance with their eyelids, in the case of blepharochalasis or dermatochalasis in older subjects.

After the scans were taken, the examiner would examine each image of the disc and macular area to screen for the presence of any pathology that would require further referral for treatment. The scans of particular interest in this study required the OCT layer segmentation software within the Zeiss Cirrus HD-OCT, specifically the GCIPL + RNFL segmentation; as the thickness at each of the segments and the average thickness of the segments at the baseline tests and at the one year from baseline results. These values were then recorded into the data collection sheet (see annex 4) and then entered manually onto the ExCel spreadsheet to be further used in analysis.

4 Results

4.1 Demographic data

During the DVOH study, 89 subjects were tested at baseline, 9 subjects who were tested for a second time were excluded due to the exclusion criteria, 4 subjects who were tested at baseline, no longer wished to be tested at the one year follow up examination and 34 subjects were not yet tested for a second time. Therefore, of the 89 subjects from the baseline recordings, only 45 were included in this study as the subjects were examined twice, with the results summarised and compared for the initial baseline measurements and then the one year follow up results. The demographic data are summarised for the test population in table 4 below.

Table 4: Summary of demographic data for the test population

Variable	(n = 45)
Gender, n (%)	
Females	20 (44.4%)
Males	25 (55.6%)
Age,	
Years (mean, SD)	66.2 ± 8.78
Range	44 – 79 years
Absence and presence of retinopathy, n (%)	
No diabetic retinopathy	37 (62.7%)
Diabetic retinopathy	8 (13.6%)
Spherical equivalent refractive error, D (mean, SD)	
Right eye	0.156D ± 1.87
Right eye range	-4.50D - +6.00D
Left eye	-0.039D ± 1.99
Left eye range	-5.75D - +5.25D
Self-reported blood glucose levels,	
Mmol/L (mean, SD)	6.70 ± 0.992
Range	4.10 - 9.60 Mmol/L
Self-reported diabetes duration,	
Years (mean, SD)	11.51 ± 6.65
Range	1 – 26 years

4.2 Analysis of the GCIPL and RNFL thickness

4.2.1 Is there a measurable change in the retinal ganglion cell layer and inner plexiform layer thickness 1 year from baseline recordings?

Figure 5 below is a bar graph which shows the difference in the thickness (in microns) in the right eye at baseline (in blue) and one year from baseline (in red) when measuring the GCIPL thickness in the study sample. Here we can see that there is a difference as the one-year follow-up results are thinner than the baseline results for each sector.

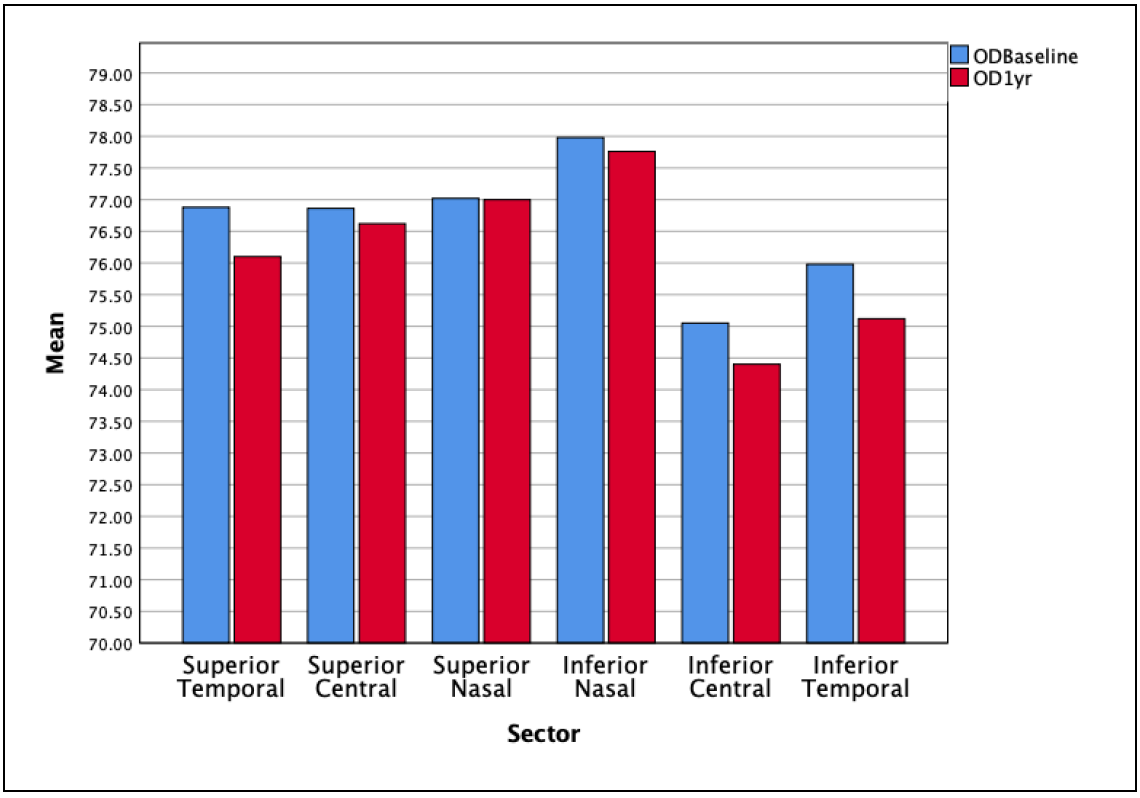
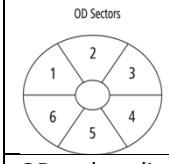


Figure 5: Graphical representation of the mean thickness (in microns) for each sector of the GCIPL; showing the difference at baseline and the one year from baseline (OD) in the type 2 diabetic subjects examined.

These values and the statistical analyses are summarised in table 5 below, where we see the average thicknesses for the GCIPL for each sector and the mean thickness for the baseline and one year from baseline results for OD; where n=42 and the degrees of freedom =41. There are 3

subjects that are excluded due to not meeting the image quality selection criteria. The mean difference is summarised, and a paired sample t-test is implemented for comparing the means at baseline and 1 year from baseline. The results show that there are differences in the means for sectors 1 (superior temporal) and 6 (inferior temporal) are statistically significant at a p-level of 0.05. We also can see that the confidence intervals for sector 1 and 6 are negative values, both the upper and the lower, also strengthening the argument that the thickness values are significantly reduced from baseline. However, sectors 2, 3, 4 and 5 did not show a significant difference in the mean thicknesses after one year; as the p values exceeded the 0.05 level of significance, and the confidence intervals cross 0. The average difference in the thicknesses was 0.548μm thinner one year from baseline, compared to the baseline recordings, and this had a p-value of 0.036, which is statistically significant with a p-value of 0.05. Therefore, when comparing the average change in OD from baseline and one year from baseline; we do not reject the null hypothesis that there is no change in the GCIPL layer thickness at baseline and one year from baseline.

Table 5 Summarised mean thickness (in microns) of the GCIPL for each sector and average thickness values for OD (using paired sample t-test):

n = 42 df = 41 	Sector 1 (superior temporal)	Sector 2 (superior central)	Sector 3 (superior nasal)	Sector 4 (inferior nasal)	Sector 5 (inferior central)	Sector 6 (inferior temporal)	Mean
OD baseline (mean ± SD)	76.88 ± 9.329	76.86 ± 9,729	77.02 ± 8.420	77.98 ± 9.259	75.05 ± 9.069	75.98 ± 9.424	76.71 ± 8.901
OD 1yr from baseline (mean ± SD)	76.10 ± 9.047	76.62 ± 9.122	77.00 ± 8.311	77.76 ± 8.700	74.40 ± 8.696	75.12 ± 9.150	76.17 ± 8.499
Mean difference ± SD	0.786 ± 1.631	0.238 ± 3.138	0.024 ± 2.454	0.214 ± 2.203	0.643 ± 2.703	0.857 ±1.802	0.548 ±1.641
$CI_{95\%}$ Lower	**-1.294**	-1.216	-0.789	-0.901	-1.485	**-1.419**	**-1.059**
$CI_{95\%}$ Upper	**-0.277**	0.740	0.741	0.472	0.200	**-0.296**	**-0.036**
Significance level (p<0.05)	**0.003**	0.625	0.950	0.532	0.131	**0.004**	**0.036**

*statistically significant values in **bold and red**

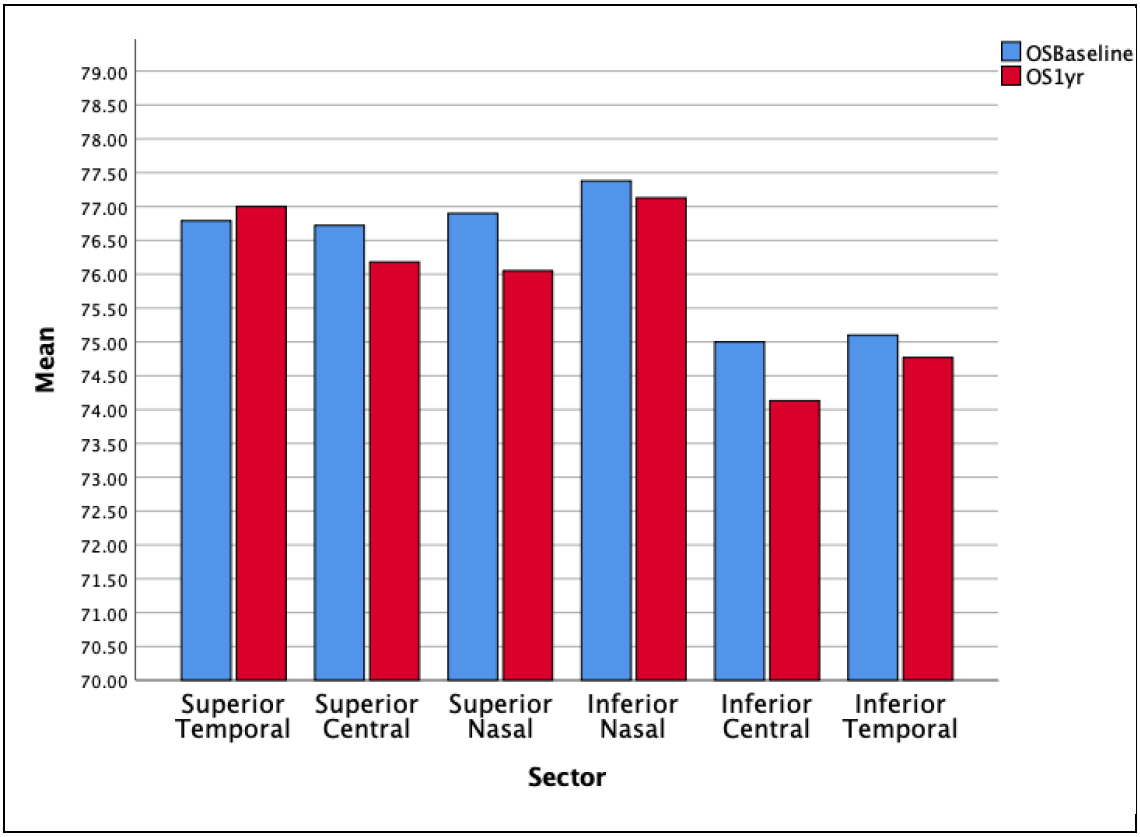


Figure 6: Graphical representation of the mean thickness (in microns) for each sector of the GCIPL; showing the difference in the baseline and the one year from baseline (OS) in the type 2 diabetic subjects examined.

Similarly, figure 6 above shows the difference in the thickness values of the GCIPL layers in the left eye at baseline and one year from baseline. These values are summarised in table 6 below, displaying the average thicknesses for the GCIPL for each sector and the mean thickness for the baseline and one year from baseline results for OS; where n=39 and the degrees of freedom =38. This is because 6 scans were excluded due to not meeting the scan quality control criteria. Here we can see that the differences for sector 2 (superior central), 3 (superior nasal) and 5 (inferior central) are statistically significant with a p-value less than 0.05. The upper and lower confidence intervals at the 95% CI also are negative values for sectors 2, 3 and 5. Therefore, we can conclude that there is a thinning in these sectors after one year. However, sector 1, 4 and 6 did not show a significant difference in the mean thicknesses after one year. The average difference in the thicknesses was 0.359μm thinner one year from baseline, compared to the baseline recordings, and this had a p-value of 0.30, and therefore is not statistically significant with a significance level of 0.05, and the 95% CI does cross 0. Therefore, when comparing the average change OS from baseline and one year from baseline; we reject the null hypothesis that there is no change in the GCIPL layer thickness at baseline and one year from baseline.

Table 6: Summarised mean thickness (in microns) of the GCIPL for each sector and average thickness values for OS (using paired sample t-test):

n = 39 df = 38 	Sector 1 (superior temporal)	Sector 2 (superior central)	Sector 3 (superior nasal)	Sector 4 (inferior nasal)	Sector 5 (inferior central)	Sector 6 (inferior temporal)	Mean
OS baseline (mean ± SD)	76.79 ± 10.224	76.72 ± 8.929	76.90 ± 7.970	77.38 ± 9.813	75.00 ± 8.808	75.10 ± 10.745	76.23 ± 9.224
OS 1yr from baseline (mean ± SD)	77.00 ± 10.024	76.18 ± 9.202	76.05 ± 8.284	77.13 ± 8.520	74.13 ± 8.805	74.77 ± 10.122	75.87 ± 8.563
Mean difference ± SD	+0.205 ±2.054	-0.538 ±1.570	-0.846 ±2.289	-0.256 ±2.890	-0.872 ±1.341	-0.333 ±1.797	-0.359 ±2.134
$CI_{95\%}$ Lower	-0.461	**-1.047**	**-1.588**	-1.193	**-1.307**	-.916	-1.051
$CI_{95\%}$ Upper	0.871	**-0.029**	**-0.104**	0.681	**-0.437**	0.249	0.333
Significance level (p<0.05)	0.537	**0.039**	**0.026**	0.583	**0.000**	0.287	0.300

*statistically significant values in **bold and red**

4.2.2 Is there a measurable change in the RNFL thickness 1 year from baseline recordings in type 2 diabetic subjects?

The RNFL measurements were taken for the 45 subjects, but of these, 6 of the OCT images were excluded due to not meeting the image quality guidelines. In table 7 below we see that the thickness levels in the RNFL OD at baseline are not significantly different from the one year from baseline results as the p-values are greater than 0.05. At the 95% confidence interval we also see that the values cross 0, so there is little significant change or decrease in thickness after one year. Though, in the nasal quadrant, we see a more significant change of -1.895μm in the thickness one year from baseline, and the p-value is 0.052, close to the 0.05 significance level. However, the global mean change in thickness was -0.949μm with a standard deviation of 3.859μm and the p-value was 0.133, therefore greater than the 0.05 significance level. The 95% CI for the mean change in thickness also crosses 0. Therefore, we reject the hypothesis that there is a measurable change or decrease in the RNFL thickness 1 year from baseline OD.

Table 7: Summarised mean thickness (in microns) of the RNFL for each sector and average thickness values for OD (using paired sample t-test):

n = 39 df = 38 	Superior	Nasal	Inferior	Temporal	Mean (global)
OD baseline (mean ± SD)	111.38 ± 15.670	75.24 ± 8.915	116.67 ± 16.503	62.51 ± 13.129	91.56 ± 10.164
OD 1yr from baseline (mean ± SD)	110.51 ± 15.204	73.34 ± 9.425	116.31 ± 16.257	61.56 ± 13.323	90.62 ± 10.261
Mean difference in thickness ± SD	-0.872 ±5.616	-1.895 ±5.811	-0.359 ±6.663	-0.949 ±3.486	-0.949 ±3.859
$CI_{95\%}$ Lower	-2.692	-3.805	-2.519	-2.079	-2.200
$CI_{95\%}$ Upper	0.949	0.015	1.801	0.181	0.302
Significance level (p<0.05)	0.338	**0.052**	0.738	0.097	0.133

These results are also represented in the graph below in figure 7; exhibiting the little difference in the thickness measurements between the one year from baseline and baseline thicknesses.

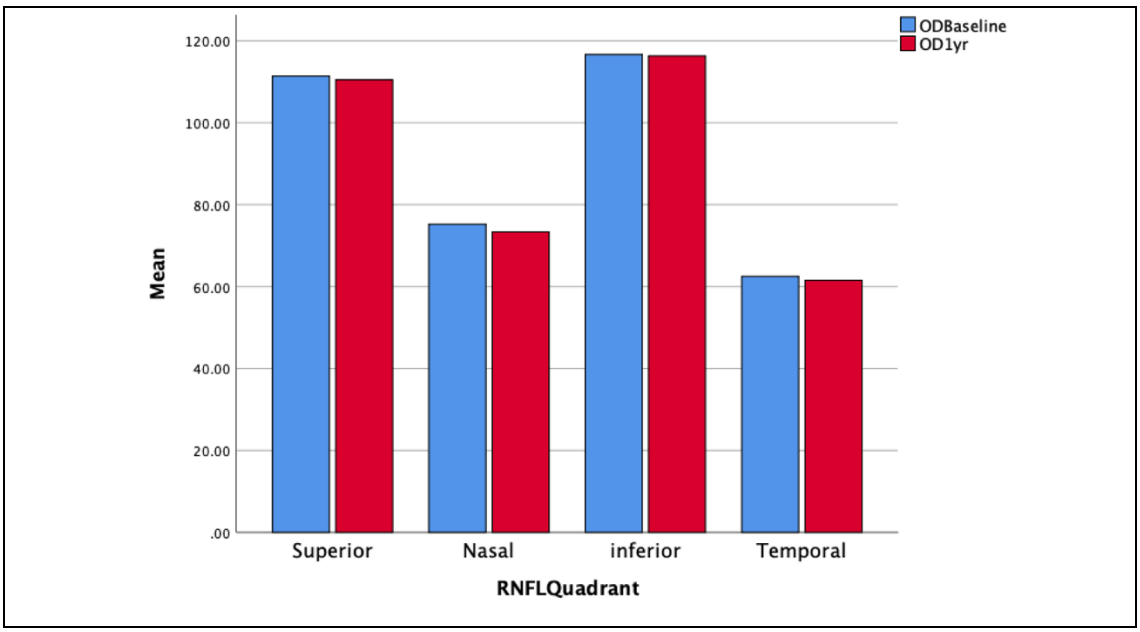


Figure 7: Graphical representation of the average change thickness (in microns) for each sector of the RNFL; showing the difference in the baseline and the one year from baseline (OD) in the type 2 diabetic subjects examined.

In a similar manner, in table 8 below, we see the results for the left eye RNFL thickness are not statistically significantly different in any of the measured quadrants when comparing the baseline thickness results to the one year from baseline results in this test population when using a significance level of p=0.05. The p-value for the mean difference when using a paired samples t - test was 0.113 which is greater than 0.05 (level of significance). The 95% CI also crosses 0. Therefore, we cannot reject the null hypothesis that there is no difference in the RNFL thickness OS when comparing baseline thickness and the thickness one year from baseline recordings. Figure 8 below also shows that in the left eye there is little change in the thickness of the RNFL at baseline and one year from baseline.

Table 8: Summarised mean thickness (in microns) of the RNFL for each sector and average thickness values for OS (using paired sample t-test):

n = 39 df = 38 	Superior	Nasal	Inferior	Temporal	Mean (global)
OS baseline (mean ± SD)	113.87 ± 14.985	69.90 ± 8.204	115.03 ± 16.145	61.03 ± 14.315	90.15 ± 10.95
OS 1yr from baseline (mean ± SD)	113.21 ± 15.208	68.64 ± 7.876	113.64 ± 14.860	61.15 ± 13.498	89.28 ± 10.195
Mean difference in thickness ± SD	-0.667 ±5.101	-1.256 ±4.632	-1.385 ±5.883	0.128 ±4.275	-0.872 ±3.357
$CI_{95\%}$ Lower	-2.320	-2.758	-3.292	-1.257	-1.960
$CI_{95\%}$ Upper	0.987	0.245	0.522	1.514	0.217
Significance level (p<0.05)	0.419	0.098	0.150	0.852	0.113

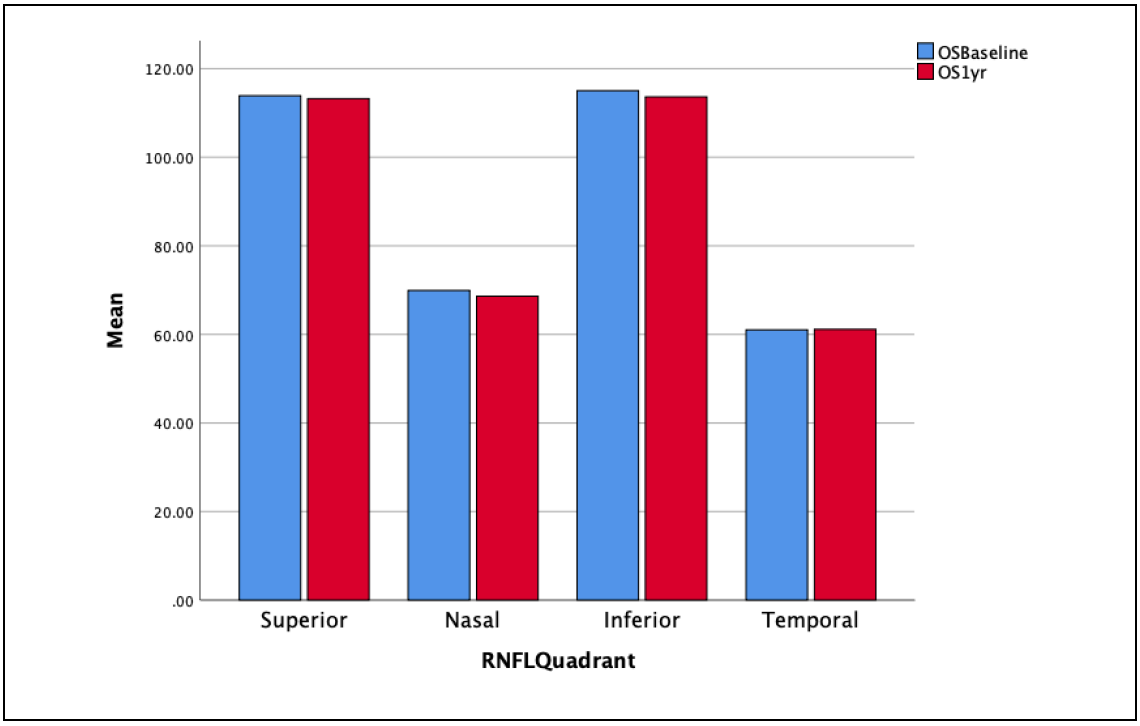


Figure 8: Graphical representation of the average change thickness (in microns) for each sector of the RNFL; showing the difference in the baseline and the one year from baseline (OS) in the type 2 diabetic subjects examined.

4.2.3 Are there any measurable changes in the visual acuity (using Log MAR) in type 2 diabetic subjects a year from baseline recordings?

The data summarised in table 9 below shows that the difference in the visual acuity is not statistically significantly different when comparing the mean VA at baseline and the mean VA 1 year from baseline recordings, in the study sample (n=45 with 44 degrees of freedom). The p-value for OD was 0.279 and for OS the p-value was 0.572, both values are greater than the 0.05 significance level, thereby rejecting the hypothesis that there is a measurable reduction in the visual acuity in the type 2 diabetic subjects one year from baseline recordings.

Table 9: The visual acuity (in Log MAR units) at baseline and at the one year from baseline recordings of the diabetic type 2 subjects and paired samples t-test and significance testing.

n = 45 Df = 44	Mean baseline	Mean 1yr from baseline	Difference in the means ± SD	95% CI of the difference		P-value (at the 0.05 significance level)
				Lower	Upper	
OD VA	-0.0836	-0.0716	-0.012 ± 0.0734	-0.0100	0.0340	0.279
OS VA	-0.0691	-0.0627	-0.00636 ± 0.0741	-0.0162	0.0289	0.572

4.2.4 Are there any measurable contrast sensitivity changes measured with the MARS contrast sensitivity test, in type 2 diabetic subjects after a year from baseline measurements?

Table 10 below shows that the contrast sensitivity was significantly different (at n=45 with 44 degrees of freedom), as p-value was less than 0.05 for both OD and OS, when testing at baseline and one year from baseline. The 95% CI also had negative values for both the lower and the upper range, not crossing 0. Therefore, these findings suggest that there is a decreased contrast sensitivity (in log units), thereby rejecting the null hypothesis that there is no reduction of the CS one year from baseline in the type 2 diabetic subjects tested. However, the clinical significance of a decrease of 0.06 log units, when one letter is equivalent of 0.04 log units, is a relatively small change after one year.

Table 10: The contrast sensitivity (using the MARS CS test – log units) at baseline and at the one year from baseline recordings of the diabetic type 2 subjects and paired samples t-test and significance testing.

n = 45 Df = 44	Mean baseline	Mean 1yr from baseline	Difference in the means ± SD	95% CI of the difference		P-value (at the 0.05 significance level)
				Lower	Upper	
OD CS	1.6131	1.5507	-0.0624 ± 0.112	**-0.962**	**-0.0287**	**0.001**
OS CS	1.6169	1.5529	-0.0640 ± 0.0741	**-0.863**	**-0.0418**	**0.000**

*statistically significant values in **bold and red**

5 Discussion

The main finding in this study showed a statistically significant reduction in the retinal GCIPL thickness one year from baseline in two sectors and global mean thickness for the right eye; and a reduction in three sectors of the left eye. However, this reduction was less than 1 micron in all sectors, and thus, this cannot be considered to have clinical significance. The results for the RNFL thickness were not significantly changed in one year, when examining the superior, inferior, nasal and temporal quadrants, as well as the average global thickness values. When simultaneously examining the visual function in these type 2 diabetic subjects; the VA results were not significantly different in the space of one year, however the CS results were reduced in the test subjects one year from baseline. These results will be further evaluated below.

When measuring changes over time, the repeatability of the instrument used is an important factor to consider. Repeatability studies conducted to test the reliability of the Cirrus HD-OCT, show good precision with posterior pole and disk measurements (Brautaset *et al.* 2016). The repeatability was evaluated by comparing macula thickness and optic disc parameters in healthy subjects with the Cirrus HD-OCT 5000, using the coefficient of repeatability (CR) which is a measure of precision representing the value below which the difference between tests may be expected to lie (with a probability of 95%) (Brautaset *et al.* 2016). It was concluded that the instrument showed high reliability and that this is believed to be a result of the improved automatic tracking systems used in the device, that increases the repeatability (Brautaset *et al.* 2016). The CR values will also be discussed with the results below.

5.1 GCIPL thickness reduction one year from baseline

Recent studies looking into the neurodegenerative changes in DR causing a reduction of retinal layer thickness have presented evidence of apoptotic activity in the inner retina prior to the onset of vascular retinopathy (Gungor *et al*. 2015). It is also hypothesised that the retinal ganglion cells in diabetic subjects synthesise less protein which thereby leads to slowed axonal transport (Chihara *et al.* 1982). In vitro studies that have observed apoptosis in neuronal and glial retinal cells in early stage diabetes leading to thinning of the inner retinal layers, and these apoptotic cells in the retina have not been dependent of the location of retinal blood vessels (Abu-El-Asrar *et al.* 2004). This neuroretinal cell loss due to apoptosis of ganglion cell bodies and glial reactivity,

subsequently leads to a thinning of the GCL in diabetic subjects compared with healthy control subjects (Abcouwer & Gardner, 2014). Therefore, the hypothesis that the GCIPL thickness is reduced in diabetic subjects is examined in relation to diabetes having a neurodegenerative effect in the retina, can be of clinical importance. In a similar study, supporting the theory that DM has a neurodegenerative effect of the retina with or without vascular DR, it was concluded that the GCIPL thickness in type 1 diabetic patients, was 5.1μm thinner than in healthy control patients, with a 95% CI of 1.1 – 9.1μm (Dijk *et al.* 2010).

In this study we examined the change in the thickness one year from baseline recordings and found that there was a reduction in the thickness of the GCIPL in the left eye only in sectors 2 (superior), 3 (superior temporal) and 5 (inferior), which are statistically significant ($p < 0.05$). The average difference in the global thicknesses was 0.359μm thinner one year from baseline, compared to the baseline recordings, and this had a p-value of 0.30, and is therefore not statistically significant with a significance level of 0.05. The results for the right eye showed that there are differences in the means for only sectors 1 and 6 (superior nasal and inferior nasal) which are statistically significant at a p-level of 0.05. Thus, we can see that there is a reduction in the thickness in sectors 1 and 6 after one year. The average difference in the thicknesses was 0.548μm thinner one year from baseline, compared to the baseline recordings, and this had a statistically significant p-value of 0.036. Therefore, when comparing the average change in OD from baseline and one year from baseline; we do not reject the null hypothesis that there is no change in the GCIPL thickness at baseline and one year from baseline. However, this change in thickness has little clinical significance due to this change being very minimal in the space of just one year. In other studies examining the neuroretinal layer thickness, specifically the RNFL and GCIPL, it was concluded that there was a 0.54μm change in thickness per year, which is comparable to severe glaucomatous damage of the retinal layers of 6-16μm thinning over a 10 year period (Sohn *et al.* 2016 & Bogunovic *et al.* 2015). Therefore, the diminutive reduction in thickness of the GCIPL observed in the results from this study have little clinical significance to be able to conclude that there is a definite neurodegenerative effect after just one year.

In another study evaluating the high reproducibility and repeatability of the Cirrus HD-OCT when measuring the GCIPL thickness in healthy subjects, with a study population of 60 healthy subjects, with no RNFL defects, concluded that the Cirrus software can successfully demarcate the macular GCIPL and exclude the RNFL (Carpineto *et al.* 2014). When evaluating the CR of two observers over two visits, the average CR for all sectors were 2.1 and 2.2 microns respectively, and the CR values ranged from 1.7 microns (inferotemporal) to 7.5 microns (inferior); therefore changes of

less than 1 micron, as found in this current study, are not considered clinically significant due the variability of the machine (Carpineto *et al.* 2014). The study did, however, establish that the high reproducibility of the Cirrus HD-OCT due to the detection and registration of the center of the macula with tracking which was used in this study to ensure that the images are comparable to baseline measurements (Carpineto *et al.* 2014). Images that did not have tracking were excluded from this study, as this would not have allowed for following the evolution of disease progression in the diabetic subjects. Repeatability and the reproducibility were greater in the global average thickness measures and sectorial scans when measuring GCIPL thickness, compared to minimum thickness scans, due to the sectorial and average scans sampling 1100-1300 points in each B-scan compared to 50-60 points when measuring the minimum thickness (Carpineto *et al.* 2014). Other similar studies evaluating the repeatability of the Cirrus HD-OCT and the GCIPL measurements also concluded that there was a high repeatability when correlating the RGC parameters by the Ganglion Cell Analysis (GCA) algorithm due to the ability to exclude the RNFL thickness, giving it a greater diagnostic value (Ng *et al.* 2015 & Mwanza *et al.* 2011). Still any change in the tissue thickness needs to exceed the variability of the instrument to be able to conclude that the change is clinically significant.

Although some of the results in this study do support that there is a reduction in the GCIPL after one year, and the Cirrus HD-OCT has good repeatability, the one year time frame is likely to be too short and the thickness change of less than 1 micron in both eyes is inconclusive and further study should be conducted to examine the results. The normal age-related change in the thickness of GCIPL should also be taken into consideration, when looking at this change over time. In a study examining the change of the GCL thickness in 52 healthy subjects; the normal age-related loss over a 4-year time span was 7877 RGCs per 1 year of increased age (Medeiros *et al.* 2012).

5.2 Little change in the RNFL thickness one year from baseline

Previously, RNFL thickness has only been of interest in terms of glaucoma treatment and management. The peripapillary RNFL area in diabetics is more likely to decrease in thickness in contrast to the macular RNFL area which has a different mechanism in diabetes and can have a predisposition to thicken due to oedema (Sugimoto *et al.* 2004). Histopathological studies that have examined this phenomenon speculate that ischemia, in diabetics, disrupts the Müller cells

and axons, which are greatly concentrated in the macular region, which is a predisposition to cystic macular oedema developing (Dick, 1999).

Similarly to the neuroretinal loss in the GCIPL, several studies have reported that there is diabetes related thinning observed in the RNFL, and the average peripapillary RNFL thickness in the superior quadrant is thinner in diabetic subjects in early DR when compared to a nondiabetic control group (Peng et al. 2009 & Lopes *et al.* 2002). Another study examining RNFL thickness in type 2 diabetic subjects using the Cirrus HD-OCT also found that the superior quadrant was more vulnerable than the other quadrants and concluded that the RNFL thickness was an early indicator of neurodegeneration prior to DR (Jeon *et al.* 2016 & Sugimoto *et al*. 2004). Studies suggest that the superior RNFL is more vulnerable to initial damage in DR than the other quadrants, as there are also twice as many microaneurysms and cellular capillaries in the superior retina compared to the inferior retina, supporting the hypothesis that the superior retina is more structurally damaged in diabetic subjects (Kern & Engerman 1995).

Variability of the RNFL measurements should also be taken into consideration, studies that have evaluated the repeatability of the RNFL measurements with the optic disc scan have deemed the peripapillary RNFL and OHN measurements with the Cirrus HD-OCT as having a good reproducibility and repeatability when examining the progression of disease (Mwanza *et al.* 2010). In a study that examined 55 subjects looking at the optic disc cube 200x200 scan; concluded that a decrease of 4μm or more would be a statistically significant change from baseline thickness when comparing RNFL thicknesses (Mwanza *et al.* 2010). Another consideration that should be made is that the age-related reduction in RNFL thickness is considered to be 0.3% per year after the age of 50 years (Wang et al. 2011). In a study examining repeatability of the Cirrus HD-OCT 5000, it was reported that the CR values ranged from 0.0-1.09 for NFL thickness in the different quadrants and 3.39 for the global average thickness (Brautaset *et al.* 2016).

In our study, there was no significant difference seen in any one particular sector or in the average thickness after one year from baseline results. When examining the results for the right eye, there was a reduction in the average thickness seen in all quadrants, ranging from the least change inferiorly which was 0.359μm thinner and the greatest change nasally which was 1.895μm thinner. The results for the left eye range from the greatest reduction inferiorly at 1.365μm thinner to an increased thickness temporally which was 0.128μm thicker than at baseline. The global mean difference in the 4 quadrants of the left eye was 0.872μm thinner. The change in the

thickness values for the right and left eye at (38 degrees of freedom); were not statistically significant when observing a p-value of 0.05; and all differences were very insignificant in the difference in thickness. Using the parameters of machine variability established in a previous study, if 4μm in difference is considered to be statistically significant, then the results in this study does not show a significant difference (Mwanza *et al.* 2010). Therefore, the thickness results for the RNFL should be further investigated with a larger population size over a longer period of time to show more conclusive results. Subsequently, the results from this study do not confirm the hypothesis that there is a measurable neurodegenerative effect after one year from baseline in DM patients measured with the OCT.

5.3 Little change in the visual function one year from baseline

The VA results did not change significantly from baseline recordings in the test population, this is likely to be a result of one year being too short of a time frame to see any change in the VA. The subjects in this study also had little change in spectacle refraction in this space of time. The difference in the VA was therefore not significantly reduced. However, the contrast sensitivity results were statistically significantly reduced from the baseline recordings in the test population. In the right eye the difference in the means from baseline and one year from baseline was 0.0623 log units with a p-value of 0.001 and in the left eye 0.064 log units ($p<0.05$ level of significance). This suggests that the CS was reduced after a year from recording in the diabetic subjects examined in this study. When examining the clinical significance of these values, one letter reduction is the equivalent of 0.04 log units, and therefore there is little difference one year from baseline. Although one letter difference after one year has little clinical significance, there is a strong indication that measuring and monitoring CS over time can have clinical significance in terms of retinal function and is therefore important to measure when evaluating diabetic patients. However, any difference in both the VA and CS can be accounted for other factors such as the presence of lens opacities or corneal opacities, as well as the age-related reduction in VA and CS that can occur over time.

Other studies that have investigated the effect of DM2 on visual function that also evaluated the BCVA (using ETDRS tests) and CS (using Pelli Robson and CSV100E tests) as well as colour vision (using the Farnsworth 15D and Lanthony 15D tests) and visual fields using the Easyfield perimeter (Palomar *et al*. 2018). The study concluded that there was a significant reduction in the BCVA (2.5%) in the diabetic subjects compared to the healthy controls, but no significant difference in

the Pelli Robson CS or perimetry results, and the colour vision was reduced in subjects that had an earlier age of diagnosis (Palomar *et al*. 2018). However, in this study population there were primarily participants without DR (62.7%), and the results are likely to differ if there was a larger group of participants with DR examined and if there was a healthy control group to compare the results to.

5.4 Considerations and future implications

Previously diabetic retinopathy diagnosis and monitoring has been solely based on vascular changes in the retina examined by ophthalmoscopy and fundus photography. However, with increasing use of OCT in clinical practice, diagnosis and monitoring of early non-vascular diabetic changes is possible through subjective quantitative results of retinal layer thickness. There has been increasing interest in neurodegenerative changes which lead to reductions in the thickness of the retinal layers. By taking good quantitative baseline measurements of retinal layer thicknesses, with tracking, in diabetic subjects and following them up over time to compare results, clinicians can effectively monitor disease progress.

Although some of the results are consistent with other studies and support the hypotheses, there are several limitations of this study. The small study population can be a limitation in reaching a conclusive change in the RNFL and GCIPL layer thickness in diabetic participants one year from baseline. There is reason to believe that the time span of one year from baseline is too short to be able to have any measurable changes in the GCIPL and RNFL thickness, as well as significant changes in the visual function, specifically the VA. If the results were to be compared after 5 and 10 years, the results could show more of a trend and give more conclusive data. The study could also be repeated with a control group in order to have another comparison in terms of the thickness changes and the visual function changes over time. If the study was repeated with a larger study group, the number of patients with DR could also have been larger to have a more representative population amongst the diabetic participants with DR. The subjects in this study also had variable levels of diabetic control (medications, insulin control and lifestyle intervention), self-reported diabetes duration and blood glucose levels, that were not measured as a part of this study, and therefore likely to be somewhat unreliable. In another prospective longitudinal study, examining the pre-DR effect of DM, found that the longer the duration of DM, the thinner the RNFL and GCIPL thickness was at baseline when compared to control patients (Sohn *et al.*

2016). They concluded that per year of DM duration was associated with 0.19-0.21 μm thinner macular RNFL and 0.11-0.44 μm thinner macular GCIPL than in healthy patients (Sohn *et al.* 2016).

Diabetic retinal neurodegeneration (DRN) preceding DR, in recent years considered as the primary manifestation of ocular changes in diabetic subjects (Lynch & Abramoff, 2017). By diagnosing DRN with OCT measurements, visual loss and blindness can potentially be delayed in an ageing population, increasing quality of life and lessening the economic burden of diabetes related visual loss (Lynch & Abramoff, 2017). In the future, neurodegeneration could potentially be treated to delay neural cell apoptosis, with neuroprotective agents used to hinder DRN (Beltramo *et al.* 2016). Alternative therapies may aim to prevent the onset of visual loss by implementing neuroprotective therapies that target neurotransmitters which will preserve the neural retina integrity (Barber & Baccouche, 2017). Mechanisms for neuroprotection of diabetic changes in the retina have been investigated in several studies looking at different treatment modalities targeting neuroretinal homeostasis, the blood-retinal barrier and metabolite delivery to the retina (Imai *et al.* 2009). However, further study is required to evaluate which of the mechanisms for neurodegeneration should be in focus and which effects these neuroprotective factors could have on slowing retinal neurodegeneration in diabetic subjects (Imai *et al.* 2009). The results of such studies are of significance in terms of helping practitioners understand if the GCIPL and RNFL thickness measurements with OCT can be a useful tool in assisting the monitoring of DRN progression in diabetic subjects, and in order to screen them for DR.

The results from the literature suggests that the OCT may play a greater role in earlier detection of structural changes in the retina, both prior to and in addition to vascular DR findings. It is paramount that clinicians have good baseline measurements that can be used to track progress over time, and therefore image quality and tracking are important when following disease progression. A decrease in the thickness of the GCIPL and RNFL thickness could be indicative of a neurodegenerative effect of diabetes type 2, prior to the appearance of microvascular changes that are apparent in diabetic retinopathy. An early neurodegenerative effect of diabetic eye disease prior to retinopathy would thereby strengthen the argument that diabetes is a neurodegenerative disease as well as a vascular disease. Thereby providing useful information about whether neuroprotective treatments (such as those used in glaucoma treatment and management) could be implemented by ophthalmologists prior to vascular retinal changes to avoid neurodegeneration in the retina, and therefore avoid functional visual loss.

6 Conclusion

The GCIPL did have a significant thinning in a few of the sectors, however, the change had little clinical significance, which is likely to be due to the short time period of just one year. The RNFL thickness was not significantly changed after one year. In terms of visual function, the VA was not significantly changed after one year. However, the CS decreased after one year; though this change was minimal, with just one letter decrease in the log sensitivity. These findings, although not very clinically significant, can contribute to improved diabetic patient care, showing the importance of good baseline recordings of visual function and OCT scans which could be compared over longer periods of time. Even though the data was collected from patients in a large region of Norway, the small study population and the short time frame does limit the clinical applications of the results. Therefore, the study should be repeated with a larger population and ideally over longer periods of time to establish a more conclusive relationship between diabetes and retinal neurodegeneration.

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7 List of tables

8 List of figures

9 Annexes

Annex 1: Written concent and information given to patients:

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

Diabetes, syn og øyehelse

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

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

HVA INNEBÆRER PROSJEKTET?

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

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

MULIGE FORDELER OG ULEMPER

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

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

ubehagelig da dråpene kan svi noe, og at man blir mer lysømfintlig i etterkant. Effekten av øyedråpene vil avta gradvis og opphører helt etter noen timer. Du bør ikke kjøre bil før synet er normalisert.

Det er gratis å delta i prosjektet.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling ved NOSØ. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte førsteamanuensis Tove Lise Morisbakk (tlf 31 00 97 55, tovelm@usn.no) eller førsteamanuensis Vibeke Sundling (tlf 31 00 89 55, vibeke.sundling@usn.no).

HVA SKJER MED INFORMASJONEN OM DEG?

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

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

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

FORSIKRING

Pasientskadeloven.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, (2018/804).

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato

Signatur

Annex 2: Data registration booklet (excluding questionnaires that are not relevant for this study)

ID-Number:

DIABETES, VISION AND OCULAR HEALTH

Name:

Date of birth:

Phone-number:

Mail address:

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

Date:

Signature:

ID-Number: _____

DIABETES, VISION AND OCULAR HEALTH

1 Patient history

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

ID-Number: _____

2 Visual function

2.0 Pd:

		OD	OS	OU
2.1	Habitual refraction	/ x	/ x	
2.2	Habitual visual acuity (logMAR)			
2.3a	Autorefractor			
2.3b	Pachymetry			
2.4	Subjective refraction	/ x	/ x	
2.5	Best corrected visual acuity (logMAR)			
2.6	Visual acuity with pinhole (logMAR ≤ 0.2)			
2.7	Near add at 40 cm			
2.8	Near visual acuity at 40 cm			

2.9 Cover test

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

Comments:

2.10 Color vision – HRR at 66 cm

OD	OS
☐ Normal	☐ Normal
☐ Deficiency	☐ Deficiency

2.11 Amsler at 30 cm

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

2.12 Contrast sensitivity MARS at 50 cm

OD	OS

2.14 Pupillary responses

☐ Normal
☐ Abnormal

2.13 Motility

☐ Normal
☐ Abnormal

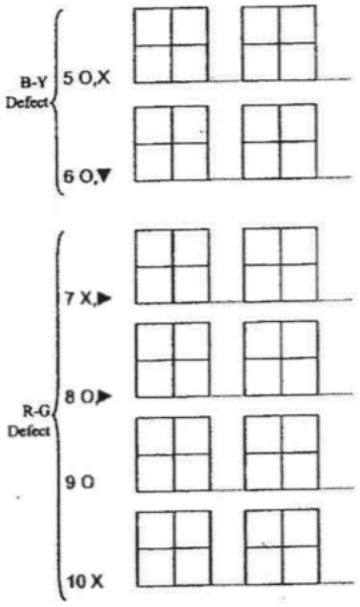
*** Remember to check blink rate before switching room!**

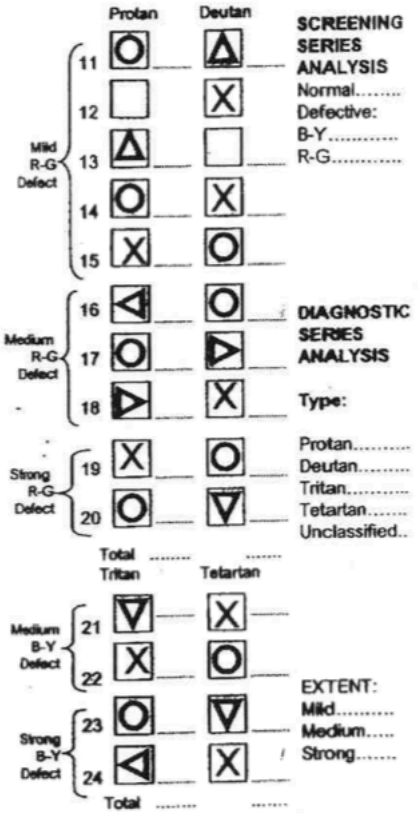
H R R PSEUDOISOCHROMATIC PLATES

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

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

SCREENING SERIES





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

DIAGNOSTIC SERIES ANALYSIS

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

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

1021 South Rogers Circle Suite 6 Boca Raton, FL 33487

Laminated Version P/N 4458

ID-Number:_____

3 Ocular health

Have you used eye drops today? ☐ No ☐ Yes, type and time:

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

ID-Number:_____

3 Ocular health

OD				OS		
…… mm /5 min.			3.10 Schirmer 1 Test 15 minutes after ocular staining	…… mm/5 min.		
*** Remember to clean lid margin!**						
☐ Meibomian glands in line ☐ Even lid margin: Other:			3.11a Eye lid examination Morphological features	☐ Meibomian glands in line ☐ Even lid margin: Other:		
No. of expressible glands OD ……..		Grade ……..	3.11b Meibum expressibility (Central 5 glands)	No. of expressible glands OS ……..		Grade ……..
…. glands x 0 = …. glands x 1 = …. glands x 2 = …. glands x 3 =		Total score	3.11c Meibum quality (central 8 glands) Clear fluid= 0 Cloudy fluid= 1 Cloudy particulate fluid = 2 Like toothpaste = 3	…. glands x 0 = …. glands x 1 = …. glands x 2 = …. glands x 3 =		Total score
Upper lid:	Lower lid:	Total	3.12 Meibography Meibomian gland drop-out Upper and lower lid according to scale	Upper lid:	Lower lid:	Total
			3.13 Corneal senstivity (Cochet-Bonnet)*			
			3.14 Crystalline lens transparency (LOCS III grading)			
			3.15 Pupille size after dilation			

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

Comments:

ID-Number:_____

3 Ocular health

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

*** Remember to check the crystalline lens!**

3.19	Perimetry - Octopus	OD ☐ Normal ☐ Visual field loss	OS ☐ Normal ☐ Visual field loss

Retinal Assessment

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

4	**Management of participants**		
4.1	Prescription provided	☐ Yes ☐ No	
4.2	Further managment	☐ Yes ☐ No	☐ Full eye examination ☐ Dry eye ☐ Referral ☐ Emergency
4.3	Reason for further managment		☐ Symptoms ☐ Visual acuity ☐ Binocular vision ☐ Visual fields ☐ Colour vision ☐ Intraocular pressure ☐ Anterior segment / dry eye ☐ Cataract ☐ Retinopathy ☐ Maculopathy ☐ Glaucoma ☐ Other
5	**Comments:**		

Date:

Signature:

Annex 3: MARS contrast sensitivity score sheet

The Mars Numeral Contrast Sensitivity Test

Score Sheet

Patient _____ **Administered by** _____

Date _____ **Correction** _____ **Test distance** _____

Comments _____

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

Important: Allow *only* the numerals 0 1 2 3 4 5 6 7 8 9 as responses.

Row	FORM 1 Left eye ☐ Right eye ☐ Binocular ☐				
1	0 ☐ 0.04	2 ☐ 0.08	8 ☐ 0.12	5 ☐ 0.16	7 ☐ 0.20	4 ☐ 0.24
2	1 ☐ 0.28	7 ☐ 0.32	9 ☐ 0.36	4 ☐ 0.40	6 ☐ 0.44	3 ☐ 0.48
3	4 ☐ 0.52	1 ☐ 0.56	6 ☐ 0.60	2 ☐ 0.64	8 ☐ 0.68	9 ☐ 0.72
4	0 ☐ 0.76	7 ☐ 0.80	5 ☐ 0.84	4 ☐ 0.88	3 ☐ 0.92	2 ☐ 0.96
5	3 ☐ 1.00	4 ☐ 1.04	8 ☐ 1.08	1 ☐ 1.12	7 ☐ 1.16	6 ☐ 1.20
6	9 ☐ 1.24	6 ☐ 1.28	1 ☐ 1.32	3 ☐ 1.36	2 ☐ 1.40	5 ☐ 1.44
7	2 ☐ 1.48	9 ☐ 1.52	0 ☐ 1.56	8 ☐ 1.60	6 ☐ 1.64	3 ☐ 1.68
8	7 ☐ 1.72	0 ☐ 1.76	9 ☐ 1.80	1 ☐ 1.84	8 ☐ 1.88	5 ☐ 1.92

Log CS value at final correct numeral: _____

Number of errors prior to final correct numeral _____ **X 0.04 =** _____

Subtract

log Contrast Sensitivity _____

Row	FORM 2 Left eye ☐ Right eye ☐ Binocular ☐					
1	3 ☐ 0.04	7 ☐ 0.08	2 ☐ 0.12	5 ☐ 0.16	4 ☐ 0.20	0 ☐ 0.24
2	9 ☐ 0.28	1 ☐ 0.32	0 ☐ 0.36	6 ☐ 0.40	8 ☐ 0.44	5 ☐ 0.48
3	0 ☐ 0.52	3 ☐ 0.56	5 ☐ 0.60	4 ☐ 0.64	6 ☐ 0.68	7 ☐ 0.72
4	4 ☐ 0.76	7 ☐ 0.80	9 ☐ 0.84	3 ☐ 0.88	2 ☐ 0.92	1 ☐ 0.96
5	2 ☐ 1.00	4 ☐ 1.04	0 ☐ 1.08	5 ☐ 1.12	6 ☐ 1.16	9 ☐ 1.20
6	8 ☐ 1.24	3 ☐ 1.28	7 ☐ 1.32	4 ☐ 1.36	1 ☐ 1.40	6 ☐ 1.44
7	3 ☐ 1.48	6 ☐ 1.52	8 ☐ 1.56	9 ☐ 1.60	5 ☐ 1.64	7 ☐ 1.68
8	8 ☐ 1.72	9 ☐ 1.76	0 ☐ 1.80	1 ☐ 1.84	8 ☐ 1.88	2 ☐ 1.92

Log CS value at final correct numeral: _____

Number of errors prior to final correct numeral _____ **X 0.04 =** _____

Subtract

log Contrast Sensitivity _____

Row	FORM 3 Left eye ☐ Right eye ☐ Binocular ☐					
1	2 ☐ 0.04	6 ☐ 0.08	9 ☐ 0.12	8 ☐ 0.16	0 ☐ 0.20	4 ☐ 0.24
2	7 ☐ 0.28	5 ☐ 0.32	3 ☐ 0.36	1 ☐ 0.40	6 ☐ 0.44	7 ☐ 0.48
3	3 ☐ 0.52	1 ☐ 0.56	0 ☐ 0.60	8 ☐ 0.64	5 ☐ 0.68	2 ☐ 0.72
4	4 ☐ 0.76	7 ☐ 0.80	5 ☐ 0.84	9 ☐ 0.88	0 ☐ 0.92	1 ☐ 0.96
5	6 ☐ 1.00	2 ☐ 1.04	4 ☐ 1.08	3 ☐ 1.12	9 ☐ 1.16	5 ☐ 1.20
6	0 ☐ 1.24	6 ☐ 1.28	7 ☐ 1.32	8 ☐ 1.36	3 ☐ 1.40	4 ☐ 1.44
7	7 ☐ 1.48	3 ☐ 1.52	6 ☐ 1.56	4 ☐ 1.60	2 ☐ 1.64	1 ☐ 1.68
8	0 ☐ 1.72	8 ☐ 1.76	2 ☐ 1.80	1 ☐ 1.84	5 ☐ 1.88	9 ☐ 1.92

Log CS value at final correct numeral: _____

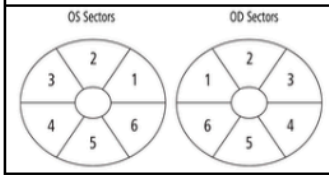
Number of errors prior to final correct numeral _____ **X 0.04 =** _____

Subtract

log Contrast Sensitivity _____

mars perceptrix

Annex 4: Data collection form

Nr:				
ID number				
Date for baseline exam:				
Date for 1yr exam:				
Age				
Gender				
Diabetes duration				
Blood glucose level				
Sph Rx equivalent				
VA baseline				
VA 1 year				
CS baseline				
CS 1 year				
	OD base	OS base	OD 1yr	OS 1yr
DR (Y/N) – fundus evaluation:				
Tracking (Y/N)				
Signal strength				
Quality **checklist				
Average RNFL thickness				
 RNFL OCT superior				
 RNFL OCT nasal				
 RNFL OCT inferior				
 RNFL OCT temporal				
1 GCL Sup nasalt				
2 GCL Superior				
3 GCL sup temp				
4 GCL inf temporalt				
5 GCL inferior				
6 GCL inf nasalt				
Average GCL thickness:				
	Comments/notes:			