EVALUATION OF ASSOCIATED FACTORS OF OPTICAL COHERENCE TOMOGRAPHY FEATURES AND THEIR ASSOCIATION WITH VISUAL ACUITY AMONG DIABETIC PATIENTS WITH CLINICALLY SIGNIFICANT MACULAR OEDEMA

DR NIK NURFARHANA BINTI NIK MOHD NOOR

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DISCLAIMER

I hereby clarify that the work in this dissertation is of my own except for quotations, some figures and summaries which have been duly acknowledged. I declare that I have no financial of interest in the instruments and the computer software used in this study.

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(Dr Nik Nurfarhana Binti Nik Mohd Noor)

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

ABSTRAK

Pengenalan:

Bengkak makula akibat diabetes (CSMO) adalah kategori khusus retinopati diabetik (DR) yang diakibatkan oleh komplikasi saluran darah kecil dalam penyakit diabetes mellitus (DM). Ia mengakibatkan perubahan struktur pada makula.

Pengimbas *optical coherence tomography* (OCT) membantu mengesan struktur dan menganalisa CSMO. Status DM dan peringkat DR boleh memberi kesan terhadap morfologi dan kuantitatif parameter CSMO. Ciri-ciri OCT secara langsung boleh mempengaruhi kejelasan penglihatan. Dengan mengenal pasti faktor-faktor berkaitan ciri-ciri OCT, kita dapat berbincang dengan pesakit tentang jenis rawatan, prognosis penglihatan dan juga hasil rawatan.

Objektif:

Matlamat kajian ini adalah untuk mengenalpasti faktor-faktor (demografi, penyakit sistemik dan faktor okular) yang memberi kesan terhadap ciri-ciri OCT bengkak makula. Kajian ini juga bertujuan untuk mengenalpasti kaitan antara ciri-ciri OCT dengan kejelasan penglihatan.

Kaedah Kajian:

Kajian rentas ini dijalankan di Klinik Oftalmologi, Hospital Universiti Sains Malaysia daripada Januari 2020 sehingga November 2021 di kalangan pesakit DM jenis 2. Pengimbas OCT dijalankan untuk mengenalpasti jenis morfologi [*sponge-like diffuse retina thickness* (SLDRT), *cystoid macular oedema* (CMO), dan *subretinal fluid* (SRF)] dan menganalisa kuantitatif OCT parameter bengkak makula [*central macula thickness* (CMT) and isipadu retina].

Keputusan:

Seramai 140 pesakit DM jenis 2 yang menghidapi bengkak makula telah dipilih untuk kajian ini. Purata jangka masa penyakit DM jenis 2 adalah 12.0±6.0 tahun dan purata bacaan HbA1c adalah 10±2.5%. Kebanyakan pesakit tergolong di dalam golongan penglihatan terhad yang ringan (lebih daripada 6/18; 45%), ini diikuti dengan penglihatan terhad jenis sederhana (6/18 – 6/60; 32.9%) dan penglihatan terhad jenis teruk (6/60 – 3/60; 9.3%). Seramai 12.9% pesakit berada pada tahap kebutaan (kurang daripada 3/60). Kebanyakan pesakit mempunyai ciri OCT morfologi jenis SLDRT (39.3%), diikuti dengan jenis kombinasi (30.0%), jenis CMO (25.0%) dan jenis SRF (5.7%). Segelintir pesakit mempunyai *epiretinal membrane* (ERM; 19.3%) dan *vitreomacular traction* (VMT; 1.4%). Faktor-faktor yang mempengaruhi ciri-ciri OCT morfologi CSMO adalah jangkamasa DM (untuk SLDRT dan jenis kombinasi), peringkat retinopati diabetik proliferatif (PDR) (untuk SLDRT), CMT (untuk SLDRT dan CMO) dan isipadu retina (untuk CMO, SRF dan jenis kombinasi). Untuk kuantitatif OCT parameter, faktor-faktor berkaitan adalah jenis CMO (untuk CMT); umur, jenis SRF, jenis SLDRT dan CMT (untuk isipadu retina) dan jenis kombinasi (untuk CMT dan isipadu retina). Di kalangan ciri-ciri OCT morfologi, jenis SRF mempunyai hubungan yang signifikan dengan kejelasan penglihatan. Manakala untuk ciri-ciri OCT kuantitatif, CMT dan isipadu retina mempunyai hubungan yang signifikan dengan kejelasan penglihatan.

Kesimpulan:

Kebanyakan pesakit mempunyai ciri OCT morfologi jenis SLDRT dan kejelasan penglihatan terbaik dapat dilihat di kalangan pesakit yang mempunyai jenis SLDRT. Jangkamasa DM, tahap PDR, CMT dan isipadu retina adalah faktor-faktor yang mempengaruhi ciri-ciri OCT morfologi. Manakala umur dan ciri-ciri OCT morfologi mempengaruhi ciri-ciri OCT kuantitatif. SRF, CMT dan isipadu retina mempunyai hubungan signifikan dengan kejelasan penglihatan. Dengan mengawal tahap DR dengan baik, ia akan mengurangkan kerosakan pada struktur makula dan memberi kejelasan penglihatan yang terbaik

ABSTRACT

Introduction:

Clinically significant macular oedema (CSMO) is a specific category of diabetic retinopathy (DR) which is a microvascular complication of diabetes mellitus (DM) that lead to structural changes at the macular.

Optical coherence tomography (OCT) offers a structural and quantitative analysis of CSMO. DM status and severity of DR can affect the OCT morphological features and OCT quantitative parameters of CSMO. Visual acuity is directly affected by the changes of these OCT features. By identifying its associated factors, we can address to CSMO patients regarding the choice of treatment, visual prognosis and also the treatment outcome.

Objectives:

Our objective was to identify the associated factors (demographic, systemic and ocular factors) affecting OCT features (OCT morphology and OCT quantitative parameters) among CSMO patients and also to determine association of these OCT features with visual acuity.

Methods:

A cross-sectional study was conducted in the Ophthalmology Clinic, Hospital Universiti Sains Malaysia (USM), from January 2020 till November 2021 among Type 2 DM patients with CSMO. OCT was performed to identify the OCT morphological features [sponge-like diffuse retina thickness (SLDRT), cystoid macular oedema (CMO), and subretinal fluid (SRF)] and to measure OCT quantitative features [central macula thickness (CMT) and retina volume].

Results:

A total of 140 Type 2 DM patients with CSMO were recruited and analysed in this study. The mean duration of Type 2 DM was 12.0±6.0 years and the mean HbA1c were 10±2.5%. Majority of the patients had mild form of visual impairment (better than 6/18; 45%), followed by moderate visual impairment (6/18 – 6/60; 32.9%) and severe visual impairment (6/60 – 3/60; 9.3%). There was 12.9% of patients presented with blindness (worse than 3/60). The most common OCT morphological features were SLDRT (39.3%), followed by mixed type (30.0%), CMO (25.0%) and SRF (5.7%). Small number of patients had epiretinal membrane (ERM; 19.3%) and vitreomacular traction (VMT; 1.4%). The associated factors affecting OCT morphological features among diabetic patients with CSMO were DM duration (for SLDRT and Mixed type), PDR status (for SLDRT), CMT (for SLDRT and CMO) and retina volume (for CMO, SRF and mixed type). For OCT quantitative features, the associated factors were CMO type (for CMT); age, SRF type, SLDRT type, and CMT (for retina volume) and mixed type (for CMT and retina volume). Among the OCT morphological features, SRF type had significant association with visual acuity. Among the OCT quantitative features, CMT and retina volume had significant association with visual acuity.

Conclusion:

The most common OCT morphological type among CSMO was SLDRT and the best mean visual acuity was observed in SLDRT group. Duration of DM, PDR status, CMT and retinal volume are the factors affecting OCT morphological features. Whereas age and OCT morphological features are the factors affecting the OCT quantitative parameters. SRF, CMT and retina volume had significant association with the visual acuity. By stabilizing the severity of DR status, it will reduce the structural damage of macular and provide good outcome of visual acuity.

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1 Study Introduction

Diabetes mellitus (DM) is a heterogenous metabolic syndrome in which diabetic retinopathy (DR) is one of its microvascular complications. The prevalence of DR in type 2 DM in developing and developed country ranges from 12.2 to 61.0% and 9.9 to 48.1% respectively (Yao et al., 2021). Diabetic macular oedema (DMO) is its specific category in which if it involves the central macula can cause significant visual impairment (DMO Guidelines, 2015). Based on National Eye Survey (NES) conducted in 2018, DR falls second and third for the cause of blindness with moderate to severe visual impairment respectively (NES II, 2018).

DMO can occur in any stage of DR (DMO Guidelines, 2015). Clinically significant macular oedema (CSMO) is described as having thickening of the retina or presence of hard exudates within one disc diameter of the fovea (Mathew et al., 2015). In clinical presentation, they may appear the same but with different visual presentation.

The development of macular oedema is not fully understood. It causes breakdown of the inner blood retinal barrier rather than outer blood retina barrier. Vascular endothelial growth factor formation and inflammatory factors contribute to the vascular leakage process and causing accumulation of extracellular fluid from hyperpermeable retinal capillaries causing macula to be thickened (Browning et al., 2018).

With the advent of optical coherence tomography (OCT) and its evolution, a lot of aspect and study regarding the retina can be explored. It is commonly used imaging technology because it is non-invasive, provides high resolution quantitative measurements and direct visualization of the layered retinal structures (Leung et al., 2008). It is used both for early diagnosis and monitoring of disease progression of retinal and macular. It offers a structural and quantitative

analysis of CSMO. There are multiple morphological changes of the CSMO that can be detected by OCT such as sponge-like diffuse retinal thickness (SLDRT), cystoid macular oedema (CMO) and subretinal fluid (SRF). Beside the OCT morphological features, OCT can also measure the thickness of the retina. The established quantitative parameters that can be measured by OCT include central macular thickness (CMT) and retinal volume.

The identification of the OCT morphologic features and quantitative parameters of CSMO which cannot be done via the clinical examination, making prediction of disease evolution and its response to treatment possible. Furthermore, certain type of morphologic features will produce better visual outcome as compared to the other type and the thicker the retinal layer, that is increased in CMT will produce greater visual impairment (Yassin et al., 2019; Alkuraya et al., 2005).

1.2 Study Rationale

During the early years, the management of the DMO is only clinically and subjectively based on patient's visual acuity. Nowadays, with the introduction of OCT in ophthalmology field, we are able to understand further regarding the retinal and choroidal diseases. With the evolving technology and the latest OCT machine, multimodal approach in diagnosis and management of retinal diseases can be done in addition to DMO. OCT machine is invasive and can measure DMO accurately based on its quantitative measures and even able to know its morphologic features.

There are still few disadvantages of OCT machine for example, it needs full cooperation from the patient and limited usage among patients with media opacities. Patient with cataract, corneal opacities and vitreous haemorrhages will be at the disadvantage as OCT uses light waves which may interfere with the signal.

The rationale of the study is to assess common types of OCT morphologic features among DMO patients in our country and also its quantitative parameters. Profiling the OCT features may predict the subsequent response to treatment and also predict the visual outcome. Baseline visual acuity is associated with OCT morphologic features. Early detection of OCT morphologic features by evaluating the foveal microstructure changes and identify features that affect the visual acuity will determine the prognosis of visual outcome. OCT imaging provide a valuable tool for detecting disease at the earlier stage, tracking progression and monitoring treatment response. It has the potential to be considered as imaging biomarkers in DMO (Markan et al., 2020).

This study will identify the associated factors that affect the OCT features and to determine its association with visual acuity. By identifying its associated factors for example, duration of DM, severity of DR and age, these factors can be addressed firmly as it may become the contributing factors towards the visual acuity. Not only the advancement of treatment is needed to tackle the patient's problem, but also patients themselves need to be educated regarding the factors which may affect the treatment outcome.

CHAPTER 2

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 Diabetic Macular Oedema

DM is a chronic disease with its global prevalence rate among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 that is 422 million people (WHO, 2018). Whereas in Malaysia, the prevalence has increased to twofold from 11.6% reported in 2006 to 22.6% in 2013 (Wan Nazaimoon et al., 2013). Up to 10% of all patients with DM will develop DMO during their lifetime and up to 4% of diabetic patients will develop DMO that affects the central fovea. Up to 30% will develop CSMO (Fareed, 1997).

2.2 Clinically Significant Macular Oedema

The structure that plays an important role for central vision, visualization of fine details and image resolution is macula lutea, which become the target zone for DMO. OCT is used for diagnosis and follow up of the patients and allow to visualize the multiple layers of retina.

Muller cells among the first cells to be affected with increase swelling intracellularly. As the fluid passes through the cell membrane, cyst formation will be formed due to accumulation of fluid in the interstitial space. Fluid accumulation also will be seen under the neurosensory retina due to rupture of retinal pigment epithelium (RPE). All of these features can be seen via OCT machine which allows analysis of different layers of retina with high resolution of tomographic cross sections (Romero-Aroca et al., 2016).

CSMO is a form of DMO which was defined by Early Treatment Diabetic Retinopathy Study (ETDRS, 1985) as follow:

i. Retinal thickening at or within 500 µm of the centre of the macula (Figure 2.1A)

ii. Exudates at or within 500 µm of center of the macula if adjacent retina thickened (Figure 2.1B)

iii. A zone or zones of retinal thickening of one disc area or larger, any part of which is within one disc diameter from center of macula (Figure 2.1C)

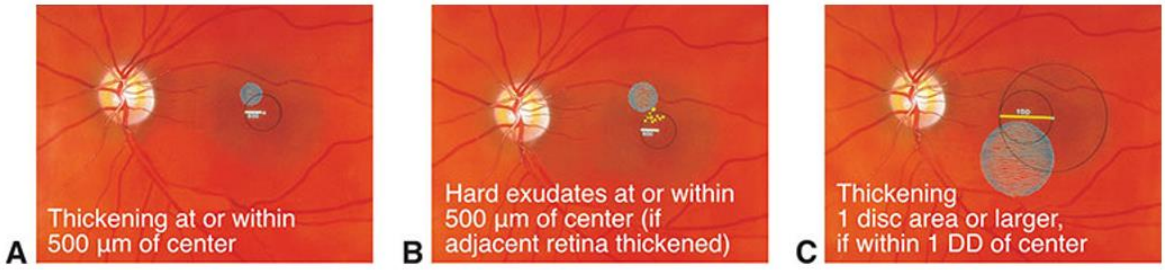

Figure 2.1: Clinically significant macular oedema

2.3 OCT Features of Diabetic Macular Oedema

The introduction of OCT in ophthalmology provided the study of DMO morphologic features and its quantitative parameters possible. OCT machine was traced back in early 90's where it was commercially made available after its 10 years of innovation as third generation. The OCT machine use the basic principle of low-coherence interferometry; whereby light wave is directed to the target tissue and the scattered back-reflected light is combined with a reference beam, which was split off from the original light beam. The technology also evolving with time from time domain to spectral domain and the latest one is swept source OCT. They differ in the light source, the speed of the A-scan rate capture and imaging depth to name a few (Baumann B et al., 2011).

Based on OCT assessment, DMO can be classified according to its morphologic features (Yassin et al., 2019) and quantitative features.

2.3.1 OCT morphological features of CSMO

Morphological features of CSMO that can be detected by OCT includes SLDRT, CMO, SRF and mixed type (Yassin et al., 2019).

2.3.1.1 Sponge-like diffuse retinal thickness

SLDRT is characterized by smaller inter-retinal and broad layers reflectivity by OCT (Figure 2.2). A retrospective observational study among Saudi populations done by Yassin et al., (2019) showed that SLDRT (67.84%) is the most common type of DMO pattern followed by CMO (19.82%) and SRF (2.20%). Study done by Kim et al., (2006), the SLDRT type still common among their patients but he obtained a lower percentage which was 39.5%.

In correlation with DR stages, SLDRT pattern is more common among mild-to-moderate NPDR in comparison to severe NPDR and PDR (Alkuraya et al., 2005). Whereas, Yassin et al., (2019) found that SLDRT is more common in severe NPDR and high-risk PDR stages.

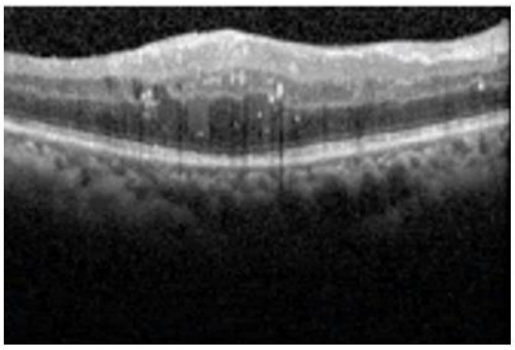

Figure 2.2: Sponge-like diffuse retinal thickness (SLDRT)

2.3.1.2 Cystoid macular oedema

CMO represent a morphological type of CSMO whereby there is cyst formation between the outer plexiform layer and the inner nuclear layer around the fovea (Figure 2.3). Aside from DMO, CMO could also be seen in post intraocular surgery, as complications of uveitis or patient received laser photocoagulation (Bravo-Alcobendas et al., 2015).

Kim et al., (2006) found that CMO type was significantly associated with visual acuity. Necrosis of the Muller cells and chronic accumulation of the fluid intracellularly causing formation of large cystoid cavities. This may explain why CMO type had the worse visual acuity than other OCT morphological type of CSMO (Yamamoto et al., 2001).

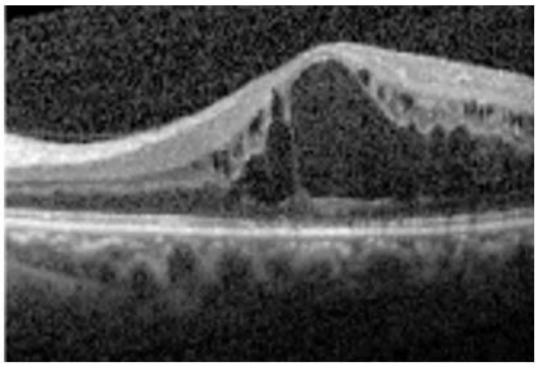

Figure 2.3: Cystoid macular oedema (CMO)

2.3.1.3 Subretinal fluid

Due to disruption of RPE tight junctions or its protective function, fluid will be accumulated in the subretinal space giving rise to SRF (Figure 2.4). Alkuraya et al., (2005) found that SRF type has the thickest CMT and the worst visual acuity. Ahmadpour-Baghdadabad et al., (2013) found that male gender and mean serum triglyceride had strong association with SRF type of OCT morphological features. SRF and vitreomacular traction (VMT) was seen more common among severe NPDR and proliferative diabetic retinopathy (PDR) patients (Alkuraya et al., 2005).

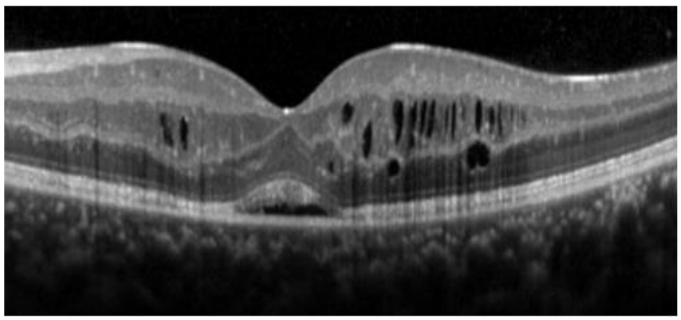

Figure 2.4: Subretinal fluid (SRF)

2.3.2 OCT quantitative features of CSMO

The established quantitative features of CSMO that can be measured by OCT are CMT and retinal volume.

2.3.2.1 Central macular thickness

CMT is the average retinal thickness within the 1-mm ETDRS circle centred on the fovea (Figure 2.5). OCT provides a cross-sectional image of the diabetic retina and comparison was made between CMT values with those of an age-matched normative database (Arthur et al., 2019). Previous study among healthy adult had shown that male gender had greater thickness

in central macular as compared to female gender (Pokharel et al., 2016, Al-Zamil et al., 2017). Yassin et al., (2019) and Browning et al., (2018) found that severe NPDR and high-risk PDR had thicker macula in comparison to other stages of DR. Previous studies also noted that the increment of CMT associated with greater visual impairment (Yassin et al., 2019).

2.3.2.2 Retina volume

Retinal volume is sum of all volumes of all nine sections of ETDRS grid (Figure 2.5). Average mean normal value is 8.49±0.31 $mm^{3.}$ Study among healthy Saudi adults found that male gender had significantly greater retinal volume than female gender (Al-Zamil et al., 2017). This is in line with study done by Pokharel et al., (2016), whereby male almost always has greater retina volume than female. They also found that for each year of increasing age, macular volume decreased by 0.0156 mm^3. However, it did not significantly correlate with age.

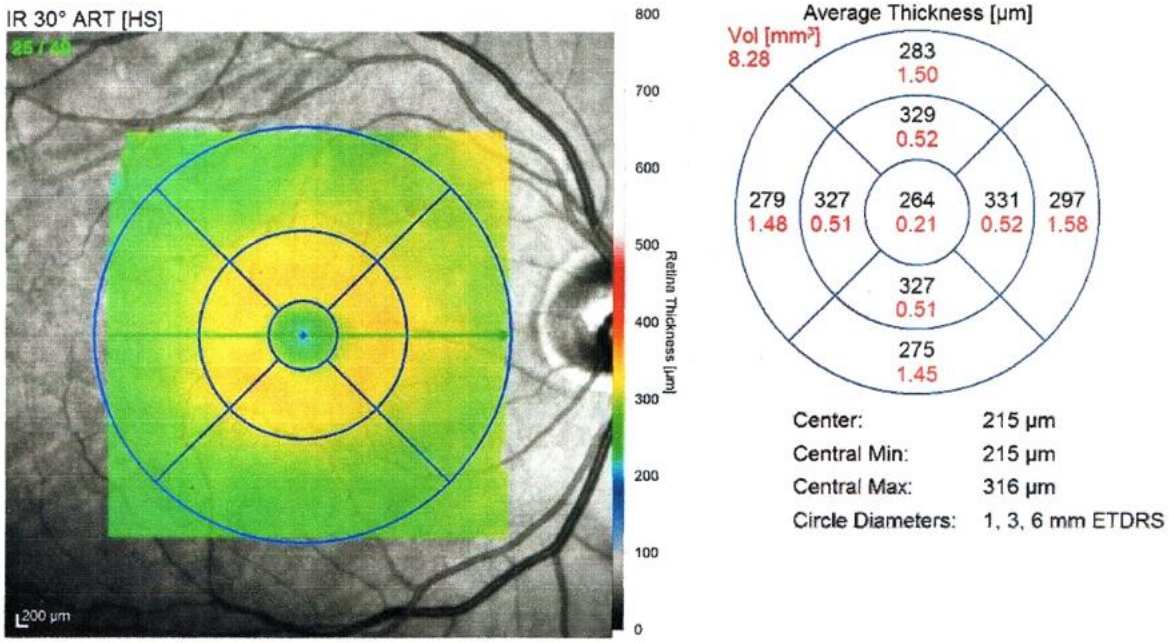

Figure 2.5: Central macular thickness (CMT) – µm
Retinal volume – mm^3

2.4 Visual Acuity

Visual acuity is based on the theory that the smallest object which can be resolved by eyes and it measures clarity of the object. Visual acuity can be measured using various tools for example Snellen chart, LogMAR chart or ETDRS chart. The category of visual impairment is based on the ICD-10 2015 (Table 2.1).

Table 2.1: Category of visual impairment

Category	Presenting distance visual acuity	
	Worse than:	Equal to or better than:
0 Mild or no visual impairment		6/18 3/10 (0.3) 20/70
1 Moderate visual impairment	6/18 3/10 (0.3) 20/70	6/60 1/10 (0.1) 20/200
2 Severe visual impairment	6/60 1/10 (0.1) 20/200	3/60 1/20 (0.05) 20/400
3 Blindness	3/60 1/20 (0.05) 20/400	1/60* 1/50 (0.02) 5/300 (20/1200)
4 Blindness	1/60* 1/50 (0.02) 5/300 (20/1200)	Light perception
5 Blindness	No light perception	
9	Undetermined or unspecified	
	* or counts fingers (CF) at 1 metre.	

The leading global causes of visual impairment among adult older than 50-year-old are cataract and refractive error which are reversible. DR follows third after glaucoma and age-related macular degeneration for the causes of irreversible visual impairment (Global vision database 2020).

Visual acuity can be impaired among diabetic patients who developed complications to the eye. The visual acuity impairment could be due to DMO; ischemic and non-ischemic type, vitreous haemorrhages, advanced diabetic eye disease or neovascular glaucoma.

2.5 Visual Acuity and OCT Features of Diabetic Macular Oedema

Few studies had done to show the associations between OCT features and visual acuity among the DMO patients.

Yassin et al. (2019) found that, there was a statistically significant positive correlation between stages of DR with CMT. SLDRT associated with the least affected mean visual acuity and SRF signified the worst mean visual acuity. They also found that, increase in CMT significantly correlated with reduced visual acuity (Yassin et al., 2019).

Alkuraya et al., (2005) performed a prospective study to investigate the correlation between the features of OCT and the severity of concurrent retinopathy, CMT and best corrected visual acuity (BCVA) in CSMO. The visual acuity was statistically significant correlated with CMT in DMO.

CMT does not stand alone as a visual prognostic indicator as similar CMT may have different degree of Muller cells dysfunction and neuronal atrophy. Different retinal layer involved should be taken into account (Sen et al., 2021).

CHAPTER 3

OBJECTIVES

3. RESEARCH OBJECTIVE

3.1 General Objective

To evaluate the associated factors of OCT features and their association with visual acuity among diabetic patients with CSMO.

3.2 Specific Objectives

i. To identify the associated factors (demographics, systemic factors, and ocular factors) affecting OCT morphologic features (SLDRT, CMO, SRF) among diabetic patients with CSMO.

ii. To identify the associated factors (demographics, systemic factors, and ocular factors) affecting OCT quantitative parameters (CMT, retinal volume) among diabetic patients with CSMO.

iii. To determine the association between OCT morphologic features (SLDRT, CMO, SRF) and visual acuity among diabetic patients with CSMO.

iv. To determine the association between OCT quantitative parameters (CMT, retinal volume) and visual acuity among diabetic patients with CSMO.

3.3 Research Question

i. What are the factors (demographics, systemic factors, and ocular factors) associated with OCT morphologic features (SLDRT, CMO, SRF) among diabetic patients with CSMO?

ii. What are the factors (demographics, systemic factors, and ocular factors) associated with OCT quantitative features (CMT, retinal volume) among diabetic patients with CSMO?

iii. Are there any significant associations between OCT morphologic features (SLDRT, CMO, SRF) and visual acuity among diabetic patients with CSMO?

iv. Are there any significant associations between OCT quantitative features (CMT, retinal volume) and visual acuity among diabetic patients with CSMO?

3.4 Research Hypothesis

i. There are factors (demographics, systemic factors, and ocular factors) associated with OCT morphologic features (SLDRT, CMO, SRF) among diabetic patients with CSMO.

ii. There are factors (demographics, systemic factors, and ocular factors) associated with OCT quantitative features (CMT, retinal volume) among diabetic patients with CSMO.

iii. There are significant associations between OCT morphologic features (SLDRT, CMO, SRF) and visual acuity among diabetic patients with CSMO.

iv. There are significant associations between OCT quantitative features (CMT, retinal volume) and visual acuity among diabetic patients with CSMO.

CHAPTER 4

RESEARCH METHODOLOGY

4. METHODOLOGY

4.1 Study Design

A cross-sectional study was conducted in the Ophthalmology Clinic, Hospital Universiti Sains Malaysia (USM), Kubang Kerian from January 2020 till November 2021. The study population involved all Type 2 DM (T2DM) with CSMO attending Eye Clinic at Hospital USM during the study duration and fulfilled the selection criteria.

4.2 Ethical Approval

The study was conducted after approval by the local Human Research Ethical Committee (Universiti Sains Malaysia [USM])/Jawatankuasa Etika Penyelidikan Manusia (JEPeM). The Registration Number was 20010060 (Appendix A). The committee is according to the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) – Harmonised Tripartite Guideline for Good Clinical Practice (GCP).

4.3 Selection Criteria

The inclusion criteria include T2DM patients with clinical diagnosis of CSMO age above 40 years old. Any patients with history of ocular trauma or surgery, received intravitreal anti vascular growth factor injection, laser photocoagulation (either pan-retinal photocoagulation, focal or grid laser) and periorbital or intravitreal steroid injections were excluded from this study. Other ocular exclusion criteria include retinal disorder (e.g., tractional retinal detachment, uveitis, choroidal neovascular membrane, retinitis pigmentosa). Poor quality in OCT scan image that hinder proper evaluations (e.g., dense cornea scarring, dense cataract, vitreous haemorrhages) were also excluded from this study.

4.4 Sample Size Estimation

Objective 1: **To identify the associated factors (demographics, systemic factors, and ocular factors) affecting OCT morphologic features (SLDRT, CMO, SRF) among diabetic patients with CSMO**.

Sample size was calculated using PS Power and Sample Size software, version 3.1.6 with multiple logistic regression formula applied.

Factor : Severity of DR

Author : Alkuraya et al. (2005)

P0 : 0.5

P1 : 0.88

m : 0.5

n : 84

Total sample size + 20% dropout rate: 101

Objective 2: To identify the associated factors (demographics, systemic factors, and ocular factors) affecting OCT quantitative parameters (CMT, retinal volume) among diabetic patients with CSMO.

Sample size was calculated using G*power software, version 3.1.9.2 with linear multiple regression formula applied.

Input parameters: -

Effect size f^2 : 0.15

α err prob : 0.05

Power (1-β err prob) : 0.8

Number of predictors : 8

Output parameters: -

Noncentrality parameters λ : 16.35

Critical F : 2.0323276

Numerator df : 8

Denominator df : 100

Total sample size : 109

Actual power : 0.8040987

Total sample size + 20% dropout rate: 131

Objective 3: To determine the association between OCT morphologic features (SLDRT, CMO, SRF) and visual acuity among diabetic patients with CSMO.

Sample size was calculated using G*power software, version 3.1.9.2 with linear multiple regression formula applied.

Input parameters: -

Effect size f^2	: 0.15
α err prob	: 0.05
Power (1-β err prob)	: 0.8
Number of predictors	: 2

Output parameters: -

Noncentrality parameters λ	: 10.20
Critical F	: 3.1381419
Numerator df	: 2
Denominator df	: 65
Total sample size	: 68
Actual power	: 0.8044183

Total sample size + 20% dropout rate: 82

Objective 4: To determine the association between OCT quantitative parameters (CMT, retinal volume) and visual acuity among diabetic patients with CSMO.

Sample size was calculated using G*power software, version 3.1.9.2 with linear multiple regression formula applied.

Input parameters: -

Effect size f^2 : 0.15

α err prob : 0.05

Power (1-β err prob) : 0.8

Number of predictors : 2

Output parameters: -

Noncentrality parameters λ : 10.20

Critical F : 3.1381419

Numerator df : 2

Denominator df : 65

Total sample size : 68

Actual power : 0.8044183

Total sample size + 20% dropout rate: 82

The biggest number of subjects will be chosen as sample size.

Final calculated sample size will be : 131

4.5 Sampling Method

Non probability sampling method was applied to participants who attending the Ophthalmology Clinic Hospital USM who fulfilled the criteria along the duration of the study.

4.6 Definition of Term

4.6.1 Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a chronic and progressive medical condition that results from two major metabolic dysfunctions, that is insulin resistance and then pancreatic islet cell dysfunction causing a relative insulin deficiency (Diagnosis and Classification of Diabetes Mellitus, 2010).

4.6.2 Clinically Significant Macular Oedema (CSMO)

CSMO is retinal thickening or hard exudates at or within one disc diameter of the centre macula and meet at least one of the criteria below (Mathew et al., 2015).

- Thickening of the retina at or within 500 µm of the centre of macula
- Hard exudates at or within 500 µm of center of the macula if adjacent retina thickened
- Retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula

4.6.3 Non-Proliferative Diabetic Retinopathy (NPDR)

NPDR is defined by the presence of early intraretinal microvascular findings and is classified into different stages of severity, according to international proposed classifications: (Wang and Lo, 2018).

- Mild NPDR
- Moderate NPDR
- Severe NPDR

4.6.4 Proliferative Diabetic Retinopathy (PDR)

PDR is marked by the presence of neovascularization arising from the disc and/or retinal vessels and the consequences of this neovascularization includes, preretinal and vitreous haemorrhage with subsequent fibrosis, and traction retinal detachment (Wang and Lo, 2018).

4.6.5 OCT Morphologic Features of CSMO

i. Sponge-Like Diffuse Retinal Thickness (SLDRT)

Retinal thickness greater than 250 µm characterized by smaller inter-retinal reflectivity and broad layers of reflectivity higher than 250 µm (Yassin et al., 2019).

ii. **Cystoid Macular Oedema (CMO)**

Presence of oval and round parts of the image indicating low reflect-ability (Yassin et al., 2019).

iii. **Subretinal Fluid (SRF)**

Dome-like fluid accumulation in the subretinal space (Yassin et al., 2019).

4.6.6 OCT Quantitative Parameters of CSMO

i. Central Macular Thickness (CMT)

Measurement was obtained at the centre of the fovea. Normal value measured by SD-OCT Heidelberg is 271.4 ± 19.6 μm (Grover et al., 2010).

ii. Retinal Volume

Sum of all volumes of all nine sections in ETDRS grid. Average mean normal value 8.49±0.31 mm^3 (Pokharel et al., 2016).

4.6.7 Visual Acuity

Visual acuity is based on theory that the smallest object which can be resolved by eyes and it measures clarity of the object. In this study, visual acuity is taken as best corrected vision from the Snellen chart and it will be converted into the LogMAR scale.

4.7 Research Tools

i. Slit lamp biomicroscope

Slit lamp biomicroscope (Figure 4.1) with 90 dioptre (D) and 78D lenses (Volk) double aspheric (Figure 4.2) were used in this study for comprehensive ophthalmic examination.

Figure 4.1: Slit lamp biomicroscopy

Figure 4.2: Lens 90D and 78D

ii. Topical Proparacaine HCL 0.5% (Alcon Laboratories, Texas, USA)

Gutt Proparacaine HCL 0.5% were used as a topical anaesthetic agent prior to application of the dilating eyedrops (Figure 4.3).

iii. Topical Phenylephrine HCL 2.5% (Alcon Laboratories, Texas, USA)

Gutt Phenylephrine HCL 2.5% is a mydriatic agent. It is a sympathetic agonist that acts directly on alpha-adrenergic receptors in the eyes resulting in contraction of dilator pupillae muscle (Figure 4.3).

iv. Topical Tropicamide 1% (Alcon Laboratories, Texas, USA)

Gutt Tropicamide 1% is a mydriatic agent. It is parasympatholytic agent that acts via inhibiting the acetylcholine thus resulting in relaxation of sphincter pupillae muscle (Figure 4.3).

Figure 4.3: Gutt Proparacaine, Gutt Tropicamide and Gutt Phenylephrine (L-R)

v. Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany)

OCT examinations for OCT morphological features, macular thickness and retinal volume were performed using Spectralis HD SD-OCT machine (Figure 4.4).

Figure 4.4: Spectralis SD-OCT

4.8 Variables

4.8.1 Independent variable

i. T2DM patients with CSMO

4.8.2 Dependent variable

i. OCT morphologic features

ii. OCT quantitative parameters

4.8.3 Cofounders

i. Patient's demographic factors

ii. Patient's stage of diabetic retinopathy

iii. Patient's systemic disease control

4.9 Data Collection Procedure

4.9.1 Recruitment of Patients

The study was conducted after obtaining approvals from the Ethical Committee of USM. T2DM patients were identified and patients with CSMO on clinical examination were recruited. Selection of patients was strictly based on inclusion and exclusion criteria. Patient's information was obtained during clinic visit and through medical records. All the data of consented patient were entered into date report form (Appendix B) including the demographic data (age, race and gender), duration of DM, type of medications, HbA1c level and systemic illnesses (hypertension, hyperlipidaemia, chronic kidney disease and ischemic heart disease).