OVERVIEW OF DRY EYE SEVERITY IN DIABETIC RETINOPATHY PATIENTS

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ABSTRACT

Dry eye is often found in patients with diabetes mellitus. One of the microvascular complications of diabetes mellitus is diabetic retinopathy. Dry eye in diabetic retinopathy patients is caused by chronic hyperglycaemia which causes microvascular and nerve damage resulting in decreased tear secretion and hyperosmolarity and activates inflammatory mediators that can damage conjunctival goblet cells and decrease mucin secretion. Objective: This study aims to determine the description of dry eye severity through the OSDI scoring system and ferning test in diabetic retinopathy patients based on its degree. Method: This study uses a descriptive method with a cross sectional design. The number of samples in the study were 64 people with a diagnosis of diabetic retinopathy. The sampling technique in this study was carried out by consecutive sampling. Result: The study was conducted using the OSDI questionnaire and ferning test examination on samples that had been diagnosed with diabetic retinopathy based on predetermined inclusion and exclusion criteria. The research data were compiled using Microsoft Excel and then reviewed for completeness. Then the complete data was processed using a computer programme, namely the Statistical Package for Social Sciences (SPSS). The results obtained from this research are most patients were female (64.1%), aged 45-65 years (79.7%), diabetes mellitus duration >5 years (60.9%). The most common degree of retinopathy with dry eye was PDR (64.1%). The most common degree of dry eye and type of ferning was severe dry eye (62.5%) and type IV (59.4%) which mostly occurred in patients with PDR. Conclusions: Based on the OSDI score and ferning test in the study conducted on diabetic retinopathy patients based on the degree, all patients had dry eye (100%).

Keywords: diabetes mellitus; diabetic retinopathy; dry eye; ferning; OSDI

INTRODUCTION

Dry eye is a multifactorial disease of the ocular surface characterized by loss of tear film homeostasis accompanied by multiple ocular symptoms that cause discomfort and affect quality of life. The causes of dry eye are tear film instability and hyperosmolarity, inflammation and damage to the ocular surface, and neurosensory abnormalities (American Academy Ophthalmology, 2019; Craig et al., 2017; Iskandar, 2020; Rahmadilla, 2020). A study in Sumatra showed that the prevalence of dry eye was around 27.5% (Lukandy et al., 2020). Dry eye is one of the eye surface problems of patients with diabetes mellitus due to reduced tear production or excessive tear evaporation (Legoh et al., 2019; Oktavian et al., 2011). Diabetes mellitus (DM) is a chronic metabolic disorder with multiple etiologies characterized by high blood sugar levels accompanied by metabolic disorders of carbohydrates, lipids, and proteins as a result of insufficient insulin function. DM can cause complications such as neuropathy, retinopathy, and nephropathy. DM is also one of the risk factors for dry eye (Craig et al., 2017; Foulks, 2007; World Health Organization, 2021).

The longer a person suffers from DM, the greater the possibility of complications, one of which is the eye. The most common microvascular complication in DM patients is diabetic retinopathy (Prasetia, 2016; Salsabila et al., 2020). Diabetic retinopathy is an abnormality in the retina of the eye which is a microvascular complication in patients with prolonged DM, characterized by venous dilation and accumulation of fatty exudates that take place chronically and progressively which has the potential to threaten vision, which is the main cause of blindness in DM patients (Setyoputri et al., 2017; Sitompul, 2011). The prevalence of diabetic retinopathy based on the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) is 28.8% in populations with DM duration of less than 5 years and 77.8% in populations with DM duration of more than 15 years (Klein et al., 1984). Within 20 years, according to the WESDR, 99% of people with type 1 DM and 60% with type 2 DM are expected to develop diabetic retinopathy. The number of people in the world with diabetic retinopathy has been estimated to increase to 191 million by 2030 as the number of people with type 2 DM continues to increase. Based on the results of research at Dr. M. Djamil Padang Hospital in 2016, there were 12.5% (187 people) suffering from diabetic retinopathy out of 1500 DM patients (Salsabila et al., 2020). As the prevalence of DM increases, the population ages, and the duration of the patient's disease, the incidence of diabetic retinopathy in all DM populations will continue to increase (Oktavian et al., 2011).

Dry eye in DM patients is caused by changes in the microvasculature of the lacrimal gland, diabetic sensory, or as a result of autonomic neuropathy, so DM patients, especially those with diabetic retinopathy complications, tend to experience dry eye (Foulks, 2007; Kaiserman et al., 2005; Setiawan et al., 2016; Yazdani et al., 2001). Based on its etiology, dry eye is divided into ADDE (Aqueous Deficient Dry Eye) and EDE (Evaporative Dry Eye), so based on its etiology diabetic retinopathy is included in ADDE due to impaired tear secretion by the lacrimal gland due to prolonged hyperglycemia conditions (Bron et al., 2017). In a study by Shaikh et al, the prevalence of dry eye was 20% in patients without retinopathy, 21.6% in patients with mild retinopathy, 47.7% in moderate retinopathy, 100% in severe retinopathy (Shaikh, 2015). Research conducted by Khurana et al regarding the severity of dry eye in patients with diabetic retinopathy is higher than patients without diabetic retinopathy (Khurana et al., 2017). Research by Uma Devi and Gowda states that there is a statistically significant relationship between diabetic retinopathy patients and dry eye (Devi & Gowda, 2016).

Diagnosing dry eye requires subjective and objective assessment. The examination for subjective assessment is through questionnaires, one of which is the Ocular Surface Disease Index (OSDI) (Özcura et al., 2007; Rahmadilla, 2020; Wolffsohn et al., 2017). According to the International Dry Eye Workshop (DEWS), the OSDI questionnaire is a valid and reliable questionnaire to quickly and easily evaluate the severity of individualized dry eye based on symptoms and assess the impact on the patient's quality of life (Rajagukguk et al., 2016). The OSDI has a sensitivity of 47% and specificity of 77% (Özcura et al., 2007; Schiffman et al., 2000). If the OSDI score is positive, it is necessary to perform a specific clinical examination objectively using the ferning test, this is because in diabetic retinopathy there is chronic hyperglycemia which affects conjunctival goblet cells resulting in decreased mucin secretion as a result of hyperosmolarity due to changes in tear film composition and concentration, especially in the mucin layer. The ferning test is one of the non-invasive and easy to perform tests that can be used to assess the quality of the mucin layer and the stability of the tear film (Masmali et al., 2014; Wolffsohn et al., 2017). The ferning test has a sensitivity of 82.2% and specificity of 92.5% (Rajagukguk et al., 2016). Early diagnosis of dry eye and timely referral will result in appropriate management of the patient and prevent sight-threatening

complications. Patients with diabetic retinopathy are considered to be at higher risk for dry eye and clinical evaluation for dry eye should be performed in addition to routine fundus evaluation of DM patients, especially in patients with evidence of diabetic retinopathy (Khurana et al., 2017).

The prevalence of diabetic retinopathy is found in type C hospitals. RSKM Padang Eye Center is one of the type C eye specialty hospitals located in the city of Padang which is one of the secondary referral hospitals, and has 4 ophthalmologists with vitreoretina subspecialists who handle many diabetic retinopathy cases and have adequate supporting examination equipment such as microscopes that can be used by researchers in conducting ferning tests, and based on observations of patient visit data, there are quite a lot of diabetic retinopathy cases. Based on the description above, seeing the important role of tears in maintaining and protecting the surface of the eyeball, and several studies found that the prevalence and severity of dry eye is higher in patients with diabetic retinopathy than in patients without diabetic retinopathy. Therefore, the purpose of this study was to determine the severity of dry eye in patients with diabetic retinopathy, and to provide information, data, and knowledge about the incidence of dry eye in patients with diabetic retinopathy so that prevention can be done.

METHOD
This study used a descriptive method with a cross sectional design. The number of samples in the study were 64 people with a diagnosis of diabetic retinopathy. The sampling technique in this study was carried out by consecutive sampling. The study population was all patients diagnosed with diabetic retinopathy at RSKM Padang Eye Centre. The study sample was part of the population diagnosed with diabetic retinopathy who met the inclusion and exclusion criteria. The inclusion criteria were diabetic retinopathy patients who were willing to be included in the study and signed the examination consent form, and were able to read and write. The sample size used was determined using the Lemeshow Formula. Data collection was carried out for 13 months, from February 2021 to March 2022. The level of dry eye was measured with the Ocular Surface Disease Index (OSDI) questionnaire. The OSDI questionnaire has good concurrent validity, internal consistency (Cronbach's alpha = 0.78-0.92), and test-retest reliability (intraclass correlation coefficient (ICC) = 0.70-0.82). The OSDI total score and each subscale score were also significantly associated with disease severity in multivariate analyses adjusted for sociodemographic factors (age, gender, education, and employment status) and number of medical comorbidities ($P \leq 0.005$) (Okumura et al., 2020; Schiffman et al., 2000).

After the patient signed informed consent as a respondent and filled out the OSDI questionnaire, a ferning test was performed by collecting tears in the fornix with a micropipette without topical anaesthesia. The tear sample was placed on a glass slide, covered and allowed to dry (5-10 minutes) at room temperature, then viewed under a light microscope with a magnification of 40-100 times and then interpretation of the results obtained. The result of the ferning test is a fern leaf image consisting of 4 types based on the ronaldo classification, namely type I and type II are normal images while type III and type IV are images of dry eye patients. (Bitton, 2007; Rajagukguk et al., 2016) The data obtained were the frequency distribution of the characteristics of diabetic retinopathy patients (gender, age, and duration of diabetes mellitus), the frequency distribution of the highest degree of retinopathy that experienced dry eye, and a description of the severity of dry eye through OSDI values and ferning tests in diabetic retinopathy patients based on the degree of disease. Ethical

permission for this research has been obtained from the Faculty of Medicine at Andalas University with letter number 567/UN.16.2/KEP-FK/2021.

RESULTS

This research was conducted at RSKM Padang *Eye Center*. The research was conducted from February 2021 to March 2022. Research data were obtained through interviews and patient medical record data, then examined using the OSDI questionnaire and ferning test to see the description of *dry eye* severity. This study involved 64 diabetic retinopathy patients who met the inclusion and exclusion criteria as research subjects. The results of the study are presented in Tables 1-5.

Table 1.
Frequency Distribution of Respondent Characteristics (n=64)

Characteristics	f	%
Gender		
Male	23	35,9
Female	41	64,1
Age		
<45 years old	10	15,6
45-65 years	51	79,7
>65 years old	3	4,7
DM Duration		
≤5 years	25	39,1
>5 years	39	60,9

Table 1 shows the characteristics of respondents based on gender, age, and duration of DM. The most common gender was female with 41 people (64.1%). The age group of 45-65 years was the most patients with diabetic retinopathy, 51 people (79.7%). The duration of DM of diabetic retinopathy patients is mostly >5 years, namely 39 people (60.9%).

Table 2.
Frequency Distribution of the Degree of Diabetic Retinopathy with Dry Eye (n=64)

Degree of Diabetic Retinopathy	f	%
Mild NPDR	1	1,6
Moderate NPDR	12	18,8
Severe NPDR	10	15,6
PDR	41	64,1

Table 2 shows that PDR is the most common degree of diabetic retinopathy with 41 people (64.1%). Of the 64 total diabetic retinopathy patients based on the degree examined in this study, all had dry eye (100%). Dry eye has occurred in all stages of NPDR.

Table 3.
Overview of Dry Eye Severity through OSDI Value in Retinopathy Patients Diabetic by Disease Degree (n=64)

Degree of Diabetic Retinopathy	OSDI Score			
	Normal	Mild Dry Eye	Moderate Dry Eye	Severe Dry Eye
Mild NPDR	-	-	1	-
Moderate NPDR	-	-	11	1
Severe NPDR	-	-	1	9
PDR	-	-	11	30

Based on Table 3, it was found that all diabetic retinopathy patients based on the degree examined got OSDI scores of 23-32 and 33-100 with the interpretation of the results experiencing moderate dry eye and severe dry eye. The most common dry eye severity was severe dry eye as many as 40 people (62.5%). Severe dry eye was mostly experienced by

diabetic retinopathy patients with PDR degree, namely 30 people. Moderate dry eye was mostly experienced by moderate NPDR and PDR patients, namely 11 people. There were no mild dry eye or patients who did not experience dry eye (normal). All diabetic retinopathy patients examined had dry eye (100%) based on the OSDI score.

Table 4.
Overview of Dry Eye Severity through Ferning Test in Retinopathy Patients Diabetic by Disease Degree (n=64)

Degree of Diabetic Retinopathy	Interpretation of Ferning Test Results			
	Type I	Type II	Type III	Type IV
Mild NPDR	-	-	1	-
Moderate NPDR	-	-	11	1
Severe NPDR	-	-	1	9
PDR	-	-	13	28

Based on table 4, the results showed that all diabetic retinopathy patients based on the degree examined had a picture of type III and type IV ferning. The most common ferning type was type IV with 38 people (59.4%). PDR is the degree of retinopathy that has the most dry eye with a type IV ferning picture as many as 28 people and type III as many as 13 people. No type I and II ferning was found in diabetic retinopathy patients based on the degree examined in this study. All diabetic retinopathy patients by degree examined through the ferning test had dry eye (100%).

Table 5.
Overview of the Degree of Diabetic Retinopathy Based on Dry Eye Severity Levels and Ferning Type (n=64)

OSDI	Ferning	
	Type III	Type IV
Moderate Dry Eye		
Mild NPDR	1	-
Moderate NPDR	11	-
Severe NPDR	1	-
PDR	11	-
Severe Dry Eye		
Mild NPDR	-	-
Moderate NPDR	-	1
Severe NPDR	-	9
PDR	2	28

Based on table 5 which is the combined result of table 3 and table 4, it is found that the most diabetic retinopathy patients based on their degree are PDR with OSDI results of severe dry eye and type IV ferning images, namely 28 people. In this study, there was no group without dry eye (normal) or mild dry eye group. Therefore, the ferning type in both groups could not be determined (not shown in table 4.5).

DISCUSSION
Based on the results of the study in table 1 regarding the characteristics of diabetic retinopathy patients, it was found that the highest gender was female (64.1%). This is in line with research conducted at Dr Mohammad Hoesin Palembang Hospital in 2014-2015, the most diabetic retinopathy was found in women (64%) compared to men (36%), which the results of this study are not different from the results of previous studies. This is related to the hormone estrogen which has an influence on DM patients, where high estrogen levels can reduce leptin which plays a role in suppressing appetite in the hypothalamus, resulting in uncontrolled food intake which can lead to the accumulation of excess fatty tissue accompanied by high blood sugar levels due to decreased sensitivity of peripheral tissues to insulin. In addition, it is also associated with high rates of obesity in women related to genetics and lifestyle which are risk

factors for DM, which in women is more difficult to change lifestyles, especially diet and physical activity (Utami et al., 2017). The same thing was found in a study by Lima et al. (2016) in which diabetic retinopathy patients who were female were more numerous (63.8%) but the study stated that there was no significant relationship between gender and the incidence of diabetic retinopathy because several studies found that the incidence of diabetic retinopathy was more in men which could be influenced by the population, the lack of representation of the number of samples taken or the influence of incomplete data on medical records or the influence of patient visits to the hospital in the study period (Wibawa et al., 2018).

Based on age, the results of this study are in line with research at Dr. M. Djamil Padang Hospital for the period January - December 2016, where the highest age was 45-65 years (79.6%) and only a few patients aged < 45 years (9.3%) and > 65 years (11.1%) (Dewi et al., 2019). A person aged ≥ 45 years has an increased risk of developing DM and is at risk for DM complications, namely diabetic retinopathy. This is supported by the existing theory that a person aged ≥ 45 years has an increased risk of glucose intolerance due to degenerative factors that cause decreased body function, especially the ability of β cells to produce insulin for glucose metabolism, besides that DM can also occur due to insulin resistance due to age factors (Betteng et al., 2014). The cause of the low incidence of diabetic retinopathy at the age of < 45 years is due to the long course of the disease and the average age of the patient is quite old both when suffering or when diagnosed, and the age recommendation to start DM screening according to the American Diabetes Association (ADA) is 45 years. While the incidence rate at the age of > 65 years is low due to the low life expectancy factor of DM sufferers (Dewi et al., 2019; Ilery et al., 2014). In addition, with age the conjunctival goblet cell function decreases, although the number remains but the mucin produced is small (Manullang et al., 2016; Singh et al., 2018).

Based on the duration of DM, the results of this study are in line with research at Dr. M. Djamil Padang Hospital from January to December 2016, where patients with a duration of > 5 years suffered more DM, namely 68%. The duration of DM plays an important role in predicting the occurrence of diabetic retinopathy, where the longer a person suffers from DM can cause the formation of many free radicals such as advanced glycation end (AGE) products, sorbitol and reactive oxygen species triggered by prolonged hyperglycemia conditions, which can result in circulation disorders, hypoxia and retinal inflammation (Dewi et al., 2019). This is also in line with the research of Wibawa et al. (2018), where the highest proportion of diabetic retinopathy was also found in patients with a duration of DM for 5-10 years, namely 55.6% (Wibawa et al., 2018). The main risk factor related to diabetic retinopathy is the duration of DM, where 25% of DM patients will experience diabetic retinopathy after 5 years, nearly 60% experience diabetic retinopathy after 10 years, and 80% experience diabetic retinopathy after 15 years (Klein et al., 1984). The longer a person suffers from DM, the more likely it is to suffer from diabetic retinopathy (Perkumpulan Endokrinologi Indonesia, 2015).

Based on the results of the study in table 2, it was found that the highest degree of diabetic retinopathy was PDR (64.1%) and all of them experienced dry eye. This is because dry eye has occurred in all stages of NPDR so that if the diagnosis of diabetic retinopathy (NPDR stage) means that dry eye is possible, and the number of PDR stages found is associated with the control time of NPDR stage patients (mild and moderate) which is quite long, namely 9-12 months and plus the research was conducted in a private eye hospital that has become a reference from various regions in West Sumatra so that many diabetic retinopathy patients

seek treatment with more severe conditions or stages (PDR). This is in line with research at Dr. M. Djamil Padang Hospital for the period January to December 2016, it was found that the highest degree of diabetic retinopathy was PDR. This is because at Dr. M. Djamil Padang Hospital most patients have suffered from DM for >5 years so that the development of the disease has been more progressive and many are diagnosed with the PDR stage. Different things were found in the research of Ilery et al. (2013) who reported the highest incidence of mild NPDR. The difference in results may occur because the mild NPDR stage has been found in the first 5 years of DM and usually has not affected the patient's visual function so that they have not checked themselves to the Health facility, eventually developing into more severe and the degree of severity continues to increase with the longer a person has DM (Dewi et al., 2019).

Based on the research of Najafi et al. (2013), Shaikh et al. (2015), and Nadeem et al. (2020), it was found that there is a significant relationship between dry eye and the degree of diabetic retinopathy, so that the increasing severity of diabetic retinopathy also increases the incidence of dry eye in patients, and shows that dry eye is more common in patients with PDR (Nadeem et al., 2020; Shaikh, 2015; Wibawa et al., 2018).Based on the results of the study in table 3, the severity of dry eye that occurs most in diabetic retinopathy patients based on the degree of disease is severe dry eye (62.5%) then moderate dry eye (37.5%), where severe dry eye occurs in diabetic retinopathy patients with PDR, and moderate dry eye occurs in moderate NPDR and PDR. Based on the OSDI score in this study, it was found that all diabetic retinopathy patients based on the degree examined had dry eye (100%), because dry eye has occurred in all stages of NPDR so that all diabetic retinopathy patients both NPDR and PDR stages examined in this study had dry eye. Based on the 12 questions on the OSDI questionnaire, the most common symptoms felt by patients are blurred and decreased vision, eye sensitivity to light, something feels blocky or sandy, so that it can interfere with patient activities in seeing or reading, and some patients feel uncomfortable in windy environments or air- conditioned rooms. The difference in symptoms felt by patients is due to differences in activity, environment, age, perception of pain, and others.

Based on research by Nadeem H et al (2020), among 56 respondents there were 42 NPDR patients (31.1%) and 14 PDR patients (10.3%), which in assessing the degree of dry eye used the OSDI questionnaire so that the results were obtained, namely among 42 NPDR patients, there were 11 people (25.6%) experiencing mild dry eye, 21 people (38.2%) moderate dry eye, and 10 people (45.5%) experiencing severe dry eye, and there were no patients with normal eyes (no dry eye). While among the 14 PDR patients, there were 2 people (12.5%) who did not have dry eye (normal), 3 people (7.0%) had mild dry eye, 7 people (12.7%) had moderate dry eye, and 2 people (9.1%) had severe dry eye (Nadeem et al., 2020).Research conducted by Sethia R et al (2021), found that 38 out of 43 patients with diabetic retinopathy experienced dry eye based on the OSDI score. Dry eye in diabetic retinopathy patients produces a significant relationship with OSDI, which is obtained based on the OSDI score, the prevalence of dry eye is more in diabetic retinopathy patients compared to those without diabetic retinopathy. This is in line with the research of Han JX et al (2021), the increasing severity of diabetic retinopathy, the increasing severity of dry eye so that more symptoms appear which can be seen by the increasing OSDI score (Fuerst et al., 2014; Han et al., 2021; Sethia et al., 2021). In DM conditions over a long period of time there is chronic hyperglycemia which causes fluid to accumulate in the lens of the eye which regulates focus so that it can change the curvature of the lens, eventually causing blurred vision (American Diabetes Association, 2010; Wibawa et al., 2018).

Based on the results of the study in table 4, it was found that the most ferning types were type IV (59.4%) then type III (40.6%), where type IV and type III ferning images were found most in PDR. Types III and IV are ferning images that indicate patients have dry eye, so in this study it was found that all diabetic retinopathy patients based on the degree examined through the ferning test had dry eye (100%). The ferning test results in the form of ferning patterns are influenced by the composition and concentration of tears. In chronic DM patients, especially in diabetic retinopathy, there has been prolonged hyperosmolarity which causes changes in the composition or concentration of tears resulting in changes in the ferning pattern (deterioration). The ferning pattern is formed from the ratio of salts such as sodium and potassium to macromolecules such as proteins, which can change due to increased osmolarity and decreased macromolecular concentration in dry eye. As the degree of diabetic retinopathy increases, the severity of dry eye increases and the ferning pattern becomes worse (Masmali et al., 2015; Masmali et al., 2014). Based on the research of Masmali AM et al (2018), it was found that the prevalence of dry eye was high, especially in patients with uncontrolled DM. The ferning results obtained showed that 35% experienced dry eye, most of whom had uncontrolled DM (72.7%). Based on the results of this study, it was found that PDR was the degree of retinopathy that experienced the most dry eye with a type IV and type III ferning picture due to changes in vascularization where there was blockage of blood vessels, causing conjunctival hypoxia which reduced the number of goblet cells in the conjunctiva. There is a correlation between changes in goblet cell density and fern test values, where a decrease in the number of goblet cells can reduce mucin production, thus showing a higher ferning type with a worsening fern pattern (Abigail et al., 2016; Abusharha et al., 2022; Masmali et al., 2017).

The difference in measurement results can be related to whether or not the hyperglycemia experienced by the patient is controlled, which is a state of chronic hyperglycemia and poor blood sugar control can cause innervation disorders in the cornea resulting in decreased corneal sensitivity which can affect the progressive level of neuropathy complications resulting in decreased lacrimal gland secretion in diabetic retinopathy patients (Setiawan et al., 2016). Until now there has been no research on dry eye in diabetic retinopathy patients assessed by the ferning test. Researchers performed the ferning test because the test is simple, effective, cost-effective, and the tear film layer affected in diabetic retinopathy is the mucin layer (Masmali et al., 2015; Masmali et al., 2014).

CONCLUSION
Based on the results of the study regarding the description of the severity of dry eye in diabetic patients through the OSDI scoring system and the ferning test, it can be concluded that diabetic retinopathy most often occurs in the age range of 45-64 years, dominated by female gender, and the duration of DM is mostly >5 years. The most common degree of diabetic retinopathy with dry eye is Proliferative Diabetic Retinopathy (PDR). Based on the OSDI score and ferning test in the study conducted on diabetic retinopathy patients based on the degree, all patients experienced dry eye. The most common degree of dry eye was severe dry eye, and the most common ferning type was type IV. Many patients with PDR had severe dry eye with type IV ferning.

REFERENCES
Abigail, M., Wildan, A., & Johan, A. (2016). Perbedaan Tear Film Break Up Time pada Pasien Retinopati Diabetika Non Proliferatif Dibandingkan Retinopati Diabetika Proliferatif. Jurnal Kedokteran Diponegoro, 5(4), 1261–1268.

Abusharha, A., El-Hiti, G. A., Alsubaie, M. H., Munshi, A. F., Alnasif, A. R., Fagehi, R., Alanazi, M. A., & Masmali, A. M. (2022). Evaluation of Tear Evaporation Rate in Patients with Diabetes Using a Hand-Held Evaporimeter. Healthcare, 10(1), 1–8.

American Academy Ophthalmology. (2019). External Disease and Cornea 2019-2020 Basic and Clinical Science Course (BCSC). San Francisco: American Academy Ophthalmology.

American Diabetes Association. (2010). Diagnosis and Classification of Diabetes Mellitus. Diabetes Care, 33 Suppl 1(Suppl 1), S62–S69.

Betteng, R., Pangemanan, D., & Mayulu, N. (2014). Analisis Faktor Risiko Penyebab Terjadinya Diabetes Melitus Tipe 2 pada Wanita Usia Produktif di Puskesmas Wawonasa. Jurnal e-Biomedik, 2(2), 404–412.

Bitton E. (2007). Tear ferning : a valuable tool in determining dry eye. Optician, 32–35.

Bron, A. J., de-Paiva, C. S., Chauhan, S. K., Bonini, S., Gabison, E. E., Jain, S., Knop, E., Markoulli, M., Ogawa, Y., Perez, V., Uchino, Y., Yokoi, N., Zoukhri, D., & Sullivan, D. A. (2017). TFOS DEWS II Pathophysiology Report. The Ocular Surface, 15(3), 438–510.

Craig, J. P., Nelson, J. D., Azar, D. T., Belmonte, C., Bron, A. J., Chauhan, S. K., de-Paiva, C. S., Gomes, J. A. P., Hammitt, K. M., Jones, L., Nichols, J. J., Nichols, K. K., Novack, G. D., Stapleton, F. J., Willcox, M. D. P., Wolffsohn, J. S., & Sullivan, D. A. (2017). TFOS DEWS II Report Executive Summary. The Ocular Surface, 15(4), 802–812.

Devi, R. S. U., & Gowda, M. S. S. (2016). Dry Eye in Diabetes Mellitus Patients and its Relationship with Diabetic Retinopathy. International Journal of Scientific Study, 4(8), 67–72.

Dewi, P. N., Fadrian, & Vitresia, H. (2019). Profil Tingkat Keparahan Retinopati Diabetik Dengan Atau Tanpa Hipertensi pada di RSUP Dr. M. Djamil Padang. Jurnal Kesehatan Andalas, 8(2), 204–210.

Foulks, G. N., Lemp, M. A., Jester, J. V., Sutphin, J., Jr., Murube, J., Novack, G. D., Erickson, S., Brookline, Abelson, M. B., Asbell, P. A., Baudouin, C., Beuerman, R. W., Bonini, S., Bron, A., Dana, M. R., Dartt, D. A., Dua, H. S., Fleiszig, S. M. J., Fonn, D., . . . Wilson, G. (2007). Report of the International Dry Eye WorkShop (DEWS). The Ocular Surface, 5(2), 65–204.

Fuerst, N., Langelier, N., Massaro-Giordano, M., Pistilli, M., Stasi, K., Burns, C., Cardillo, S., & Bunya, V. Y. (2014). Tear osmolarity and dry eye symptoms in diabetics. Clinical Ophthalmology, 8, 507–515.

Han, J. X., Wang, H., Liang, H. H., & Guo, J. X. (2021). Correlation of the retinopathy degree with the change of ocular surface and corneal nerve in patients with type 2 diabetes mellitus. Int J Ophthalmol, 14(5), 750–758.

Ilery, T., Sumual, V., & Rares, L. (2014). Prevalensi Retinopati Diabetik pada Poliklinik Ilmu Kesehatan Mata Selang Satu Tahun. e-Clinic, 2(1), 1–9.

Iskandar, F. (2020). Diquafosol Tetrasodium: Tatalaksana Terkini untuk Dry Eye Disease (DED). CDK Journal-288, 47(7), 542–546.

Kaiserman, I., Kaiserman, N., Nakar, S., & Vinker, S. (2005). Dry Eye in Diabetic Patients. American Journal of Ophthalmology, 139(3), 498–503.

Khurana, G., Khurana, D., & Jain, R. (2017). Dry Eye in Patients With Diabetic Retinopathy: A Clinical Study. Delhi Journal Ophthalmology, 27(3), 190–193.

Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & de-Mets, D. L. (1984). The Wisconsin Epidemiologic Study of Diabetic Retinopathy: Prevalence and Risk of Diabetic Retinopathy When Age at Diagnosis Is Less Than 30 Years. Arch Ophthalmol, 102(4), 520–526.

Legoh, C. G. F., Setiono, K. W., & Cahyaningsih, E. (2019). Hubungan Lama Menderita Diabetes dengan Dry Eye pada Penderita Diabetes Melitus Tipe II di RSUD Prof. Dr.W.Z Johannes Kupang. Cendana Medical Journal (CMJ), 18(3), 364–370.

Lukandy, A., & Albar, M. Y. (2020). Prevalensi dry eye pada pasien diabetes melitus tipe 2 di Rumah Sakit Mata Mencirim 77 Kota Medan. Intisari Sains Medis 2020, 11(3), 1193–1197.

Manullang, Y. R., Rares, L., & Sumual, V. (2016). Prevalensi Retinopati Diabetik pada Penderita Diabetes Melitus di Balai Kesehatan Mata Masyarakat (BKMM) Propinsi Sulawesi Utara Periode Januari-Juli 2014. E-Clinic, 4(1), 1–6.

Masmali, A. M., Al-Qhtani, S., Al-Gasham, T. M., El-Hiti, G. A., Purslow, C., & Murphy, P. J. (2015). Application of a new grading scale for tear ferning in non-dry eye and dry eye subjects. Contact Lens & Anterior Eye, 38(1), 39–43.

Masmali, A. M., Maeni, Y. A., El-Hiti, G. A., Murphy, P. J., & Almubrad, T. (2017). Investigation of Ocular Tear Ferning in Controlled and Uncontrolled Diabetic Subjects. Eye & Contact Lens, 44, S70–S75.

Masmali, A. M., Purslow, C., & Murphy, P. J. (2014). The tear ferning test: a simple clinical technique to evaluate the ocular tear film. Clinical and Experimental Optometry, 97(5), 399–406.

Nadeem, H., Malik, T. G., Mazhar, A., & Ali, A. (2020). Association of Dry Eye Disease with Diabetic Retinopathy. Journal of the College of Physicians and Surgeons Pakistan, 30(05), 493–497.

Oktavian, L. I., Supono, T. S., & Suharno. (2011). Korelasi Kadar Glikohemoglobin (HbA1c) dengan Kuantitas Sekresi Air Mata pada Pasien Diabetes Melitus Studi di RSUD Margono Soekarjo. Mandala of Health, 5(3), 390–394.

Okumura, Y., Inomata, T., Iwata, N., Sung, J., Fujimoto, K., Fujio, K., Midorikawa-Inomata, A., Miura, M., Akasaki, Y., & Murakami, A. (2020). A Review of Dry Eye Questionnaires: Measuring Patient-Reported Outcomes and Health-Related Quality of Life. Diagnostics, 10(559), 1–21.

Özcura, F., Aydin, S., & Helvaci, M. R. (2007). Ocular Surface Disease Index for the

Diagnosis of Dry Eye Syndrome. Ocular Immunology and Inflammation, 15(5), 389–393.

Perkumpulan Endokrinologi Indonesia. (2015). Konsensus Pengelolaan dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia 2015. Jakarta: PB PERKENI.

Prasetia, T. (2016). Pola Komplikasi Sistemik pada Pasien Diabetes Melitus Tipe 2 di Rumah Sakit Pertamina Bintang Amin Lampung Periode 1 Januari - 31 Desember 2015. Jurnal Medika Malahayati, 3(1), 55–60.

Rahmadilla, A. P. (2020). Hubungan Pemakaian Lensa Kontak Lunak (Soft Contact Lens) dengan Dry Eye Syndrome. Jurnal Medika Hutama, 02(01), 271–277.

Rajagukguk, C., Santoso, S. A., & Basoeki, S. (2016). Pengaruh Kemoterapi terhadap Sindroma Mata Kering Menggunakan Tes Ferning Okuler. Majalah Kesehatan FKUB, 3(2), 57–64

Salsabila, N., Vitresia, H., & Rustini, R. (2020). Efektivitas Injeksi Intravitreal Anti-VEGF terhadap Tajam Penglihatan pada Pasien Retinopati Diabetik. Jurnal Ilmu Kesehatan Indonesia (JIKESI), 1(2), 125–133.

Schiffman, R. M., Christianson, M. D., Jacobsen, G., Hirsch, J. D., & Reis, B. L. (2000). Reliability and Validity of the Ocular Surface Disease Index. Arch Ophthalmol, 118(5), 615–621.

Sethia, R., Patel, J., Pothuri, N. A., Shah, S., Mehta, J., & Vora, J. (2021). Tear film changes in type II diabetes mellitus with and without diabetic retinopathy. Journal of Clinical and Diagnostic Research, 15(2), p1–p4.

Setiawan, D., Wildan, A., & Johan, A. (2016). Perbedaan Hasil Pengukuran Schirmer Test pada Pasien Retinopati Diabetika Non Proliferatif dan Proliferatif. Diponegoro Medical Journal (Jurnal Kedokteran Diponegoro), 5(4), 694–702.

Setyoputri, N. T., Soelistijo, S. A., & Sasono, W. (2017). Prevalensi dan Karakteristik Pasien Retinopati Diabetik di Poli Mata RSUD Dr. Soetomo. JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga, 9(1), 20–25.

Shaikh, R. (2015). Prevalence of dry eye disease in type 2 diabetic patients and its co-relation with the duration, glycemic control and retinopathy. Al Ameen J Med Sci, 8(3), 225–229.

Singh, A. K., Nagpal, S., & Tyagi, R. (2018). A Study of Tear Ferning Patterns in Elderly Individuals with Dry Eye Disorder. Journal of Clinical and Diagnostic Research, 12(5), NC01–NC04.

Sitompul, R. (2011). Retinopati Diabetik. J Indon Med Assoc, 61(8), 337–341.

Utami, D. R., Amin, R., & Zen, N. F. (2017). Karakteristik Klinis Pasien Retinopati Diabetik Periode 1 Januari 2014 - 31 Desember 2015 di RSUP Dr. Mohammad Hoesin Palembang. Majalah Kedokteran Sriwijaya, 49(2), 66–74.

Wibawa, I. M. S., Budhiastra, P., & Susila, N. K. N. (2018). Karakteristik Pasien Retinopati

Diabetik di Rumah Sakit Umum Pusat Sanglah Denpasar Periode April 2016 – April 2017. E-Jurnal Medika, 7(11), 1–6.

Wolffsohn, J. S., Arita, R., Chalmers, R., Djalilian, A., Dogru, M., Dumbleton, K., Gupta, P. K., Karpecki, P., Lazreg, S., Pult, H., Sullivan, B. D., Tomlinson, A., Tong, L., Villani, E., Yoon, K. C., Jones, L., & Craig, J. P. (2017). TFOS DEWS II Diagnostic Methodology Report. The Ocular Surface, 15(3), 539–574.

World Health Organization. (2021). Diabetes, June 2021, (https://www.who.int/news-room/fact-sheets/detail/diabetes).

Yazdani, C., McLaughlin, T., Smeeding, J. E., & Walt, J. (2001). Prevalence of Treated Dry Eye Disease in a Managed Care Population. Clincal Therapeutics, 23(10), 1672–1682.