# DRY EYE AND VISUAL FUNCTION IN YOUNG ADULT DIABETICS

BY

AZIIMAH BINTI AWANG ABD RAHMAN @ JUSOH

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International Islamic University Malaysia

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# ABSTRACT

The escalating prevalence of diabetes in the world, and in Malaysia particularly is a concern**.** Limited studies have linked the dry eye status in the young adult diabetic population using standardised questionnaire with standard tear film function and clinical tests, and the more subtle aspects of visual function.

This thesis presents two studies relating to the use of a localized version of the standard questionnaire in elucidating dry eye symptoms in relation to the other clinical tests used in dry eye diagnosis, and in relation to best corrected visual acuity, contrast sensitivity and colour vision, in young diabetics.

The first study validated the translated version of Ocular Symptom Disease Index (OSDI) in Bahasa Malaysia, referred to as the OSDI-Bahasa; an instrument meant to overcome the difficulties in responding to the questionnaire in English for some Malaysians who are not fluent in the English language. The original OSDI was translated and transformed into an online questionnaire using JotForm program and was distributed to 195 bilingual participants to assess its reliability. The Cronbach's alpha values for each item in the questionnaire ranged from 0.88 to 0.94. Factor analysis revealed that 12 items in OSDI-Bahasa clustered together to create three latent subscales which were vision-related function, ocular symptoms and environment triggers. For repeatability, the OSDI-Bahasa score in 23 subjects were compared after a week. There was no significant difference between the two sessions ($p = 0.692$). The OSDI-Bahasa was found to be both reliable and repeatable.

The second (main) study investigated dry eye symptoms scores (as determined by the OSDI-Bahasa validated in the first study), clinical tests of dry eye (Phenol red thread, tear break up time, corneal staining, Marx line displacement, meibomian gland count and meibomian gland quality) and visual functions (visual acuity, contrast sensitivity and colour vision) in 37 young (age range: 19 to 39 years) adult patients with diabetes mellitus, comparing these measures with a similar age range as controls. The main inclusion criterion was diagnosed diabetes without any other ocular diseases.

The results obtained for the diabetic group without significant diabetic retinopathy, were not significantly different from the control group in all parameters. Multiple regression analysis revealed contrast sensitivity as a significant predictor of dry eye symptoms in diabetics, accounting for 46.5% of the variance in OSDI ($p=0.006$). It is concluded that contrast sensitivity is a predictor of dry eye symptoms in young adult diabetics within this population, having been shown also as a sensitive measure of subclinical visual changes in the said population.

# نبذة مختصرة


إن الانتشار المتصاعد لمرض السكري في العالم ، وفي ماليزيا بشكل خاص يشكل مصدر قلق. وقد ربطت بعض الدراسات المحدودة حالة العين الجافة في البالغين من المصابين بالسكر باستخدام استبيان موحد مع وظيفة قياسية لتمزق المسيل للدموع والاختبارات السريرية، وبعض الوظائف الأخرى المتعلقة بالوظيفة البصرية.

تقدم هذه الدراسة دراستين تتعلقان باستخدام نسخة محلية من استبيان قياسي في توضيح أعراض جفاف العين المتعلقة بالاختبارات السريرية الأخرى والتي تستخدم في تشخيص العين الجافة ، وفيما يتعلق بأفضل حدة بصرية مصحوبة وحساسية التباين ورؤية اللون، في مرضى السكر الصغار.

وقد أقرت الدراسة الأولى النسخة المترجمة من (مؤشر أمراض الأوعية العينية) (OSDI) في اللغة الماليزية، والمشار إليها باسم OSDI-Bahasa؛ وهي أداة تهدف إلى التغلب على الصعوبات في الرد على الاستبيان باللغة الإنجليزية لبعض الماليزيين الذين لا يجيدون اللغة الإنجليزية.

تمت ترجمة النسخة الأصلية من الـ ( OSDI ) وتحويله إلى استبيان عبر الإنترنت باستخدام برنامج JotForm وتم توزيعه على 195 مشارك مجيد للغتين (الإنجليزية والماليزية) لتقييم موثوقيته. وقد تراوحت قيم (Cronbach's alpha /ألفا كرونباخ) لكل عنصر في الاستبيان من 0.88 إلى 0.94. وكشف تحليل العوامل أن 12 عنصرا في OSDI باللغة الماليزية تجمعوا معاً لإنشاء ثلاثة مقاييس فرعية متعلقة بالوظائف البصرية وما يخص أمراض العيون والمؤثرات البيئية . وتكراريا، سجل الـ OSDI باللغة الماليزية على 23 شخصا حالة بعد أسبوع. لم يكن هناك فرق كبير بين الدورتين (P = 0.692). وقد تم تأسيس OSDI الماليزية لتكون موثوقة وقابلة للتكرار.

درست الدراسة الثانية (وهي الرئيسية) نتائج أعراض جفاف العين (كما حددتها الـ OSDI الماليزية المصادق عليها في الدراسة الأولى) و الاختبارات السريرية لأعراض العين الجافة (Phenol red thread, tear break up time, corneal staining, Marx line displacement, meibomian gland count and meibomian gland quality) والوظائف البصرية (حدة البصر ، حساسية التباين ورؤية اللون) في 37 شاب وفتاة (الفئة العمرية: من 19 إلى 39 سنة) المصابين بمرض السكري ، وبمقارنة هذه التدابير بنطاق عمر مشابه كمجموعة تحت الملاحظة ، تم تشخيص معيار الإدراج الرئيسي لمرض السكري دون أي أعراض لأمراض العين الأخرى.

النتائج التي تم الحصول عليها للمجموعة المصابة بالسكري (without diabetic retinopathy) دون اعتلال كبير للشبكية ، لا تختلف كثيرا عن المجموعة التي كانت تحت الملاحظة في جميع العوامل. أظهر تحليل الانحدار المتعدد حساسية التباين (multiple regression analysis)كمؤشر هام لأعراض جفاف العين في مرضى السكري ، وهو ما يمثل 46.5 ٪ من التباين في OSDI (P = 0.006). وخلص إلى أن حساسية التباين هي مؤشر لأعراض جفاف العين في مرضى السكري من البالغين الشباب ضمن هذه الفئة من السكان ، بعد أن تبين أيضا كمقياس حساس للتغيرات البصرية تحت الإكلينيكية (clinical) في مجموعة السكان السابق ذكرها .

# APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Health Science.

……..
Dr Noor Ezailina Binti Badarudin
Supervisor

……..
Dr Mohd Zulfaezal Che Azemin
Co-Supervisor

……..
Prof Dr Azrin Esmady Bin Ariffin
Co-Supervisor

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Health Science.

……..
Internal Examiner

……..
External Examiner

This thesis was submitted to the Department of Optometry and Visual Science and is accepted as a fulfilment of the requirement for the degree of Master of Health Science.

……..
Head, Department of Optometry
and Visual Science

This thesis was submitted to the Kulliyyah of Allied Health Sciences and is accepted as a fulfilment of the requirement for the degree of Master of Health Science.

……..
Dean, Kulliyyah of Allied Health
Sciences

# DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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Firstly, it is my utmost pleasure to dedicate this work to my dear husband, who granted me the gift of their unwavering belief in my ability to accomplish this goal: thank you for your support and patience. Not to forget my mother with her continuous doa.

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# ABBREVIATIONS

| | |
|---|---|
| DM | Diabetes mellitus |
| DR | Diabetic retinopathy |
| VA | Visual acuity |
| OSDI | Ocular Surface Disease Index |
| CS | Contrast sensitivity |
| DED | Dry eye disease |
| NPDR | Non-proliferative diabetic retinopathy |
| PDR | Proliferative diabetic retinopathy |
| TBUT | Tear break up time |
| PRT | Phenol red thread |
| FM | Farnsworth Munsell |
| TES | Total error score |
| RE | Right eye |
| LE | Left eye |
| Hba1c | Glycated haemoglobin |

# LIST OF EQUATION

$$\text{OSDI} = \frac{(\text{sum of scores}) \times 25}{(\text{number of questions answered})}$$

# CHAPTER ONE

# INTRODUCTION

## 1.1 BACKGROUND OF THE STUDY

### 1.1.1 Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in either insulin secretion (Kanski, 2003) or action, or both (American Diabetes Association, 2014). This progressive disease that may adversely affect healthy functioning of the body (Watkinson & Seewoodhary, 2008) such as visual function; (Shrestha & Kaiti, 2014) and deteriorate the quality of life (Ministry of Health Malaysia, 2010).

The prevalence of diabetics is growing rapidly worldwide and becoming a major public health concern (Meo, 2009). According to Rios et al. (2013), 15.2% (2.6 million) of adult worldwide have DM. In Malaysia, based on Malaysian National Health Morbidity Survey III, the overall prevalence of DM was 11.6% in 2006 (Letchuman et al., 2010). Quite recently, Wan Nazaimoon et al. (2013) reported that the prevalence of DM among Malaysians aged 30 years and above has increased by more than twofold over a 20-year period and is projected to rise to 21.6% by the year 2020 (Feisul & Azmi, 2013). The figure warrants for attention and hence action from the Malaysian population and healthcare providers.

A major complication of DM is diabetic retinopathy (DR) which becomes a major concern in Malaysian eye care practices (Ngah et al., 2011). DR was responsible for the 86% of legal blindness (best corrected visual acuity in the better eye of 6/60 or worse) in

young-onset diabetics (Klein, Klein, & Moss, 1983). Furthermore, based on the National Diabetic Registry Report, DR covers up to 30% of DM complications, which may include blindness, in Malaysia (Feisul & Azmi, 2013). These statistics should motivate the eye care professionals to take part accordingly in this population.

### 1.1.2 The Effect of Diabetes Mellitus on the Ocular Surface and Visual Functions

Diabetic retinopathy (DR) is a global concern in causing visual impairment and blindness (Usuelli & Rocca, 2014; Yau et al., 2012; Fong et al., 2004). This was supported by a positive relationship between visual functions impairment and DR (Shrestha & Kaiti, 2014). Apart from DR and other retinal complications, neuropathy, glaucoma, cataract and corneal alteration were also reported (Vieira-Potter et al., 2016). DiLeo et al. (1992) suggested that diabetes may cause neuronal damage of visual pathways even before the onset of clinical sign of DR, which may reduce the contrast sensitivity. These findings suggest that DR may result in other ocular changes and affecting oculo-visual functions.

Visual functions of a human eye consist of visual acuity, contrast sensitivity and colour vision. Each of them has its own ideal state of function in order to produce a good vision. Table 1.1 shows normative values for these parameters.

Table 1.1 Normative Value for Visual Function Parameters

| Parameter (unit) | Normative value |
|---|---|
| Visual Acuity (LogMar unit) | 0.0 LogMar |
| Contrast Sensitivity(log) | 1.65- 1.95 (Mäntyjärvi & Laitinen, 2001) |
| Total Error Score of FM-100 Hue Test | 124 and lower (Verriest, Van Laethem, & Uvijls, 1982) |

In diabetics, one or more visual functions might be affected and this was investigated in many previous studies. Legal blindness was reported in 3.3% of young adult diabetics and the rate increases with age (Klein, Klein & Moss, 1983). Various oculo-visual manifestation of DM also have been reported through numerous studies such as fluctuation of refractive error and premature cataractogenesis (Idu & Oghre, 2010), poor vision (Klein, Klein, & Moss, 1983; Klein et al.,1991), poor contrast (Krásný et al., 2006; Sun & Zhang, 2012; Stavrou & Wood, 2003; DiLeo et al., 1992; Ghafour et al., 1982), and poor colour vision (Ismail, 2013a; Daley, Watzke & Riddle, 1987; Roy, Gunkel & Podgor 1986; Bresnick et al., 1985; Green et al., 1985). These findings suggest that DM has become a global concern for eye care practitioners since a few decades ago.

In Malaysia, diabetic complication is the commonest cause of visual loss among adults of working age (Ngah et al., 2011). Looking at the impact of DR on the quality of life, parallel with the data of DM in Malaysia, the Malaysian Ministry of Health proposes on a comprehensive DR screening program covering all individuals with DM in Malaysia (Letchuman et al., 2010). This screening is part of the effort to detect ocular complication as early as possible, before it worsens.

It is important to investigate the effects of DM on the eye specifically in young adults since they are the productive working age group in the community. A morbidity and mortality rate in this group is vital for a household survival (Yamano, 2004). In a broader view, a country also depends on this group to develop. Almost all regular working fields including volunteer works were dominated by this age group (Herzog et al., 1989). This age group made a vast contribution to the family, society and country. Thus, this study is conducted to investigate the influence of DM on the visual function parameters and ocular surface changes in diabetic young adults.

## 1.2 LITERATURE REVIEW

### 1.2.1 The Retinal Pathophysiological Changes in Diabetes

Diabetes mellitus (DM) is a complex chronic metabolic disorder that associated with metabolic disturbances which is hyperglycemia or high blood glucose level (Kowluru & Chan, 2007). Diabetics with poor glycemic control have a greater rate in developing DR (Stratton, 2000), suggesting a strong relationship between chronic hyperglycemia and DR (Matthews et al., 2004). Additionally, prolonged hyperglycemia can cause macrovascular and microvascular damage (Watkinson & Seewoodhary, 2008). A poor glycemic control may affect retina in several ways.

The first effect of hyperglycemia is microvascular dysfunction which is a major component of DR (Gardner et al., 2002; Hovind et al., 2003). Gardner et al (2002) added that the microvascular is a weak vessel which is prone to leak that leads to a distorted vision. In its most advanced stage, new abnormal blood vessels proliferate (increase in number) on the surface of the retina, which can lead to scarring and cell loss in the retina (Gardner et al., 2002).

The second impact of hyperglycemia is loss of pericytes in the retina (Beltramo & Porta, 2013). Pericytes play important role in a repairing process to provide vessel stability and control of endothelial proliferation (Armulik, Genove, & Betsholtz, 2011). Loss of pericytes leads to microvascular with a further damage and proliferation (Ejaz et al., 2008).

The third component that responds very well to abnormal blood glucose level is vascular endothelial growth factor which is also known as VEGF (Sone et al., 1996; Sayin, 2015). VEGF is not only responsive to high blood glucose level but also in sharp drop of it as well (Sone et al., 1996). VEGF is an important factor in the development of

proliferative DR and diabetic macular oedema (Caldwell et al. 2003; Sayin, 2015) by altering retinal vessel permeability (Antonetti et al. 1999; Sayin, 2015).

The last and most direct effect of hyperglycemia is advanced glycation end-products (AGEs), products from the chemical reaction of the glucose with proteins (Alves et al., 2005). AGEs also involves in the ocular complication of DR and macular oedema (Sayin et al., 2015). Since visual functions are derived from the retina before being processed in the higher level (Foster & Hankins, n.d.), it can be postulated that the affected structure of the retina may reduce the quality of visual functions.

### 1.2.2 The Tear Functions Changes in Diabetes

Poor glycemic control may also affect the anterior part of the eye and its functions (Vieira-potter, Karamichos, & Lee, 2016). According to Zhang et al. (2016), DM has been identified as one of the leading causes of dry eye disease (DED). In diabetics, decreased stability of tear film correlates with neuropathy, poor glucose control, and reduced density of conjunctival goblet cells (Dogru, Katakami & Inoue, 2001;Yoon, Im & Seo 2004). These studies postulated that diabetes may bring changes in the ocular surface and tear functions.

Alves (2008) suggested three possible causes of tear film and corneal changes in diabetics which are hyperglycemia, corneal nerve damage and impairment on insulin action. Alves added that these factors may further lead to tissue injury in lacrimal gland which further causes inflammation, oxidative stress and accumulation of AGEs. The accumulation of AGEs may cause the stromal layer to swell and central corneal thickness to increase (Ljubimov, 2017). A chronic hyperglycemia condition may lead to corneal nerve alteration which promotes neurotrophic lesions that block the feedback mechanism

of tear secretion control (Alves et al., 2008). Subsequently, a reduction of tears secretion increases dry eye incidence in diabetics (Dogru et al., 2001; Yoon et al., 2004). In addition, tears osmolarity increases (Beckman, 2014) and tear stability reduces (Yoon et al., 2004) in diabetics.

Corneal nerve damage caused by DM may lead to a reduction in corneal sensitivity and delay the corneal wound healing (Ljubimov, 2017). Since cornea and lacrimal gland are interrelated in tear film sensory nervous system (Dartt, 2009), a corneal nerve damage may damage the lacrimal system as well. Figure 1.1 illustrates the integration between nervous system, lacrimal gland and lacrimal drainage system. It starts with (1) activation of afferent sensory nerves from the cornea and conjunctiva that project through the central nervous system (CNS), to stimulate (2) efferent parasympathetic and sympathetic nerves that innervate the lacrimal gland acinar and ductal cells and induce (3) secretion of lacrimal gland fluid containing proteins, electrolytes, and water through the duct system onto the ocular surface that (4) drains into the lacrimal drainage system. The neural response regulates lacrimal gland aqueous layer secretion is an integral part of the lacrimal gland which consists of sensory afferent nerves of the ocular surface (cornea and conjunctiva), the efferent parasympathetic and sympathetic nerves that innervate the lacrimal gland, the lacrimal gland secretory cells, and the lacrimal gland excretory ducts.

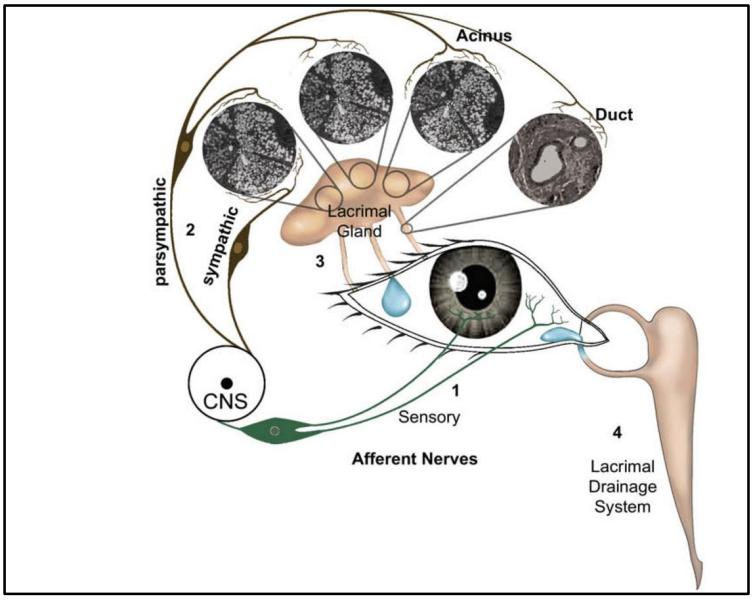


Figure 1.1 Schematic components of the lacrimal gland functional unit

Source: (Dartt, 2009)

Herber (2001) stated that tear film composition of protein pattern in diabetics is different from healthy people. Rocha et al. (2017) supported the statement with a finding of insulin in diabetics' tear film. The insulin may cause metabolic and mitogenic effects which further affects lacrimal gland cell duplication (Hann, Kelleher, & Sullivan, 2017) by imitating the mechanism of growth factors in lacrimal glands of diabetics (Sasaoka et al., 1996). Besides that, DM also causes reduction in goblet cell density (Yoon et al., 2004). Since lacrimal gland contributes to the major production of tears aqueous layer and goblet cells contributes to the production of mucin layer, these alterations later cause tear instability (Yoon et al., 2004) and lead to reduced tear function (TBUT) and tear volume (Schirmer)(Idu & Oghre, 2010). Furthermore, diabetics tear film also contains inflammatory protein which may lead to tissue injury and create an inflamed environment to the ocular surface (Alves et al., 2008). These conditions promote dry eye in diabetics and give chances for microbial infection and corneal ulceration (Umadevi & Choudhary, 2015).

### 1.2.3 Dry Eye Disease

Dry eye is a well-known condition that may bring discomfort to the eye. The latest International Dry Eye Workshop in 2017 defined dry eye disease (DED) as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Iannucci et al., 2017). Globally, there are a few terms that are used for DED such as Keratoconjunctivitis sicca, dry eye syndrome, chronic dry eye disease, or keratitis sicca (Sheppard, 2003). According to Tavares et al. (2010), DED is a common clinical problem and is among the most frequently diagnosed in ophthalmology clinic. Table 1.2 shows the non-dry eye value in common dry eye clinical test.

Table 1.2 Normative Value of Non-Dry eye in Clinical Tests

| **Parameter (unit)** | **Non Dry Eye value** |
|---|---|
| Tear Volume; PRT (mm) | 19.7± 5.9<br>(Doughty et al. 2007) |
| TBUT (sec) | ≥ 6 seconds<br>(Tsubota et al., 2017) |
| Corneal Staining (Grade) | 0-2<br>(Bron et al 2003) |
| Marx's Line displacement (Grade) | 2.8 ± 1.6<br>(Yamaguchi et al 2006) |
| Secretion Quality | 0-2<br>(Tomlinson et al 2011) |