Prevalence of Dry Eye Syndrome in A South African Diabetic Paediatric Population: A Single-Centre Based Case Study

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PREFACE

This study is a presentation of the original work by the author and has not been submitted to other universities in any form. The work of this research is under review in accredited journals and in line with the thesis guidelines of the University of KwaZulu-Natal. Acknowledgement has been made where the work of others was used.

The research described in this project was supervised by Dr N. Ebrahim Khan (Discipline of Optometry, College of Health Sciences, University of KwaZulu-Natal, South Africa), and was conducted in the above-mentioned institution (on the Westville Campus) and ------ Hospital, Durban, KwaZulu-Natal, South Africa.

DECLARATION

I, Ms Seyuri Bisetty, declare that:

i. The work described in this thesis has not been submitted to the University of KwaZulu-Natal or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

ii. This dissertation does not include another person's data, graphs, tables, or other information unless clearly acknowledged as being sourced from other persons.

iii. This dissertation does not incorporate another person's writing unless specifically acknowledged as being sourced from other persons. In the case where other written sources have been quoted, the information utilised has been referenced accordingly.

iv. The research reported in this thesis unless where otherwise stated, is my original work. My contribution to the project was as follows:

- Development and design of the research topic and protocol
- Conduction of research methodology
- Collection and analysis of required data
- Interpretation of the obtained data
- Formulation of manuscript
- Final write-up of thesis

v. The contribution of others to this project was as follows:

Dr N. Ebrahim Khan (Supervisor)

- Development and refining of research design and methodology
- Assistance with analysis of data and statistical analysis
- Review and editing of manuscript and thesis prior to submission

Signed:

_____ 4 December 2023

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Date

[redacted]

Dr Naimah Ebrahim Khan

DEDICATION

In memory of those who are forever present in our hearts,

Some of my favourite people

My best friends;

My mom (the Late Mrs Hilda Bisetty)

&

Uncle Neal (the Late Mr Neal Soobramoney)

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS AND ABBREVIATIONS

DM	Diabetes Mellitus
DED/DES	Dry Eye Disease/Syndrome
FBS	Foreign Body Sensation
HbA1c	Haemoglobin A1c
IDF	International Diabetes Federation
LFU	Lacrimal Functional Unit
OSDI	Ocular Surface Disease Index
PRT	Phenol Red Thread
SD	Standard deviation
T1D/T2D	Type 1/Type 2 DM
TBUT	Tear Break-Up Time
TFO	Tear Film Osmolarity
UKZN	University of KwaZulu-Natal
WHO	World Health Organisation

ABSTRACT

Background: Diabetes Mellitus is a chronic condition resulting from elevated blood glucose levels. Timeous intervention is vital as poor management may give rise to serious secondary complications, thereby impacting health status and quality of life of patients. The current incidence of diabetes in South Africa is 8.27%, with an occurrence rate of 0.8/100 000 for the younger population, aged 0 to 14 years. Numerous studies have highlighted the fact that diabetes mellitus affects the ocular surface in terms of tear stability and function. Dry eye syndrome is described as a lack of tears on or around the eye or a decrease in the quality of tears produced. An optimal production of tears ensures that the ocular surface is kept moist and healthy. Literature on the prevalence of dry eye in paediatric patients diagnosed with diabetes is sparse.

Aim: To determine the prevalence of dry eye in a group of diabetic children and adolescents/young adults in eThekwini, South Africa.

Methods: A mixed method, single-centre-based case study approach was employed. A quantitative approach was used to determine the prevalence of dry eye in children with diabetes, using the following tear function tests; Tear Break-Up Time (TBUT), Phenol Red Thread (PRT) and Tear Film Osmolarity (TFO). A qualitative approach was adopted to understand the dry eye-related signs, symptoms, and visual functions of children with diabetes mellitus, using two dry eye questionnaires, Ocular Surface Disease Index (OSDI) and McMonnies questionnaire. Duration of diabetes was used as a parameter in this study. Statistical data analysis was conducted using R Statistical computing software of the R Core Team, 2020, version 3.6.3 (R Studio, Boston, MA, USA). All inferential statistical analysis tests were be conducted at 5% levels of significance. A p-value of $p<0.05$ was considered statistically significant.

Results: Thirty-seven children with diabetes and forty healthy, age group-matched controls who met the respective inclusion criteria, were enrolled in this study. The results of this study revealed that dry eye syndrome was more common among diabetics, with 40.5% participants being from the diabetic population compared to 10.0% from the control group. TBUT values were significantly reduced among the diabetics ($p<0.001$) indicating tear film instability. PRT results showed statistical significance ($p<0.001$) between the two groups and were found to be lower in the study group. TFO values were higher in participants with diabetes. No statistically significant differences were reported between the study and control groups, for both questionnaires. However, detailed question-analysis showed that participants of the control group were more

symptomatic to dry eye. No relationship between the duration of diabetes and diagnosis of dry eye was established.

Conclusion: Due to the constant increase in the number of children and adolescents diagnosed with diabetes mellitus, knowledge on the characteristics and prevalence of dry eye syndrome in this population has become a necessity. This study contributes to the literature by providing novel dry eye results as well as the prevalence in a select South African population. The findings accentuate a need to create awareness among healthcare practitioners working with children diagnosed with diabetes, to ensure timeous referral of ophthalmic assessment which ideally should include a complete dry eye assessment.

Keywords: Dry eye syndrome; paediatric diabetes, tear break-up time, phenol red thread, tear film osmolarity, type 1 diabetes

CHAPTER 1: INTRODUCTION

1.1. Introduction

The prevalence of diabetes is steadily increasing and fast becoming a public health concern, especially among the developing countries.[1] According to the International Diabetes Federation (IDF), in 2011, 370 000 000 people were diagnosed with diabetes and this was predicted to reach approximately 550 000 000 by 2030.[2] Literature has shown that at least 80% of the diabetic population are from developing countries. By 2017, the total number of children and adolescents, across the world, living with diabetes reached 1 106 500.[3] The IDF recently reported that of the total population living with Type 1 diabetes in 2022, 1 520 000 (17.0%) were younger than 20 years old, while 5 560 000 (64.0%) were aged between 20 and 59 years.[2]

Diabetes Mellitus (DM) is a set of complex metabolic diseases associated with defects in insulin secretion and/or insulin efficacy, resulting in chronic hyperglycaemia.[4] It is known to be one of the most common chronic disorders amongst paediatric patients today.[5] There are two broad categories, Type 1 (T1D) and Type 2 (T2D). T1D, also referred to as insulin-dependent or juvenile-onset diabetes, primarily results from the autoimmune-mediated destruction of beta cells within the Islets of Langerhans found in the pancreas, which results in an insulin deficiency.[6] This is usually accompanied by mutations in lipid metabolism, increased hyperglycemia-mediated oxidative stress, endothelial cell dysfunction and apoptosis. In a similar manner, the increased glucotoxicity, lipotoxicity, endoplasmic reticulum-induced stress, and apoptosis leads to the progressive loss of beta cells, giving rise to the second type of diabetes. Whilst T1D is defined by the presence of beta cell autoantibodies, a combination of peripheral insulin resistance and dysfunctional insulin secretion by the beta cells of the pancreas is implicated in the pathogenesis of T2D. The degree of hyperglycemia tends to fluctuate over time, based on the extent of the underlying conditions. In some cases, the condition may have not progressed far enough to result in hyperglycemia.[6] Both types, however, are closely associated with a wide range of complications which include the more severe cases of cardiomyopathy, nephropathy as well as neuropathy.[7]

Various physiological and psychological side effects may arise as the disease progresses. Blurry vision, dry eye, hormonal imbalances, acute renal diseases requiring dialysis or in severe cases, a kidney transplant, myocardial infarction, cerebrovascular diseases such as a stroke, hypertension and occasional severe vision loss are some of the most commonly reported complications associated with this condition. Diabetes mellitus is a disease that relies on numerous factors and

may vary over time and region. Therefore, regular monitoring of patients is vital and should be implemented accordingly.[5]

Dry eye disease (DED), commonly referred to as Dry Eye Syndrome (DES) is a multifactorial disorder of the preocular surface - defined by a loss of homeostasis of the tear film.[8] Dysfunction may result in one or both layers of the tear film, viz., the lipid layer and the muco-aqueous layer.[9] Reduced tear production or a tear film of poor quality result in an instability of the tear film as a whole, thereby allowing for rapid evaporation of tears from the surface of the eye.

Dry eye disease can be grouped dichotomously into (1) Aqueous-deficient dry eye and (2) Evaporative dry eye, depending on the aetiology. Some characteristics may present in both classifications.[10]

1. *Aqueous-deficient dry eye*

   This form of dry eye usually presents as a result of a decrease in the production of aqueous humour by the lacrimal gland.[11] This group can be broken down further into Sjogren and Non-Sjogren related.[12] These patients are at a higher risk of developing evaporation-related dry eye if a lipid or mucin deficiency is found, as this further disrupts tear stability.

2. *Evaporative dry eye*

   Evaporative dry eye usually presents with a meibomian gland dysfunction resulting in an insufficient lipid layer production which allows for increased rates of tear evaporation from the ocular surface. Most patients usually present with this type of dry eye.[13] Reduced Tear Break-Up Times are usually characteristic of evaporative dry eye.[10] Based on the signs and symptoms upon evaluation, evaporative dry eye can be classified as being either intrinsic or extrinsic.[12]

Dry eye disease may be triggered by a wide range of intrinsic and extrinsic factors which include age, sex, hormonal levels, autoimmune disorders, local environmental conditions, contact lens wear and exposure to certain medication[8]. Most patients report ocular irritation, red eyes, blurred vision, a foreign body sensation and/or easily fatigued eyes.[14] DED is closely associated with the reduced ability to perform certain activities such as reading, driving, and computer related work - tasks that require visual attention.[15] Patients experience dry eye symptoms constantly and at varying severities. It is known to be one of the most common reasons for seeking help from eye care professionals.[16] Lack of sufficient tears can leave the interpalpebral ocular surface susceptible to damage, affecting the quality of life of these patients.[17]

Dry eye assessments may be implemented based on a combination of dry eye signs and symptoms. A diagnostic evaluation of dry eye disease is vital and should include one or more of the following; a comprehensive case history, a thorough slit lamp examination, administration of relevant dry eye questionnaires, and clinical objective tests.[18]

Numerous studies have reported that diabetes is closely linked to an increased risk of developing chronic complications. With regards to the eye itself, patients may develop ocular surface diseases such as dry eye or keratopathy, retinopathy, glaucoma, cataract, refractive abnormalities, all of which could result in a decrease in visual acuity and if not managed effectively, could lead to blindness.[14] Tear function may also be reduced in diabetic patients due to either, the impairment of the autonomic nervous system or damage to the lacrimal gland's microvasculature. [19]

Aetiology and Pathophysiology of Diabetes Mellitus related Dry Eye

The incidence of dry eye is closely associated with the level of glycated hemoglobin. Patients with higher levels of glycated hemoglobin are at an increased risk of developing dry eye. The lacrimal functional unit (LFU) helps to regulate tear secretion, formation of the tear film as well as maintain the normal tear physiology. The effects of hyperglycemia on the lacrimal functional unit may be transferred across the entire system through the neural connections resulting in decreased tear production, an increase in tear evaporation rates, blinking abnormalities, and changes to the tear film.[20] Diabetes can often cause an epithelial barrier dysfunction or damage, which in turn gives rise to other corneal complications and LFU dysfunction.

i. *Reduced mucin secretion*

   Damage to the corneal and conjunctival epithelium results in a reduced number of goblet cells, which means that mucin production decreases. The hydrophilic nature of the ocular surface itself is altered, leading to tear film instability.[21]

ii. *Abnormal tear dynamics*

   Aldose reductase is an enzyme that plays a vital role in the pathway linked to the pathogenesis of dry eye. High levels of glucose trigger the polyol pathway which activates aldose reductase. Sorbitol begins to accumulate, causing oedema and subsequently, cell dysfunction. Eventually, this results in lacrimal gland damage, dysfunction and lower tear secretion levels.[20]

Numerous histopathologic alterations, such as acinar atrophy; periacinar fibrosis; periductal fibrosis; interlobular ductal dilatation; interlobular ductal proliferation; lymphocytic infiltration;

and fatty infiltration are observed in the lacrimal glands of older patients.[22] Anecdotal evidence suggest that due to the anatomy of the eye and naturally occurring aging process, the older population are generally said to be more prone to developing dry eye syndrome. However, patients with underlying systemic conditions such as diabetes, regardless of their age, are more prone to developing ocular dryness and require timeous intervention. Epidemiology studies carried out to date revolving around dry eye and diabetic paediatric patients only reported the incidence of the syndrome[23,14], a relationship between fasting blood glucose, HbA1c levels[24] as well as changes to the ocular surface.[23,24,25] However, limited literature is available with regard to the prevalence of dry eye in children with and without diabetes.

This study is warranted, as it attempts to bridge the gap within the current literature by determining and comparing the prevalence of dry eye disease between children with and without diabetes in a select South African population. Since dry eye investigations are usually implemented based on patient responses, dry eye complications are often overlooked in younger patients as compared to adults.

Dry eye syndrome may impact one's visual function significantly and hence, reduce their quality of everyday living. Studies have shown that this frequently overlooked ocular condition, adversely impacts the pivotal daily tasks of modern living, this includes the use of digital devices, reading, and driving.[16] The results of this study may also be utilised to enhance physician awareness of dry eye in children as well as promote early screening and close follow-up of dry eye disease in children with diabetes which should be implemented, especially in children with a long duration of diabetes.[14] The future of diabetes mellitus management depends on an increase in awareness of the importance that ocular surface health plays in the condition. A better understanding of the ocular surface amongst the general health profession is essential in ensuring optimal management of diabetic patients. Early intervention is important as scarring of the cornea may occur in some dry eye cases, leading to mild-to-severe visual impairment.

1.1.1. Research Question

- What is the prevalence of dry eye syndrome in a select population of diabetic children and young adults?

1.1.2. Aim

- To determine the prevalence of dry eye in a group of diabetic children and young adults/adolescents in eThekwini, KwaZulu-Natal, South Africa.

1.1.3. Objectives

- To measure the stability of the tear film by assessing the Tear Break-up Time (TBUT) in diabetic children and young adults.
- To measure the integrity of the lacrimal secretion system using the Phenol Red Thread test.
- To measure the osmolarity of tears of children and young adults with diabetes, using an osmometer.
- To compare significant findings of two dry eye questionnaires (OSDI and McMonnies).

1.2. Literature Review

The literature review for this study has been prepared in manuscript format and presented in Chapter 2. However, a summary of the literature has been provided in Table 1.

TABLE 1. Summary of the literature investigating dry eye or ocular surface changes in diabetic paediatric patients

TITLE	AUTHOR	YEAR	TBUT	SCHIRMER	TFO	OSDI	PREVALENCE	OTHER
Dry eye syndrome in diabetic children	Akinci et al.[23]	2007	TBUT results were significantly lower in patients with more than 10 years duration of T1DM	Schirmer test results were significantly lower in patients with more than 10 years duration of T1DM	-	-	Prevalence of DES was significantly higher in diabetic children ($\chi 2$=5.2, p=0.03).	Prevalence of dry eye symptoms was also significantly higher in the T1DM group ($\chi 2$=8.8, p=0.029). Prevalence of dry eye signs was significantly higher in T1DM group ($\chi 2$=4.9, p=0.034).
Ocular manifestations of Type 1 diabetes mellitus in pediatric population	Akil et al.[26]	2016	TBUT was 13.3 ± 3.3s in the diabetic group and 12.0 ± 1.8s in the control group. There was no statistically significant difference.	Schirmer test was found to be 15.5 ± 3.9 mm in diabetic group and 19.8 ± 3.9 mm in the control group. There was a statistically	-	-	-	-

				significant difference ($p<0.001$).				
Ocular Surface Characteristics in Diabetic Children	Gunay et al.[24]	2016	TFBUT results were lower in diabetic group - but not statistically significant.	Significantly lower Schirmer test scores in diabetic children in our study.	Significantly higher TFO values in diabetic children as compared with that in healthy controls.	Significant differences of OSDI ($p=0.006$) between the two groups.	-	-
Alterations of Tear Film and Ocular Surface in Children with Type 1 Diabetes Mellitus	Inanc et al.[25]	2019	TBUT was significantly shorter in the diabetic group (9.98 ± 3.97s) than in the control group (12.13 ± 3.23s) ($p=0.001$).	Schirmer test scores were 12.09 ± 5.73 mm in the diabetic group and 15.09 ± 4.01 mm in the control group. The differences between the two groups were statistically	-	OSDI scores of all participants were within the normal range.	-	Correlation analysis of results of OSDI, TBUT, and Schirmer tests with DM-related variables revealed - only statistically significant, moderate correlation between TBUT results with duration of DM.

				significant (p=0.001).				
Dry Eye Disease Is More Prevalent in Children with Diabetes than in Those without Diabetes	Wang et al.[14]	2019	Tear film break-up time were also significantly lower than those in the control group.	-	-	Number of children with OSDI values above normal was 13 in the diabetes group.	Prevalence of dry eye disease in children with diabetes was 28.95%, which was significantly higher than that in the control group.	Duration of diabetes was an independent risk factor for dry eye disease. Longer duration of diabetes was associated with lower (less severe) OSDI scores.
A Cross-Sectional Study of Ocular Changes in Children and Adolescents with Diabetes Mellitus in Selected Health Facilities in Ghana	Essuman et al.[27]	2022	Reduced TBUT in the diabetic group.	-	-	-	-	

1.3. Materials and Methods

1.3.1. Study Design

This study utilised a prospective, quantitative as well as qualitative clinical approach to determine the prevalence of dry eye in children and adolescents/young adults diagnosed with diabetes mellitus.

#Adolescence according to WHO, may be described as any persons between 10 and 19 years old.[28]

#Young adults refer to any person who falls in the age category, 18 to 26 years.[29]

1.3.2. Study Setting

Study group: Patients were recruited from the Centre for Paediatric Endocrinology and Diabetes based at a private hospital in Westville.

Control group: Participants were sought from a local private child and youth care centre and included patients that presented to the hospital being treated for other endocrine conditions which did not alter the tearfilm. It should be noted that participants within the control group undergo regular medical check-ups and according to the caregivers at the centre, none of the participants were previously diagnosed with diabetes nor were they at risk of developing the condition.

1.3.3. Study Population

Study group: Diabetic paediatric patients between 6 – 21 years old presenting to the centre.

Control group: Non-diabetic, healthy children between the ages of 6 and 21.

The data collection for the study was carried out during the period of April 2023 to September 2023.

1.3.4. Sample Size

Study groups: 37 patients with a confirmed diagnosis of Diabetes Mellitus met the inclusion criteria and consented to participate in the study.

Control group: 40 age group-matched participants met the inclusion criteria and consented to participate.

1.3.5. Inclusion and Exclusion Criteria

Inclusion Criteria

Study group

i. Informed consent.

ii. Male or Female between 6 to 21 years.

iii. Diagnosed with T1D or T2D based on the WHO diagnostic criteria.

iv. Diagnosed at least 6 months to a year, prior to assessment.

v. No signs of neuropathy.

vi. Free from any active ocular disease or systemic conditions that may compromise tear test values.

Control group

i. Age-related healthy children with no history of systemic conditions or ocular conditions that may be associated with dry eye disease.

ii. Not on any chronic medication that may cause dry eye.

Exclusion Criteria

Study group

i. If the patient does not meet any of the inclusion criteria

ii. Diagnosed with eye diseases that can affect the quality or volume of tears or the secretion of tears. These included: eyelid diseases - eyelid entropion, eyelid ectropion, eyelid, ptosis, and palpebral dyskinesia; conjunctival diseases - pterygium and conjunctivitis.

iii. History of ocular surface chemical injury.

iv. History of ocular surgery or retinal laser photocoagulation over the past 6 months.

v. Systemic diseases such as Sjogren's syndrome, Parkinson's disease, Rheumatoid arthritis, Grave's disease, Systemic lupus erythematosus.

vi. Chronic use of oral or topical antibiotics, prescribed eye medication, steroids, diuretics, antihistamines, or decongestants, isotretinoin or other medication commonly associated with dry eye.

Control group:

i. History of systemic conditions or ocular conditions that may be associated with dry eye disease.

ii. Chronic use of ocular medication or chronic medication associated with dry eye.

1.3.6. Data collection tools and Relevant information

The materials and equipment required to obtain the necessary data for this study consisted of the standard optometric tools:

i. An ophthalmoscope, Phenol Red Thread, fluorescein strips, preservative-free saline, Tetracaine Hydrochloride (anaesthetic), TearLab osmolarity System, TearLab test cards and a stopwatch.
ii. Ocular Surface Disease Index (OSDI) and McMonnies questionnaires (Appendix J).
iii. Record forms (Appendix K)

Participants who met the inclusion criteria and were willing to be a part of the study were required to fill in an indemnity form (signed by both, parent/guardian, and child), in accordance with the POPI Act. Candidates were allocated a code that was unique to each patient, for example A001. This code reflected on all documents (indemnity form, OSDI and McMonnies questionnaires and the record form) pertaining to that specific participant - ensuring patient confidentiality throughout the study.

The following information was obtained from the above:

Patient demographics (age, sex, race, duration of diabetes)

Tear function test results

(a). Tearfilm osmolarity (TFO)
(b). Tear Break-up Time (TBUT) – 2 readings
(c). Phenol Red Thread (PRT)

Results of the two dry eye questionnaires

(a). OSDI
(b). McMonnies

1.3.7. Data Collection Process

Data for this study was collected over a period of 6 months (April 2023 – September 2023) Upon arrival to the doctor's rooms and awaiting consultation, an information document - providing a brief overview of the study, it's purpose and the relevant tests - was handed out to parents and in some cases the patients themselves. Those who were willing to participate in the study were required to complete consent and assent (for under 16-year-olds) forms signed by both parent and child, respectively.

Thereafter, all participants underwent a complete dry eye assessment comprising of 2 parts, i.e., subjective (dry eye questionnaires) and objective (clinical tests). Firstly, patients were required to complete the dry eye questionnaires – McMonnies and Ocular Surface Disease Index (OSDI), followed by meibomian gland evaluation and lastly the clinical dry eye tests (Tear Film Osmolarity, Tear Breakup Time and Phenol Red Thread) were performed.

The same process was applied upon data collection for the control group.

1.3.7.1. Questionnaires

Ocular Surface Disease Index (OSDI)

Upon completion of this questionnaire, a final score was calculated using the standard grading scale which ranged from 0 to 4, based on how often patients were affected by the factors in question as well as the following formula.[30]

$$\text{OSDI} = \frac{(sum\ of\ scores\ for\ all\ questions\ answered) x\ 100}{(total\ number\ of\ questions\ answered)\ x\ 4}$$

Table 2. Classification of dry eye according to the overall scores:

Total Score	Classification of dry eye
0 -12	Normal
13 – 22	Mild
23 – 32	Moderate
33 - 100	Severe

McMonnies Questionnaire

Each question had its own score range and the McMonnies Index is calculated by adding individual scores per question. An index of 14.5 and above, warranted a dry eye diagnosis.[31]

Meibomian Gland Evaluation

Under normal room illumination, the ocular adnexa which included the lids, lashes, and orbit, were evaluated using a handheld ophthalmoscope with a medium power magnification. The main aim of this step was to identify the possibility of a meibomian gland dysfunction which is commonly associated with evaporative dry eye. Ruling out Meibomian gland dysfunction (MGD) was vital to ensure that diabetes mellitus was the major contributing factor of this study and to obtain accurate tear test results.
Upon presentation of MGD, one would usually find yellow-like cappings at the orifices also known as "plugging", telangiectasias and dents at the margin of the eyelid.[32]

The fluid secreted by the meibomian gland was also evaluated. Mild pressure was applied by the thumb of the researcher to the patient's lower eyelid margin. Normal meibum was considered to appear clear.

1.3.7.2. Tear Function Tests

All participants enrolled for this study underwent three dry eye tests (explained in detail below). Tests were performed on both eyes, on the same day and by the same individual - to maintain consistency and ensure standardization of each step of the testing process. Test procedures were explained in detail prior to the test being performed by the researcher.

Tear Film Osmolarity (TFO)

Patients were seated and instructed to lift their chin while their gaze was directed to the opposite direction of the eye being tested. A demonstration was performed prior to the exam to show younger patients exactly what was required. A single-use disposable test card with a chip, was inserted into the osmometer (TearLab) device and then positioned slightly above the lower eyelid. When a sufficient amount of tears was collected, the device beeped and a top edge on the test card illuminated with a green light. Thereafter, a number was selected by the researcher, corresponding to the test card that was used for the patient, and a result was thereafter displayed on the reader.[33]

Normal: Mean 309.9 mOsms/L ± 11.0 (288–331 mOsms/L; 90% CI 288–331)
Dry Eye Disease: Mean 324.3 mOsms/L ± 20.1 (291–382 mOsms/L; 90% CI 284–392).
According to literature, various test norms have been proposed in terms of tear osmolarity, however, there is no set cut-off due to the overlap of test values.[34]

Tear Break-Up Time (TBUT)

A drop of 0.9% sterile saline was utilized as a wetting agent for the fluorescein strip. Patients were asked to hold his/her gaze superiorly while the examiner touched the inferior bulbar conjunctiva with the fluorescein strip and ensured an adequate amount (approximately 0.05ml) was present on the ocular surface. This was performed with extreme caution ensuring that no corneal laceration occurred due to the fluorescein strip edges. Patients were initially asked to blink a few times which aided in the mixture of tears with the fluorescein. Patients were then instructed to perform a complete blink and thereafter hold their blink while looking straight ahead. The cobalt blue filter on the WelchAllyn ophthalmoscope was used by the examiner to assess the corneal surface, on medium magnification. Fluorescein viewed through a cobalt blue filter presents as a bright green. A stopwatch was used to measure the time immediately after patients holds blink until a black spot appeared in the fluorescein, which indicated a break in the tear film. This process was carried out twice, results were recorded in seconds and an average of the two test results were taken.

Phenol Red Thread (PRT)

Patients were required to be seated in an upright position. A drop of topical anesthetic (Tetracaine Hydrochloride, 1.0%) was administered followed by immediate punctal occlusion. The use of anesthetic eliminated reflex tearing and ensured that the reading gained was purely as a result of the basal tear secretion. Participants were instructed to avoid rubbing their eyes for the next 20 minutes, post administration of the drop. Phenol Red thread, a yellow (acidic) thread was utilised. A small portion of the thread, bent to approximately 3mm was placed in the inferior fornices of both eyes and a timer was then set for 15 seconds. Patients were allowed to blink as normal during the waiting period. At the end of the 15 seconds, the thread was carefully removed and the wet portion, which turned red, was measured using the scale printed at the back of the pocket of each pair of phenol red thread. Results were recorded individually, per eye. Readings below 10mm indicated dry eye while a reading below 20mm indicated a marginal dry eye.[35]

1.3.7.3. Criteria for Diagnosing Dry Eye

a. Participants were classified as having dry eye:

    i. Based on the results of the Tear Film Osmolarity test itself. Tear osmolarity may be used as a diagnostic tool for dry eye syndrome.

TFO > 305mOsm/L in RE or LE

i. OSDI > 13 or McMonnies >14.5 AND TBUT≤10s and PRT<10mm

ii. TBUT≤ 10s and PRT <10mm

b. The following results warrant patients to be monitored/probable diagnosis:

i. TFO < 305 but difference between TFO (RE)/TFO (LE) >8mOsm/L

ii. OSDI > 13 or McMonnies >14.5 AND 303 ≤ TFO < 305mOsm/L

iii. OSDI > 13 or McMonnies >14.5 AND TBUT < 15mm or 10>PRT < 20

All aspects of the data collection process were managed by the researcher and tear function test results were obtained twice, where possible, to ensure accuracy and reliability. Environmental factors were kept as constant as possible at both centres i.e., environmental conditions, such as air-conditioning and humidity of the room, that may be affect the rate at which the ocular surface dries out, were kept within constant throughout the study's data collection period. The questionnaires used in this study fall within the standard scope of optometry and have been previously validated.

1.3.8. Data Management

All results and the relevant information for each aspect of the dry eye assessment were recorded on either on the data sheet itself, or on record forms. Thereafter, this data was captured electronically in the form of word documents and excel spreadsheets – ready for data analysis. Documents pertaining to a particular patient was marked with a designated number or code (e.g., C001) in the database, ensuring that the patient's name does not appear on neither the questionnaires nor on the record form. None of the participants names and personal details were included in the study at any point of the research or data analysis. The electronic files were password protected and were only accessed by the researcher, when required. Original documents will be kept, safely, for a minimum of 5 years after which they will be destroyed.

1.3.9. Data Analysis

Statistical data analysis was conducted using the R Statistical computing software of the R Core Team, 2020, version 3.6.3 (R Studio, Boston, MA, USA). The results were presented in the form of descriptive and inferential statistics. Where applicable, the descriptive statistics of numerical

measurements were summarized as the minimum, maximum, quartiles, interquartile range, means, standard deviation and the coefficient of variation. Multidimensional numerical variables were presented as correlation plots. Correlation analysis was applied to determine the association between different numerical measurements. On the other hand, the categorical variables were described as counts and percentage frequencies where multiple bar charts were also used to visually display the categorical variables. Depending on the distribution of the numerical variables between two independent groups, mean or median differences were assessed using either t-test or Wilcoxon respectively. In order to assess the mean difference of numerical variables across at least three levels of a categorical variable, ANOVA test was used for normally distributed measurements and Kruskal Wallis for assessing the median difference of the non-normally distributed measurements. To determine the association between categorical variables, a Chi-Square Test was used and when the distribution of the cross tabulations contained an expected value of less than five, a Fisher's exact test was applied. In the case of significant difference between the Chi-Square or Fisher exact test, a row wise paired z-test was used as a post hoc analysis following the omnibus tests (Chi-Square or Fisher exact test). All the inferential statistical analysis tests were conducted at 5% levels of significance. Statistical significance was set at $p<0.05$.

1.3.10. Ethical Considerations

Approval to conduct this clinical study was sought from the Biomedical Research and Ethics Committee (BREC), Faculty of Health Sciences, University of KwaZulu-Natal **(BREC/00004451/2022)** (Appendix C). The relevant gatekeeper permissions were obtained from the hospital's ethics committee (HHREC)(**LHCHREC-PR-25102022/21**)(Appendix D) and the Ethelbert Child and Youth Care Centre (Appendix E).

Informed consent was obtained prior to participation. Patient anonymity and confidentiality was maintained at all times. Participation was voluntary.

1.3.11. Significance of the Study

With the continuous increase in the number of children and adolescents being diagnosed with DM, the characteristics and risk factors of dry eye disease in this population has become more valuable and of social significance. Dry eye is known to be associated with many causative factors, with systemic conditions being the most common. At present, a large majority of the literature focuses on the prevalence and factors associated with dry eye disease in diabetic adults,

but very few studies have been performed on children with diabetes. Information obtained from the results of the study will be beneficial to the healthcare practitioners in South Africa by enhancing physician awareness of dry eye in children and encourage early ophthalmic screening – which should include dry eye assessments - and close follow-up of dry eye disease in children with diabetes which should be implemented, especially in children with a long duration of diabetes.

1.4. Structure of Thesis

This thesis was prepared according to the guidelines outlined by the College of Health Sciences, University of KwaZulu-Natal, South Africa (Appendix L). Specific methodologies utilised for the study are detailed in the respective manuscripts to address the overall aim and objectives. Vancouver referencing was used in this thesis with the exception of the manuscripts, which have been structured, formatted, and referenced according to the author guidelines provided by the respective scientific journals. References cited in each chapter are listed at the end of the respective chapter. The structural outline of the thesis is as follows:

1.4.1. Chapter 1: Introduction

This chapter presented a background and summary of the literature reviewed on the incidence of dry eye and ocular surfaces changes in patients with diabetes, as well as an overview of the study. The aim, objectives, research question as well as an overview of the methodology were included in this chapter. Figures for materials and methods were not included in this chapter as they have been included within the respective manuscripts in the forthcoming chapters.

1.4.2. Chapter 2: Scientific Manuscript 1

This chapter comprised of an original scientific manuscript titled: Paediatric Diabetes and Dry Eye: An Overview. This manuscript analysed the current available literature which investigated prevalence of dry eye syndrome in children with diabetes, as well as documented any ocular surface alterations and tear function test results. A total of 6 articles were analysed and the results were reported under the different categories: Tear Film Osmolarity, Tear Break-Up Time, Schirmer test, presence of dry eye signs and symptoms and lastly, prevalence of dry eye,

This manuscript was submitted to *Eye and Contact Lens: Science and Clinical Practice* for review and possible publication – Manuscript number: ECL-23-269 (Appendix A (1)).

1.4.3. Chapter 3: Scientific Manuscript 2

This chapter comprised the second original scientific manuscript titled: Prevalence of Dry Eye Syndrome in A Diabetic Paediatric Population. This manuscript analysed and documented the incidence of dry eye in a cohort of South African diabetic paediatric population. The study

entailed a study group (n=37) and a control group (n=40). The results were compared between the two groups to determine statistically significant relationships.

This manuscript was submitted to *Contact Lens & Anterior Eye* for review and possible publication - Manuscript number: CLAE-D-23-00397 (Appendix A (2))

1.4.4. Chapter 4: Synthesis

This chapter further discussed the key findings of Chapters 2 and 3 and concluded the findings of the prevalence of dry eye syndrome in a select South African population. The possible limitations encountered and recommendations for future studies have been highlighted and elucidated in this chapter. Following Chapter 4 are the appendices.

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CHAPTER 2: SCIENTIFIC MANUSCRIPT 1

Chapter 1 provided a brief overview on diabetes mellitus and dry eye syndrome as well as a summary of present literature, demonstrating that literature on the prevalence of dry eye in children with diabetes is scarce. Additionally, no previous study has analysed the prevalence of dry eye and documented the tear film changes in South African paediatric patients with diabetes mellitus.

Contributions of this chapter

This chapter is comprised of a scientific manuscript that took the form of a review paper and analysed the results of available published literature. The results of this review highlight different aspects with regard to the tear film and diabetes in the paediatric population.

The following manuscript has been submitted and is currently under review by the scientific journal:

Title: Paediatric Diabetes and Dry Eye: A Review
Authors: S Bisetty, N Ebrahim Khan
Journal: Eye & Contact Lens: Science and Clinical Practice
Manuscript Number: ECL-23-269 (Appendix A (1))

Please note: This manuscript has been written, formatted, and presented according to the author guidelines outlined by *Eye & Contact Lens: Science and Clinical Practice*. The American Medical Association (AMA) manual of style was used for reference formatting, as required by the journal.

Title:

Paediatric Diabetes and Dry Eye: A Review

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2.1. ABSTRACT

Diabetes Mellitus (DM) is a set of complex metabolic diseases associated with defects in insulin secretion and/or insulin efficacy, resulting in chronic hyperglycemia. It is known to be one of the most common chronic disorders amongst paediatric patients today. Dry eye disease is a multifactorial disorder of the preocular surface which is defined by a loss of homeostasis of the tear film. This review aimed to collate (1) studies that reported on dry eye amongst children with diabetes and (2) studies that reported on possible ocular surface changes in this population. A literature review of current scientific papers from online databases that support dry eye prevalence and ocular surface changes in children diagnosed with diabetes mellitus. Literature supports that even the paediatric population diagnosed with diabetes may present with various ocular surfaces changes, with a probable dry eye diagnosis. Healthcare practitioners dealing with diabetic children should be aware of diabetic-related ocular changes. Early diagnosis and management are vital as this prevents the possibility of secondary ocular surface complications that may further cause patient discomfort.

Keywords: dry eye, diabetes, paediatric patients, ocular surface changes, children

Tears spread over the anterior ocular surface forming a protective interface between the epithelium and the external environment.[1] Previously, the tear film was known for comprising of three layers viz. the lipid layer, aqueous layer and the mucin layer. However, recent evidence has shown that the mucin and aqueous layers merge, due to the decreasing gradient of concentration elicited by the mucin layer, giving rise to a single layer known as the mucous-aqueous layer.[2]

The superficial lipid layer comprises of substances secreted by the meibomian glands which aid in providing stability to the tear film by increasing surface tension.[3] This protects the tear film against gravity, ensuring optimum ocular protection as well as decreases the rate at which tears evaporate from the surface. Majority of the tear film is comprised of the muco-aqueous layer, which lies below and to an extent is interspersed with the lipid layer.[4] The aqueous layer is secreted by the lacrimal gland which is found in the superior temporal angle of the orbit, consisting of two parts, the palpebral and orbital lobes. This layer of the tear film consists of electrolytes, to maintain tear osmolarity, ions which are vital for epithelial integrity as well as proteins which are responsible for various actions such as wetting of the ocular surface, reducing surface tension as well as providing protection against infectious agents.[5]

The mucin layer is made up of mucin, immunoglobulins, urea, salts, glucose, leukocytes, cellular debris, and enzymes, primarily secreted by the goblet cells of the conjunctiva. This layer provides lubrication as well as protection to the cornea while anchoring the aqueous tear film to the corneal epithelium. It also helps to prevent desiccation of the ocular surface and infections.[6]

2.2. DIABETES MELLITUS

Diabetes mellitus (DM) can be defined as a biomedical disorder, resulting from either the inability of insulin to perform its normal functions or a decreased insulin secretion, at times both concurrently.[7] Consequently, glucose accumulates in the bloodstream and if left untreated, results in various secondary health complications. Loss of weight, frequent urinating, excessive thirst and visual disturbances are among the most frequently reported symptoms of diabetes.[8] Studies show that in the years, 2016 and 2017, diabetes was listed as being the second most common underlying cause of death in South Africa. Recent statistics showed that the number of people with diabetes globally has risen from 108 000 000 in 1980 to 463 000 000 in 2019. South Africa alone, has seen a rapid escalation in the number of people diagnosed with diabetes, where it has almost tripled from approximately 4.5% in 2010 to 12.7% in 2019.[9]

2.3. PAEDIATRIC DM

The detrimental impact of diabetes in children and young adults has been researched quite extensively, yet the prevalence of diabetes as a chronic condition amongst this population

continues to increase.[10] The diagnosis of diabetes, more specifically type 1 diabetes (T1D), peaks during adolescence with approximately 1 100 000 children below the age of 20 living with T1D globally. It is known to be the second most prevalent chronic condition in children.

Providing optimal care for children and adolescents diagnosed with diabetes mellitus demands a multidisciplinary approach comprising of a group of healthcare professionals who acknowledge the skill and expertise of each member.[11] Timeous intervention and correct management are vital as the condition is known to lead to a vast number of secondary complications, which include microvascular or cardiovascular disease, blindness, limb amputations[12] and even death.

2.4. DRY EYE SYNDROME

In recent years, dry eye syndrome (DES) has fast become a common global concern among the general population. Dry eye syndrome is a generic ocular surface disorder characterized by the loss of homeostasis of the tear film, accompanied by a variety of symptoms, in which tear film hyperosmolarity and instability, inflammation or damage of the ocular surface as well as neurosensory abnormalities may play etiological roles. DES is closely associated with a reduced ability to perform certain activities such as reading, driving, and computer related work, tasks that require visual attention.[13] Lack of sufficient tears can leave the interpalpebral ocular surface susceptible to damage, affecting the quality of life of these patients.[14]

Aqueous-deficient Dry Eye

This form of dry eye usually presents as a result of decreased aqueous production by the lacrimal gland.[15] This group can be broken down further into Sjogren and Non-Sjogren related.

Evaporative Dry Eye

Evaporative dry eye usually presents with a meibomian gland dysfunction resulting in an insufficient lipid layer production which allows for increased rates of tear evaporation from the ocular surface. Most patients usually present with this type of dry eye.[16] Based on the signs and symptoms upon evaluation, evaporative dry eye can be classified as being either intrinsic or extrinsic.[15]

2.5. PATHOPHYSIOLOGY OF DIABETES-RELATED DRY EYE

Chronically elevated blood glucose levels, peripheral neuropathy, reduced insulin production, and systemic hyperosmotic changes are among the known risk factors for dry eye in diabetic patients. Proliferation of the corneal epithelial cells and acinar lacrimal gland requires insulin. It has been shown that hyperglycemia causes histological changes within the lacrimal gland which indicates

the diabetic-induced oxidative stress plays a vital role in the development of dry eye in the diabetic population.[12] Fluctuating glucose and insulin levels have direct and indirect implications on the structure as well as metabolism of the corneal epithelium itself. Hence, hyperglycemia changes the expressions of growth factors and mediators resulting in disruption in cell growth and integrity.[17] These alterations impair tear flow and production, leaving the ocular surface susceptible to many ocular conditions such as, dry eye syndrome. The true pathogenesis however, still remains elusive with a limited number of management approaches made available.[18]

2.6. METHODS

This integrative search was conducted on online databases such as Google Scholar, ScienceDirect and PubMed with the aim of identifying available evidence in current literature on the prevalence of dry eye in children with diabetes mellitus (type 1/2) as well as to document any ocular surfaces changes in these patients. The guiding question to elaborate the review was:

"What scientific knowledge has been produced thus far on the prevalence of dry eye syndrome among children with diabetes?"

All relevant literature documenting tear film changes and the prevalence of dry eye syndrome in children and adolescents living with diabetes, were included and summarised. The final sample comprised of six articles.

2.7. REVIEW

The findings of the search are categorized accordingly and presented along with a short description on tear film osmolarity, tear break-up time, Schirmer, dry eye signs and symptoms, and the prevalence of dry eye syndrome amongst paediatric patients diagnosed with DM.

2.7.1. TEAR FILM OSMOLARITY

Tear film osmolarity is regarded as being hallmark pathogenic component in patients diagnosed with dry eye. Therefore, tear osmolarity testing and measurements were regarded as being the "gold standard" for diagnosing dry eye. A device known as an Osmometer is utilized to assess tear osmolarity by taking a measurement of the electrical impedance.[19]

A cross-sectional study comparing the tear film osmolarity (TFO) as well as the results of other dry eye tests between younger patients with diabetes and normal, healthy children revealed a significantly higher tear film osmolarity in the cohort of children with diabetes mellitus.[20]

2.7.2. TEAR BREAK-UP TIME (TBUT) TEST

One of the most utilized tear function tests used to assess the stability of the tear film itself. A drop of unpreserved fluorescein is instilled in the eye and a slit lamp with a cobalt blue filter is used to evaluate the ocular surface. The patient is required to perform a full blink action and thereafter to avoid blinking again. The time immediately after the blink to the first tear break-up is recorded as the tear break-up time. The normal range varies between 20 and 30 seconds while values below 10 seconds are regarded as being pathological.[21]

A study by Akinci *et al*[22] revealed that the Tear Break-Up Time test results were significantly lower in patients with a longer duration of diabetes. Studies carried out by Wang *et al,*[23] Inanc et al[24] and Essuman *et al*[25] reported similar findings. However, a study by Akil *et al*[26] found that there was no statistically significant difference between the Tear Break- up Time (p=0.182) of the diabetic and non-diabetic groups.

2.7.3. SCHIRMER TEST

The Schirmer test is a diagnostic test widely used in clinical practice to assess tear volumes. Schirmer I test, performed without the use of any anesthesia, allows one to measure both the basal and reflex tears whilst Schirmer II test, measures basal secretion of tears only due to the use of a topical anesthetic which inhibits reflex tearing.[26]

In 2007, a study conducted by Akinci *et al*[22] showed that the Schirmer test results of the diabetic group were significantly lower than the controls. Furthermore, they found that the lower values were found amongst patients with more than 10 years duration of T1D. Other diabetic ocular surface studies[20,26,24] support the findings of Akinci *et al*.[22] These studies; however, used Schirmer test I - which included the use of a topical anaesthesia (0.5% proparacaine hydrochloride) to obtain basal tear secretion rates only. Gunay *et al*[20] found a significant difference between diabetic and non-diabetic Schirmer test scores, 16.7±5.1mm and 23±5.6mm respectively. Mean test scores from the study by Akil *et al*[26] showed 15.5±3.9mm for the diabetic group and 19.8±3.9mm for the controls. Inanc *et al*[24] reported similar findings; 12.09±5.37mm for the diabetics and 15.09±4.01mm for the control group resulting in a statistically significant difference (p=0.001).

However, a study by Wang *et al*[23] using the Schirmer test I showed no statistically significant difference between the results of the two groups.

2.7.4. PRESENCE OF DRY EYE SIGNS AND SYMPTOMS

Dry eye syndrome is commonly associated with ocular irritation or discomfort which could present in the following ways: foreign body sensation (FBS), burning, itching, sensitivity to light (photophobia), conjunctival discharge or luster, erythema and dryness of the bulbar conjunctiva.[22]

There are various dry eye questionnaires available and commonly used in clinical practice to assess different factors linked to dry eye syndrome, subjectively. These questionnaires are often scored based on the patient's responses.

A study[22] found that the scores for dry eye symptoms were significantly higher in the diabetic group as compared to the healthy non-diabetic group. The study also found that there was no statistically significant difference between the scores for dry eye signs for the two groups however dry eye signs were found in eight diabetic children vs one control. Wang *et al*[23] found 13 diabetic children out of a total of 38 with ocular surface disease index (OSDI) scores above the norm.

However, another study[24] reported that there was no statistically significant difference between the OSDI scores of the study and control groups.

2.7.5. PREVALENCE OF DRY EYE SYNDROME

Sparse literature is available on the prevalence of dry eye syndrome in children with diabetes. Whilst most studies thus far included dry eye tests, very few reached a definite dry eye diagnosis.

A study by Akinci *et al,*[22] found that 7.7% of the diabetic population had a definite dry eye diagnosis and 0.96% had a probable diagnosis whilst none were found amongst the controls. Wang *et al*[23] found that the prevalence of dry eye syndrome was significantly higher in the diabetic group as compared to the non-diabetic group.

This differed from the results of a study carried out by Akil *et al*[26] which reported that none of the participants were found to have dry eye, based on the Tear Break-Up Time and Schirmer test scores.

2.8. DISCUSSION

DM is a set of complex metabolic diseases associated with defects in insulin secretion and/or insulin efficacy, resulting in chronic hyperglycaemia.[27] It is known to be one of the most common chronic disorders amongst paediatric patients today.[28] According to the International Diabetes Federation, 370 000 000 people globally, were diagnosed with diabetes by the year 2011.This number was predicted to reach approximately 550 000 000 by 2030. Research studies have shown that at least 80% of the diabetic population were from developing countries. By 2017, the total number of children and adolescents, across the world, living with diabetes reached 1 106 500.[29]

Dry eye disease (DED) is a multifactorial disorder of the preocular surface which is defined by a loss of homeostasis of the tear film.[30] The dysfunction may result in one or more both layers of the tear film, namely, the lipid layer and the muco-aqueous layer.[4] Poor quality of the tear film or a deficiency in tear production, results in the instability of the tear film itself, allowing for excessive evaporation of tears from the surface of the eye.

Numerous studies have reported that diabetes is closely linked to an increased risk of developing chronic complications. With regards to the eye itself, patients may develop ocular surface diseases such as dry eye or keratopathy, retinopathy, glaucoma, cataract, refractive abnormalities, all of which could result in a decrease in visual acuity and if not managed effectively, could lead to blindness.[22] Tear function may also be reduced in diabetic patients due to either, the impairment of the autonomic nervous system or damage to the lacrimal gland's microvasculature.[30]

Anecdotal evidence suggest that older patients are said to be more prone to developing dry eye syndrome mainly due to the anatomy of the eye and the process of aging. However, patients regardless of age with systemic conditions such as diabetes, are at an increased risk and require timeous intervention. By the age of 10, annual ocular screenings are recommended for all patients diagnosed with DM.[24]

The studies introduced in the present review suggest that diabetes may lead to various ocular surface alterations, even in children. Whilst most literature aimed to merely show certain tear film changes; two studies[22,23] attempted to clinically diagnose dry eye syndrome and showed a higher prevalence in children with diabetes. Therefore, further prospective studies are needed to evaluate the presence of dry eye in children with diabetes, in different geographical locations. In this review, we found that literature on tear film osmolarity in this diabetic population is limited to just one study which showed that tear film osmolarity is generally higher in patients with diabetes.

Dry eye may result from an interruption in the flex pathways of tears or a process which affects the lacrimal gland itself, altering the secretion mechanisms. Diabetes presents with a possibility

of damage to the lacrimal gland's microvasculature and along with autonomic neuropathy, the lacrimal gland does not function at it's optimum. Diabetic sensory neuropathy, which affects the corneal surface may be the cause of decreased tear secretion.[24] Four[22,23,24,25] out of the six studies reviewed, showed that tear break-up time test values were significantly lower among children with DM as compared to the healthy controls.

2.9. CONCLUSION

Evidence of this review shows that tear film changes among diabetic children may vary. Future studies should assess ocular changes in different parts of the world, as geographics, climate and environment may influence normative tear test values. Due to the limited literature available regarding the prevalence of dry eye and tear osmolarity values in this specific population, it is recommended that more studies are conducted. Poor regulation of insulin and glucose can result in fluctuation of vision as well as place diabetic patients at an increased risk of ocular surface inflammation. With the steady increase in the number of children and adolescents with diabetes, the characteristics and risk factors of dry eye disease in this population has become more valuable and of social significance. Early detection of systemic conditions may allow eye care practitioners to be more proactive in ensuring appropriate referral and intervention which is vital as this can aid in reducing the risk of blindness as well as other diabetes-related morbidities. At present, a large majority of the literature focuses on the prevalence and factors associated with dry eye disease in adults with diabetes, but very few studies have been performed on children with diabetes. Future studies should include the paediatric population, including adolescents to provide a broader understanding on diabetic-related ocular surfaces alterations. Information obtained from these studies will be beneficial to the eye care practitioners around the world, by enhancing physician awareness of dry eye in children.

2.10. ACKNOWLEDGEMENTS

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

The authors confirm contribution to the paper as follows:

S. Bisetty: Project development, Data collection, Data analysis, Manuscript writing and editing.
N. Ebrahim Khan: Project development, Manuscript writing and editing.

All authors reviewed the results and approved the final version of the manuscript.

Ethical considerations

This article followed all ethical standards of research without direct contact with human or animal subjects.

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Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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CHAPTER 3: SCIENTIFIC MANUSCRIPT 2

Chapter 2 provided an analysis of the literature currently available regarding the prevalence of dry eye syndrome paediatric patients with diabetes mellitus. The literature search also provided an insight into tear film changes that may occur in these patients.

Contributions of this chapter

This chapter constitutes a scientific manuscript that aimed to determine the prevalence of dry eye syndrome within a select South African population, using two dry eye questionnaires (OSDI and McMonnies) to assess the presence and severity of dry eye signs and symptoms; as well as three clinical tests (TBUT, PRT, TFO) to evaluate tear function in this cohort. The results were compared to the results of a control group to determine statistically significant relationships.

The following manuscript has been submitted and is currently under review by the scientific journal:

Title: Prevalence of Dry Eye Syndrome in A South African Diabetic Paediatric Population
Authors: S Bisetty, N Ebrahim Khan
Journal: Contact Lens and Anterior Eye
Manuscript Number: CLAE-D-23-00397 (Appendix A (2))

This manuscript has been written, formatted, and presented according to the author guidelines outlined by *Contact Lens and Anterior Eye*. The IEEE manual of style for reference formatting was followed, as suggested by the journal.

CONTACT LENS AND ANTERIOR EYE

PREVALENCE OF DRY EYE SYNDROME IN A SOUTH AFRICAN DIABETIC PAEDIATRIC POPULATION

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3.1. ABSTRACT

Background: Diabetes mellitus (DM) can be defined as a metabolic disorder that results from either the inability of insulin to perform its normal functions or decreased insulin secretion. Dry eye disease is a complex ailment of the tear film resulting in discomfort characterised by pain, a feeling of heavy eyes, grittiness, burning, dryness, itchiness, foreign body sensation, and visual disturbances.

Aim: To identify the prevalence of dry eye syndrome in paediatric patients diagnosed with Diabetes Mellitus (Type 1/2).

Method: Thirty seven children with diabetes and forty healthy, age group-matched controls were enrolled in this study. Participants underwent a complete dry eye assessment in the following order: Ocular Surface Disease Index (OSDI) and McMonnies questionnaire, meibomian gland evaluation using white light, Tear Break-up Test (TBUT), Phenol Red Thread (PRT) test and Tear film Osmolarity test. Duration of diabetes was used as a parameter.

Results: The incidence of dry eye syndrome was found to be higher among diabetics, with 15 (40.5%) from the diabetic population compared to 4 (10.0%) from the control group. TBUT and PRT test values were significantly reduced in children with diabetes ($p<0.001$). TFO values were higher in the diabetics. No statistically significant differences were found the questionnaire scores of the two groups; however, the diabetic group appeared to be less symptomatic.

Conclusion: Dry eye is more common in the diabetic paediatric population. TBUT and PRT results were found to be lower in diabetics. Results showed a strong correlation between duration of diabetes and TBUT values. The results indicate that early dry eye screening and intervention should be encouraged.

Clinical significance: Due to the steady increase in the number of children and adolescents with diabetes, information regarding the characteristics and prevalence of dry eye syndrome in this population has become more valuable.

Keywords: dry eye, paediatric diabetes, tear film, diabetes mellitus, children

3.2. INTRODUCTION

Diabetes mellitus (DM) can be defined as a metabolic disorder resulting from either the inability of insulin to perform its function optimally or decreased insulin secretion, at times both may occur concurrently [1]. As a result, higher levels of glucose (sugar) remain in the bloodstream and if left untreated, gives rise to a variety of secondary complications. Loss of weight, frequent urination, excessive thirst and visual disturbances are among the most frequently reported symptoms experienced by patients diagnosed with diabetes [2]. Evidence has shown that at least 80% of the diabetic population are from developing countries [3]. The detrimental effects posed by diabetes mellitus on children and young adults has been researched quite extensively; however, the prevalence of diabetes as a chronic condition amongst this population continues to steadily increase [4]. The literature [5] has demonstrated that the diagnosis of diabetes, more specifically type 1 diabetes (T1D), peaks during adolescent years with approximately 1 100 000 children below the age of 20 living with type 1 diabetes globally. It is known to be the second most prevalent chronic condition in children [6].

Dry eye disease (DED), also known as dry eye syndrome (DES), is a multifactorial disorder of the preocular surface defined by a loss of homeostasis of the tear film [7]. The dysfunction may result in one or both layers of the tear film, namely, the lipid layer and the muco-aqueous layer [8]. Poor quality of the tear film or a deficiency in tear production, results in the instability of the tear film itself, allowing for excessive evaporation of tears from the surface of the eye. Most patients report ocular irritation, red eyes, blurred vision, a foreign body sensation and/or easily fatigued eyes [9]. DED is closely associated with a reduced ability to perform certain activities such as reading, driving, computer related work and tasks that require visual attention [10]. Patients may experience dry eye symptoms constantly and at varying severities. Lack of sufficient tears can leave the interpalpebral ocular surface susceptible to damage, affecting the quality of life of these patients [11].

Numerous studies have reported that diabetes is closely linked to an increased risk of developing chronic complications [12]. In relation to the eye, diabetes may result in ocular surface diseases such as dry eye syndrome and keratopathy, retinopathy, increased intraocular pressure, cataract, as well as refractive abnormalities, which can all lead to a decrease in visual acuity and in severe cases, blindness [9]. Tear function may be reduced in diabetic patients due to either, the impairment of the autonomic nervous system or damage to the lacrimal gland’s microvasculature [13]. Anecdotal evidence suggest that older patients are said to be more prone to developing dry eye syndrome mainly due to the anatomy of the eye and the process of aging. However, patients

regardless of age, with systemic conditions such as diabetes, are at an increased risk and require timeous intervention.

Dry eye or dry eye related changes in peadiatric patients with diabetes mellitus reported in the literature has been investigated solely based on Tear Break-Up time and Schirmer test values. [9],[11],[15],[16],[17]. One paediatric study [18] utilized Tear Film Osmolarity (TFO) testing as a parameter and reported that these tear function readings were significantly higher in the diabetic group. There are very few studies investigating the prevalence of diabetes in children and young adults in Africa. Many studies revolving around diabetes in youth, in sub-Saharan Africa, have been restricted to clinical studies on type 1 diabetes, and revealed that the peak age of onset of the condition was later in those of African background as compared to European people.[19]

This study contributes to the literature by determining the prevalence of dry eye syndrome in a South African diabetic paediatric population using TBUT, PRT, TFO, Ocular Surface Index (OSDI) and McMonnies questionnaires. Since dry eye investigations are usually implemented based on patient responses, dry eye complications are often overlooked in paediatric patients as compared to adults.

3.3. MATERIALS AND METHODS

The majority of this study utilized a hospital-based case-control approach. Thirty-seven patients with a confirmed diagnosis of Diabetes Mellitus who met the inclusion criteria and consented to participate in the study were enrolled. Inclusion criteria for the study group were: informed consent, male or female between 6 to 21 years, diagnosed with type 1 or type 2 diabetes based on the WHO diagnostic criteria, diagnosed at least 6 months to a year, prior to assessment, no signs of neuropathy, free from any active ocular disease or systemic conditions that may compromise tear test values. Subjects were excluded if the patient did not meet any of the inclusion criteria, diagnosed with eye diseases that can affect the quality or volume of tears or the secretion of tears (eyelid diseases - eyelid entropion, eyelid ectropion, eyelid, ptosis, and palpebral dyskinesia; conjunctival diseases - pterygium and conjunctivitis), history of ocular surface chemical injury, history of ocular surgery or retinal laser photocoagulation over the past 6 months, systemic diseases such as Sjogren's syndrome, Parkinson's disease, Rheumatoid arthritis, Grave's disease, Systemic lupus erythematosus and chronic use of oral or topical antibiotics, prescribed eye medication, steroids, diuretics, antihistamines, or decongestants, isotretinoin or other medication commonly associated with dry eye.

Forty age group-matched participants from a child and youth care centre were employed as controls. The inclusion criteria were: healthy, non-diabetic, no history of systemic conditions or ocular conditions that may be associated with dry eye disease and not on any chronic medication that may cause dry eye. The exclusion criteria for these participants were: history of systemic conditions or ocular conditions that may be associated with dry eye disease and chronic use of ocular medication or chronic medication associated with dry eye. All participants who met the inclusion criteria, underwent a complete dry eye assessment.

3.3.1. Dry eye questionnaires

Two dry eye questionnaires were administered. McMonnies and Ocular Surface Disease Index (OSDI) assessing risk factors and dry eye related symptoms and their effects on vision, respectively. Meibomian gland evaluation using white light followed to rule out any meibomian gland dysfunction, to ensure that DM was the major contributing factor of this study and to obtain accurate tear test results.

3.3.2. Three clinical dry eye tests

Three clinical dry eye tests were performed:
(1) Tear Film Osmolarity using the TearLab Osmolarity system, a 50 nanoliter sample of tear fluid was collected by the test card's lab-on-chip technology which was then used to obtain a reading.
(2) Tear Break-Up Time, a drop of 0.9% sterile saline was utilized as a wetting agent for the fluorescein strip, which was then used to dye the ocular surface, allowing the examiner to view the cornea using a cobalt blue filter and measuring the tear break up time. This is simply the time between the patients last complete blink and the formation of the first black spot or line, which indicates a break in the tear film. Any reading $\leq$ 10s indicates an abnormal result [15].
(3) Phenol Red Thread with anesthetic, was performed to eliminate reflex blinking and obtain basal tear secretion rate only. A drop of topical anesthetic (Tetracaine Hydrochloride, 1.0%) was administered followed by immediate punctal occlusion. After a minute, a small portion of the yellow (acidic) thread, bent to approximately 3mm was placed in the inferior fornices of both eyes and a timer was set for 15 seconds. A measurement was obtained from the wet thread using a scale provided.

3.3.3. Diagnostic criteria

Participants were classified as having dry eye (a) TFO > 305mOsm/L in RE or LE (Tear osmolarity may be used as a diagnostic tool for dry eye syndrome [20]) OR (b) OSDI > 13 or McMonnies >14.5 AND TBUT≤10s and PRT<10mm [21] OR (c) TBUT≤ 10s and PRT <10mm. The following results indicated a probable diagnosis (a) TFO < 305 but difference between TFO (RE)/TFO (LE) >8mOsm/L [22], (b) OSDI > 13 or McMonnies >14.5 AND 303 ≤ TFO < 305mOsm/L, (c) OSDI > 13 or McMonnies >14.5 AND TBUT < 15mm or 10>PRT < 20

3.4. Statistical Analysis

The statistical data analysis was conducted using R Statistical computing software of the R Core Team, 2020, version 3.6.3 (R Studio, Boston, MA, USA). The results were presented in the form of descriptive and inferential statistics. Where applicable, the descriptive statistics of numerical measurements were summarized as the minimum, maximum, quartiles, interquartile range, means, standard deviation and the coefficient of variation. Multidimensional numerical variables were presented as correlation plots. Correlation analysis was applied to determine the association between different numerical measurements. On the other hand, the categorical variables were described as counts and percentage frequencies where multiple bar charts were also used to visually display the categorical variables. Depending on the distribution of the numerical variables between two independent groups, mean or median differences were assessed using either t-test or Wilcoxon respectively. In order to assess the mean difference of numerical variables across at least three levels of a categorical variable, ANOVA test was used for normally distributed measurements and Kruskal Wallis for assessing the median difference of the non-normally distributed measurements. To determine the association between categorical variables, a Chi-Square Test was used and when the distribution of the cross tabulations contained an expected value of less than five, a Fisher's exact test was applied. In the case of significant difference between the Chi-Square or Fisher exact test, a row wise paired z-test was used as a post hoc analysis following the omnibus tests (Chi-Square or Fisher exact test). All the inferential statistical analysis tests were conducted at 5% levels of significance. $P<0.05$ was considered statistically significant.

3.5. RESULTS

Demographic results of the study population are depicted in Table 1. Thirty-seven patients diagnosed with diabetes mellitus met the inclusion criteria and were enrolled in the study. The median age of the group was 11.5 years old (range: 6.50 – 21.0 years). Twenty three (62.2%) of the patients were female, and fourteen (37.8%) were male. The majority of patients were African

(45.9%), followed by Indian (32.4%), White (16.2%) and Coloured (5.4%). Forty normal (non-diabetic) participants were enrolled as controls, with a median age of 14 years (6.00-21.0 years old). 62.5% of the control group were African, 20% were Coloured, followed by Indian (15%) and White (2.5%).

TABLE 1. Demographic data of the study population

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Age				
Mean±SD(CV%)				
Median(Q1-Q3)	11.5(9.75-15.3)	14.0(11.0-18.0)	0.093[a]	12.0(10.0-16.0)
n(Min-Max)	40(6.00-21.0)	37(6.50-21.0)		77(6.00-21.0)
Gender			0.283[b]	
Female	20 (50.0%)	23 (62.2%)		43 (55.8%)
Male	20 (50.0%)	14 (37.8%)		34 (44.2%)
Race*			0.014[c]	
African	25 (62.5%)	17 (45.9%)		42 (54.5%)
Coloured	8 (20.0%)	2 (5.4%)		10 (13.0%)
Indian	6 (15.0%)	12 (32.4%)		18 (23.4%)
White	1 (2.5%)	6 (16.2%)		7 (9.1%)

Abbreviation: SD: Standard deviation.
[a]Ranksum test
[b]Chisq
[c]Fisher's test
Bold: Statistically significant results ($p<0.05$)
*Statistics South Africa [23]

3.5.1. Medical History

The thirty seven participants included as part of the study group were diagnosed with Type 1 diabetes mellitus (T1D) and were on individual patient-specific treatment plans with Insulin as the primary first line treatment. The mean duration since diagnosis of diabetes was 7.36±4.00 years, with the timeframe since diagnosis ranging anywhere between 1 and 15 years. HbA1c levels are checked once every three months – all patients enrolled for this study during the period of data collection had fairly controlled levels i.e., 48mmol/mol (6.5%) and below. Out of the thirty seven patients, only 2.7% (n=1) had been previously diagnosed with dry eye syndrome.

3.5.2. Ocular Surface Disease Index (OSDI) Questionnaire

Overall

Table 2 shows the results for the individual questions of the OSDI questionnaire. No statistically significant findings were found, in terms of the total scores of the questionnaire between the study and control groups. The points ranged from 0 to 54.5 in the diabetic group and from 0 to 70.5 in the control group. While this finding was not found to be statistically significant, it should be noted that the higher scores were found among the non-diabetic population.

TABLE 2. Comparing the results of the OSDI questionnaire between the diabetic group vs. controls

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Sensitive to light			0.193[c]	
None of the time	18 (45.0%)	11 (29.7%)		29 (37.7%)
Some of the time	17 (42.5%)	15 (40.5%)		32 (41.6%)
Half of the time	1 (2.5%)	3 (8.1%)		4 (5.2%)
Most of the time	3 (7.5%)	8 (21.6%)		11 (14.3%)
All of the time	1 (2.5%)	0 (0.0%)		1 (1.3%)
Eyes feel gritty			0.115[c]	
None of the time	35 (87.5%)	26 (70.3%)		61 (79.2%)
Some of the time	5 (12.5%)	10 (27.0%)		15 (19.5%)
Half of the time	0 (0.0%)	1 (2.7%)		1 (1.3%)
Painful or sore eyes			0.484[c]	
None of the time	25 (62.5%)	22 (59.5%)		47 (61.0%)
Some of the time	12 (30.0%)	11 (29.7%)		23 (29.9%)
Half of the time	1 (2.5%)	3 (8.1%)		4 (5.2%)
Most of the time	0 (0.0%)	1 (2.7%)		1 (1.3%)
All of the time	2 (5.0%)	0 (0.0%)		2 (2.6%)
Blurry vision			0.262[c]	
None of the time	30 (75.0%)	24 (64.9%)		54 (70.1%)
Some of the time	7 (17.5%)	6 (16.2%)		13 (16.9%)
Half of the time	1 (2.5%)	2 (5.4%)		3 (3.9%)
Most of the time	0 (0.0%)	4 (10.8%)		4 (5.2%)
All of the time	2 (5.0%)	1 (2.7%)		3 (3.9%)

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Poor vision			0.695[c]	
None of the time	31 (77.5%)	27 (73.0%)		58 (75.3%)
Some of the time	5 (12.5%)	4 (10.8%)		9 (11.7%)
Half of the time	2 (5.0%)	1 (2.7%)		3 (3.9%)
Most of the time	1 (2.5%)	4 (10.8%)		5 (6.5%)
All of the time	1 (2.5%)	1 (2.7%)		2 (2.6%)

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Reading			0.881[c]	
None of the time	24 (60.0%)	24 (64.9%)		48 (62.3%)
Some of the time	7 (17.5%)	4 (10.8%)		11 (14.3%)
Half of the time	5 (12.5%)	3 (8.1%)		8 (10.4%)
Most of the time	2 (5.0%)	3 (8.1%)		5 (6.5%)
All of the time	2 (5.0%)	2 (5.4%)		4 (5.2%)
Not applicable	0 (0.0%)	1 (2.7%)		1 (1.3%)
Night driving			0.145[c]	
None of the time	4 (10.0%)	4 (10.8%)		8 (10.4%)
Some of the time	0 (0.0%)	3 (8.1%)		3 (3.9%)
Most of the time	0 (0.0%)	1 (2.7%)		1 (1.3%)
All of the time	0 (0.0%)	1 (2.7%)		1 (1.3%)
Not applicable	36 (90.0%)	28 (75.7%)		64 (83.1%)
Working with electronics			**0.002[c]**	
None of the time	21 (52.5%)	8 (21.6%)		29 (37.7%)
Some of the time	9 (22.5%)	6 (16.2%)		15 (19.5%)
Half of the time	1 (2.5%)	0 (0.0%)		1 (1.3%)
Most of the time	0 (0.0%)	4 (10.8%)		4 (5.2%)
All of the time	2 (5.0%)	1 (2.7%)		3 (3.9%)
Not applicable	7 (17.5%)	18 (48.6%)		25 (32.5%)
Watching TV			**0.020[c]**	
None of the time	20 (50.0%)	26 (70.3%)		46 (59.7%)
Some of the time	15 (37.5%)	4 (10.8%)		19 (24.7%)
Half of the time	2 (5.0%)	2 (5.4%)		4 (5.2%)
Most of the time	0 (0.0%)	3 (8.1%)		3 (3.9%)
All of the time	1 (2.5%)	0 (0.0%)		1 (1.3%)

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Not applicable	2 (5.0%)	2 (5.4%)		4 (5.2%)
Windy conditions			0.645[c]	
None of the time	19 (47.5%)	21 (56.8%)		40 (51.9%)
Some of the time	15 (37.5%)	9 (24.3%)		24 (31.2%)
Half of the time	2 (5.0%)	2 (5.4%)		4 (5.2%)
Most of the time	1 (2.5%)	1 (2.7%)		2 (2.6%)
All of the time	3 (7.5%)	2 (5.4%)		5 (6.5%)
Not applicable	0 (0.0%)	2 (5.4%)		2 (2.6%)
Low humidity or dry areas			0.226[c]	
None of the time	28 (70.0%)	25 (67.6%)		53 (68.8%)
Some of the time	11 (27.5%)	6 (16.2%)		17 (22.1%)
Half of the time	0 (0.0%)	2 (5.4%)		2 (2.6%)
Most of the time	0 (0.0%)	1 (2.7%)		1 (1.3%)
Not applicable	1 (2.5%)	3 (8.1%)		4 (5.2%)
Air conditioned places			0.055[c]	
None of the time	33 (82.5%)	25 (67.6%)		58 (75.3%)
Some of the time	6 (15.0%)	5 (13.5%)		11 (14.3%)
Half of the time	0 (0.0%)	3 (8.1%)		3 (3.9%)
Most of the time	0 (0.0%)	1 (2.7%)		1 (1.3%)
All of the time	1 (2.5%)	0 (0.0%)		1 (1.3%)
Not applicable	0 (0.0%)	3 (8.1%)		3 (3.9%)

[c]Fisher's test
Bold: Statistically significant results ($p<0.05$)

3.5.3. OSDI and vision-related functions

Statistically significant results were demonstrated between the diabetic and control groups for two aspects under the vision-related functions;

(a) working with electronics (p=0.002) : With regards to the control group, 22.5% (n=9) of the participants experienced some sort of limitation when working with electronic devices 'some of the time' while 2.5% (n=1) of the participants reported 'half of the time' and 5.0% (n=2) reported 'all of the time'. Within the patient group, 16.2% (n=6) of participants experienced a limitation 'some of the time', 10.8% (n=4) of the participants answered, 'most of the time' and (2.7% (n=1) answered 'all of the time'.

(b) watching tv (p=0.020): Within the control group, 37.5% (n=15) of the participants had limitations 'some of the time', 5.0% (n=2) of them experienced this half of the time

and 2.5% (n=1) 'all of the time'. Among the patient group, 10.8% (n=4) of the participants experienced a limitation when watching tv 'some of the time', 5.4% (n=2) 'half of the time' and 8.1% (n=3) 'most of the time' (Table 2).

3.5.4. Classification

Using the total OSDI score, participants were grouped as having mild, moderate, or severe dry eye. Twenty percent (n=8) of the participants of the control group were classified as having mild dry eye (13 – 22 points), followed by 12.5% (n=5) of them having moderate dry eye (23 – 32 points) and 7.5% (n=3) having severe dry eye (33 – 100 points). In the diabetic group, 13.5% (n=5) of participants had mild dry eye, 10.8% (n=4) had moderate and 24.3% (n=9) had severe dry eye.

3.5.5. McMonnies Questionnaire

Overall

No statistically significant differences were noted between the final scores of both groups, i.e., the study (diabetic) and control group. As shown in Table 3, the median score for the controls was six while the median score for the diabetic group was four. The range for the control group was also greater by one point (1-13) as compared to the range of the diabetic group (1-12).

All seventy-seven of the participants in this study were found to have no dry eye using the McMonnies questionnaire as all of them scored below 14.5 points.

Table 3. Showing the results of the McMonnies Questionnaire between the diabetics and controls

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
MCMONNIES scores				
Mean±SD(CV%)	6.35±3.42(53.9)			
Median(Q1-Q3)	6.00(4.00-9.00)	4.00(2.00-9.00)	0.143[a]	5.00(3.00-9.00)
n(Min-Max)	40(1.00-13.0)	37(1.00-12.0)		77(1.00-13.0)
MCMONNIES			0.732[b]	
Normal	40 (100.0%)	37 (100.0%)		77 (100.0%)

Abbreviation: SD: Standard deviation.

[a]Ranksum test

[b]Chisq

Bold: Statistically significant results ($p<0.05$)

3.5.6. Symptoms of dry eye

The most common dry eye symptoms experienced by both groups were scratchiness (75%), followed by burning (43.2%), soreness (29.5%), grittiness (9.1) and dryness (6.8%). The results projected in Figure 1 shows that all of the above symptoms, except grittiness, were more prevalent amongst the control group. Among the participants of the control group, 77.8% (n=21) had scratchiness, 51.9%(n=14) had experienced a burning sensation, 37.0% (n=10) had sore eyes, and 7.4% (n=2) complained of ocular dryness. In the diabetic group, 70.6% (n=12) of the participants experienced scratchiness, 29.4% (n=5) complained of burning, three 17.6% (n=3) had soreness of the eye, and 5.9% (n=1) had dryness of the ocular surface.

Between the diabetic and control groups, 11.8% (n=2) and 7.4% (n=2) of the participants experienced grittiness of the eye, respectively. This was the only dry eye symptom that showed a higher percentage of incidence in the diabetic population (Figure 1).

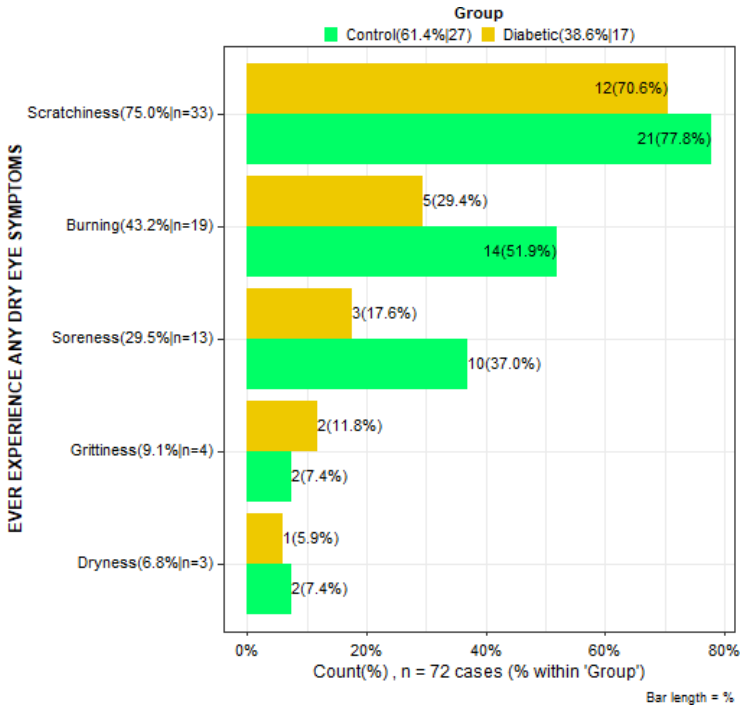

Figure 1. Bar group showing the different dry eye symptoms experienced between the diabetic and control groups.

3.5.7. Tear Function Tests

Table 4 and Table 5 compare the numerical and categorical findings, respectively, of three tear function tests - between the study and control groups. All tests were done on both, right and left eye.

TABLE 4. Tear function test results in patients with diabetes *vs*. control group

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
TBUT RE				
Mean±SD(CV%)	13.6±2.32(17.1)	6.94±2.27(32.7)		
Median(Q1-Q3)	13.3(12.0-15.0)	6.50(5.00-8.50)	**<0.001**[a]	11.5(7.00-13.5)
n(Min-Max)	40(8.00-18.0)	37(3.00-12.0)		77(3.00-18.0)
TBUT LE				
Mean±SD(CV%)	13.0±2.24(17.3)	6.75±1.95(28.8)	**<0.001**[d]	9.98±3.76(37.7)
Median(Q1-Q3)	12.8(11.4-14.1)	6.50(5.50-8.00)		10.0(7.00-13.0)
n(Min-Max)	40(9.50-19.5)	37(2.50-12.0)		77(2.50-19.5)
PRT RE				
Mean±SD(CV%)	29.3±4.55(15.5)	24.5±6.32(25.8)	**<0.001**[d]	27.0±5.95(22.0)
Median(Q1-Q3)	30.0(26.5-32.3)	25.0(20.0-29.0)		28.0(23.0-31.0)
n(Min-Max)	40(20.0-40.0)	37(12.0-35.0)		77(12.0-40.0)
PRT LE				
Mean±SD(CV%)	30.8±5.32(17.3)			28.5±6.43(22.6)
Median(Q1-Q3)	30.0(27.0-36.0)	25.0(23.0-32.0)	**<0.001**[a]	29.0(25.0-33.0)
n(Min-Max)	40(20.0-41.0)	37(10.0-35.0)		77(10.0-41.0)
TFO RE				
Mean±SD(CV%)				
Median(Q1-Q3)	300(295-302)	296(291-305)	0.882[a]	299(292-304)
n(Min-Max)	40(29.0-315)	37(277-330)		77(29.0-330)
TFO LE				
Mean±SD(CV%)	296±7.09(2.4)	300±9.89(3.3)		
Median(Q1-Q3)	298(292-301)	299(295-305)	0.066[a]	298(293-301)
n(Min-Max)	40(278-310)	37(278-325)		77(278-325)

Abbreviation: SD: Standard deviation; TBUT: Tear Break-Up Time; PRT: Phenol Red Thread; TFO: Tear Film Osmolarity; RE: Right eye: LE: Left eye.

[a]Ranksum test

[d]t-test

Bold: Statistically significant results (*p*<0.05)

3.5.7.1. Tear Break-Up Time (TBUT)

Mean TBUT results for the diabetic group were 6.94±2.27 seconds and 6.75±1.95 seconds, for the right and left eye respectively. The control group had a TBUT mean of 13.6±2.32 seconds for the right eye and 13.0±2.24 seconds for the left eye. The mean tear break-up time values were significantly lower (p<0.001) in the group with diabetes mellitus as compared to the healthy control group (Table 4).

3.5.7.2. Phenol Red Thread (PRT)

The mean PRT value for the right eye of the diabetic group was 24.5±6.32 mm. The mean values for the controls were 29.3±4.55mm and 30.8±5.32mm, for the right and left eye respectively. To avoid skewness in the data, a mean value for the left eye of the diabetic group could not be provided. However, according to the median and ranges for the test values of the two groups, there is evidence that the PRT values are significantly lower (p<0.001) in the diabetic population (Table 4).

3.5.7.3. Tear Film Osmolarity (TFO)

No statistically significant difference was found between the tear film osmolarity measurements of the diabetic and control groups. However, the diabetic group shows a slightly higher upper limit for the range of both, the right and left eye (Table 4).

TABLE 5. Tear function tests – categorical results in patients with diabetes *vs*. control group

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Tear Break-Up LE			**p<0.001[c]**	
Normal	36 (90.0%)	2 (5.4%)	**<0.001[c]**	38 (49.4%)
Marginal	4 (10.0%)	28 (75.7%)	**<0.001[c]**	32 (41.6%)
Severe	0 (0.0%)	7 (18.9%)	0.013	7 (9.1%)
Tear Break-Up RE			**p<0.001[c]**	
Normal	37 (92.5%)	3 (8.1%)	**<0.001[c]**	40 (51.9%)
Marginal	3 (7.5%)	29 (78.4%)	**<0.001[c]**	32 (41.6%)
Severe	0 (0.0%)	5 (13.5%)	0.066	5 (6.5%)
Phenol Red Thread LE			**0.012[c]**	
Borderline	1 (2.5%)	8 (21.6%)	0.024	9 (11.7%)
Normal	39 (97.5%)	29 (78.4%)	0.024	68 (88.3%)
Phenol Red Thread RE			**0.001[b]**	
Borderline	3 (7.5%)	14 (37.8%)	0.004	17 (22.1%)
Normal	37 (92.5%)	23 (62.2%)	0.004	60 (77.9%)
Tear Film Osmolarity LE			0.073[c]	
Normal	37 (92.5%)	27 (73.0%)		64 (83.1%)

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Mild	3 (7.5%)	7 (18.9%)		10 (13.0%)
Moderate	0 (0.0%)	2 (5.4%)		2 (2.6%)
Severe	0 (0.0%)	1 (2.7%)		1 (1.3%)
Tear Film Osmolarity RE			**0.020[c]**	
Normal	37 (92.5%)	26 (70.3%)		63 (81.8%)
Mild	2 (5.0%)	9 (24.3%)		11 (14.3%)
Moderate	1 (2.5%)	1 (2.7%)		2 (2.6%)
Severe	0 (0.0%)	1 (2.7%)		1 (1.3%)

NOTE: [b]Chisq; [c]Fisher; **Bold: Statistically significant results (p<0.05)** RE= Right eye; LE= Left eye

3.5.7.4. Tear Break-Up Time

According to the results of the left eye, 75.7% (n=28) of the participants of the diabetic group were found to have marginal dry eye while 18.9% (n=7) of them had severe dry eye. Only 10.0% (n=4) of the control group were found to have marginal dry eye. The results of the right eye showed 78.4% (n=29) of the participants from the diabetic group with marginal dry eye while 13.5% (n=5) of them were found to have severe dry eye. Of the controls, 7.5% (n=3) had marginal dry eye. There was a significantly higher ($p<0.001$) number of children with marginal dry eye in the diabetic group as compared to the control group (Table 5).

3.5.7.5. Phenol Red Thread

In the diabetic group, 21.6% (n=8) and 37.8% (n=14) of the participants were found to have borderline dryness with regards to the left and right eye, respectively. In the control group, 2.5% (n=1) were found to have borderline ocular dryness when assessing the left eye while 7.5% (n=3) were found using the test results for the right eye. The number of children with ocular dryness was found to be significantly greater in the group with diabetes (p=0.024 (RE); p=0.004 (LE)) (Table 5).

3.5.7.6. Tear Film Osmolarity

Upon classification of the tear osmolarity results, a statistically significant difference (p=0.020) is reported in the results of the right eye. Among the diabetic patients, 24.3% (n=9) were characterised as having mild dry eye, followed by 2.7% (n=1) having moderate dry eye and 2.7% (n=1) having severe dry eye. In the control group, only 5.0% (n=2) of the participants were found with mild dry eye and 2.5% (n=1) with moderate dry eye (Table 5).

3.5.8. Prevalence of Dry Eye Syndrome

As shown in Table 6, 24.7% (n=19) of the participants were found to have dry eye syndrome in this study. Of that total, 40.5% (n=15) of the children were from the study group while 10.0%

(n=4) were from the control group. A statistically significant (p=0.009) number of children with diabetes were found to have dry eye syndrome as compared to non-diabetic, healthy children of the control group.

TABLE 6. Prevalence of Dry Eye Syndrome in the study group *vs*. control group

Group	Control (N=40)	Diabetic (N=37)	p-value	Overall (N=77)
Diagnosis			**0.006**[b]	
Normal	19 (47.5%)	9 (24.3%)	0.171	28 (36.4%)
Probable dry eye	17 (42.5%)	13 (35.1%)	1.000	30 (39.0%)
Dry eye	4 (10.0%)	15 (40.5%)	**0.009**[b]	19 (24.7%)

[b]Chisq

Bold: Statistically significant results (*p*<0.05)

No statistically significant difference was reported between the diabetic group and the controls, in terms of probable dry eye diagnosis.

In the diabetic group only, 40.5% (n=15) participants were diagnosed with true dry eye syndrome and 35.1% (n=13) were classified as having probable dry eye – however, further testing may be required to reach a complete diagnosis. The remaining 24.3% (n=9) of the participants of the study group were found to have no dry eye (Table 6).

TABLE 7. Duration of diabetes mellitus (in years) *vs*. diagnosis of dry eye

Diagnosis	Normal (N=9)	Probable dry eye (N=13)	Dry eye (N=15)	p-value	Overall (N=37)
Duration in years				ANOVA	
Mean±SD(CV%)	6.22±2.86(46.0)	7.12±4.71(66.2)	8.27±3.95(47.8)	0.473	7.36±4.00(54.3)
Median(Q1-Q3)	7.00(5.00-8.00)	7.00(3.00-9.00)	8.00(6.00-11.0)		7.00(5.00-10.0)
n(Min-Max)	9(1.00-10.0)	13(1.00-15.0)	15(1.00-15.0)		37(1.00-15.0)

Abbreviation: SD: Standard deviation.

[#]ANOVA test

Bold: Statistically significant results (*p*<0.05)

No statistical significance was found between duration of diabetes (in years) and the prevalence of dry eye syndrome in the study group; however, trends were noticed between the tear function tests (TBUT and PRT) and duration of diabetes.

3.5.9. Correlation Analysis

- TBUT

  A strong correlation (r=-0.72; r=-0.73) was found between the duration of diabetes (in years) and the Tear Break-Up Time test values for the right and left eye, respectively (Figure 2).

- PRT

  There was a moderate correlation (r=-0.37; r=-0.43) between duration of DM in years, and the Phenol Red Thread test results for the right and left eye (Figure 2).

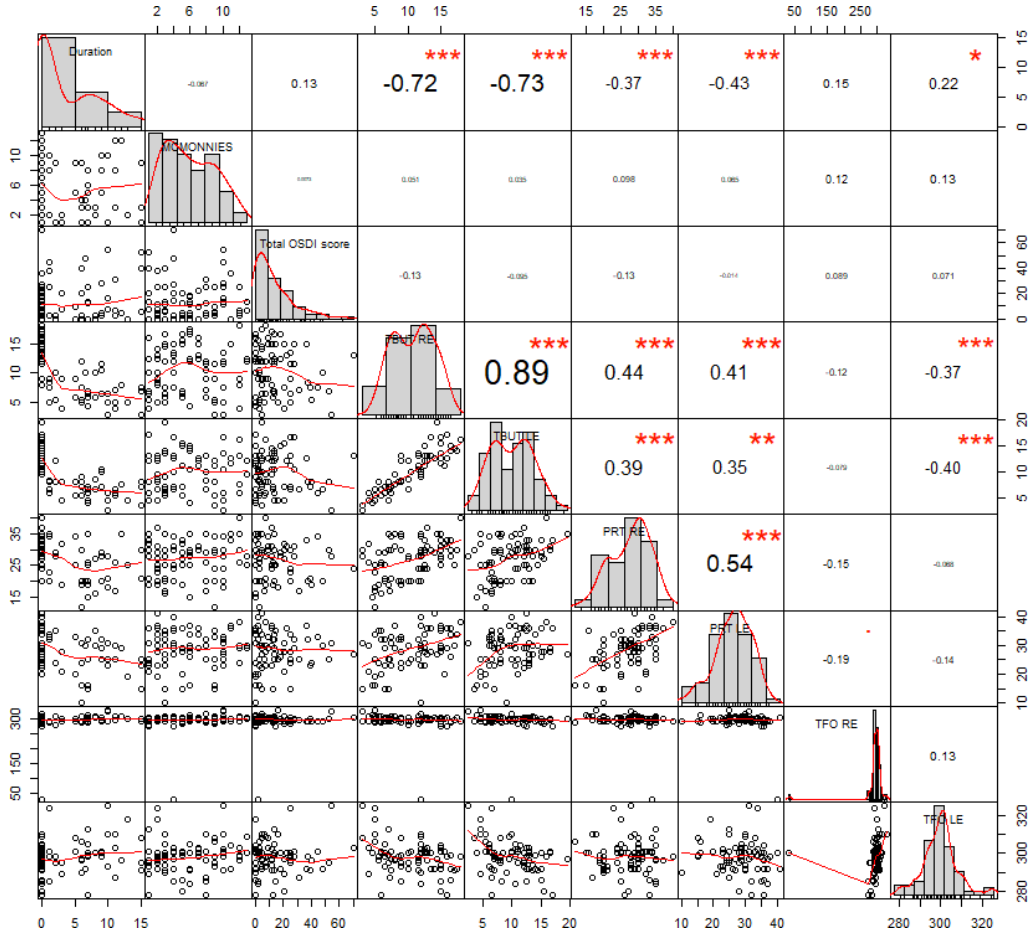

Figure 2. Correlation between duration of diabetes, dry eye tests and questionnaires
KEY: TBUT= Tear Break-Up Time; PRT= Phenol Red Thread; TFO= Tear Film Osmolarity; RE= Right eye; LE = Left eye

Table 8 (Appendix B) shows the comparison between the different variables used to assess for correlations. (-) indicates a correlation; using the absolute value, 0.67 and above indicates a strong correlation, 0.34 – 0.66 shows a moderate correlation while any value between 0 and 0.33 indicates a weak correlation (p<0.05 demonstrated statistical significance).

3.6. DISCUSSION

Based on literature search results, only two studies have previously reported on the prevalence of dry eye syndrome in paediatric patients diagnosed with DM. In 2007, a study was done to evaluate the symptoms, signs as well as the results of objective dry eye tests in a diabetic paediatric population and to compare this to a healthy control group [14]. Dry eye signs were prevalent in 7.7% of diabetic children, versus 0.96% of controls (p=0.034). A hospital-based case-control study was carried out to investigate the prevalence of dry eye disease in a diabetic paediatric population in Shanghai, Japan [9]. The study group consisted of 37 diabetic children while the control group comprised of 40 healthy individuals of matching age and gender. The prevalence of dry eye disease in the case group was significantly higher than that of participants in the control group (p< 0.01). A total of 24.7% of the participants were found to have dry eye syndrome in this study. Of the diabetic group 40.5% of the participants had dry eye. Statistical significance (p=0.009) was displayed between the number of diabetic children with dry eye and the non-diabetic, healthy control group.

In patients with diabetes mellitus, damage to the lacrimal gland's microvasculature coupled with autonomic neuropathy may result in decreased function of the lacrimal gland. Furthermore, diabetic-related sensory neuropathy of the cornea can lead to lower levels of tear secretion [15]. Studies have reported statistically lower tear break-up time values among the diabetic groups [9],[14],[16],[17]. In contrast, studies [15],[18] have found that while tear break-up time values many have been slightly reduced in the diabetic population, it was not of statistical significance. In this study, mean TBUT results for the diabetic group were 6.94±2.27 seconds and 6.75±1.95 seconds, for the right and left eye respectively. The control group had a TBUT mean of 13.6±2.32 seconds for the right eye and 13.0±2.24 seconds for the left eye. Hence, tear break-up time values were found to be significantly reduced (p<0.001) in the group with diabetes mellitus. Literature has shown reduced Schirmer test values in children with diabetes [14],[15],[16],[18]. Likewise, in this study, tear production using the PRT test was found to be significantly reduced in the diabetic population (p<0.001). The use of Tear film Osmolarity (TFO) as a parameter in the diagnosis of dry eye has been approved as a trustworthy indicator [24]. Only one study, to date, investigated TFO values in children with diabetes and established higher levels of tear osmolarity among this population [18]. In this study, the tear osmolarity results were found to be greater in the diabetic population.

The epithelial layer of the cornea plays a significant role as a defense mechanism of the ocular surface, providing a physiological as well as immunological boundary to all external agents [25]. Research has shown that patients with diabetes generally present with decreased corneal sensation

due to the reduced density of nerve fibers at the center of the cornea, especially in those with longer duration of diabetes [9]. A study [14] revealed that 15.4% of diabetic children complained of dry eye symptoms, as compared to 1.9% of the controls (p=0.029). The study also reported that the prevalence of dry eye signs was higher among the diabetic population. The present study discovered that the total scores for the diabetic group and controls, using the OSDI and McMonnies questionnaires, demonstrated no statistically significant differences. However, when investigating dry eye symptoms using the McMonnies questionnaire, the results showed that participants of the control group were more symptomatic, which may affirm the impaired corneal sensitivity amongst diabetic patients.

Studies found that TBUT [14],[16] and Schirmer test [14] results were significantly reduced in patients with longstanding DM. Similarly, the relationship between the tear function tests and duration of diabetes were investigated in the current study. A strong correlation (r=-0.73) was found between the timeframe since diagnosis and the tear break-up time test results; which simply means that patients with a longer duration of diabetes presented with lower TBUT results. The PRT test results were also found to be lower in patients with a longer duration of DM, with a moderate correlation (r=-0.43) between the two variables.

3.7. CONCLUSION

In summary, this present study found that the prevalence of dry eye syndrome in a South African population of children with diabetes mellitus is significantly higher. The diabetic population exhibited lower TBUT and PRT results as compared to the healthy, non-diabetic group. A strong correlation between the duration of diabetes and TBUT values was present. Children with diabetes were also found to be less symptomatic possibly due to the reduced corneal sensitivity induced by the condition. Dry eye investigations are usually implemented based on patient response and hence, dry eye complications are often overlooked in paediatric patients as compared to adults. With the steady increase in the number of children and adolescents with diabetes, the characteristics and risk factors of dry eye syndrome in this population has become more valuable and of social significance. All healthcare practitioners associated directly or indirectly with children diagnosed with diabetes should raise awareness and encourage early dry eye screening and intervention – especially in those with a long duration of diabetes.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

The authors confirm contribution to the paper as follows:

S. Bisetty: Project development, Data collection, Data analysis, Manuscript writing and editing.

N. Ebrahim Khan: Project development, Manuscript writing and editing.

All authors reviewed the results and approved the final version of the manuscript.

Ethical considerations

This study obtained ethical clearance from the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal **(BREC/00004451/2022)** as well as from the private hospitals research ethics committee (**LHCHREC-PR-25102022/21).** Informed consent was gained from all participants as well as parents/guardians, after the nature of the study was explained. Patients were allocated code names to ensure anonymity throughout the study.

Consent for publication

Details and images reported within the manuscript are consented for publication.

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Data availability

Data can be made available upon request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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CHAPTER 4: SYNTHESIS

Chapter 3 analysed the prevalence of dry eye within a select South African cohort of diabetic patients, using the Ocular Surface Disease Index (OSDI) and McMonnies questionnaires, and three clinical tests (Tear Break-Up Time, Phenol Red Thread and Tear Film Osmolarity). The study provided clinical findings with regards to diabetic-related tear film changes which are crucial in the management of these patients.

Contributions of this chapter

This chapter elaborated on the aim and objectives of this study and concluded the findings of the prevalence of dry eye syndrome in a select South African diabetic population. Limitations encountered during the study as well as potential areas for future research have been identified and explained.

4.1. Synthesis

This study comprised of two manuscripts: the first manuscript analysed and documented the various ocular surfaces changes as well as the prevalence of dry eye in a paediatric population with diabetes mellitus (DM). The second manuscript investigated the prevalence of dry eye syndrome in a South African diabetic paediatric population, using the available dry eye questionnaires and three dry eye tests.

Manuscript 1 took the form of a literature review which comprised of sample of six articles. The guiding question to elaborate the review was: "What scientific knowledge has been produced thus far on the prevalence of dry eye syndrome among children with diabetes?" Relevant literature reporting on tear film changes and the prevalence of dry eye syndrome in children and adolescents living with diabetes, were included. Manuscript 2 employed a mixed method approach; comprising of paediatric patients between the ages of 6 and 21, diagnosed with diabetes (n=37) and a control group (n=40), all having met the study's inclusion criteria. A summary of the findings of manuscript 2 is presented in this chapter under the aim and objectives of the study - with reference made to significant results found by the literature search in manuscript 1, where necessary.

4.2. Concluding remarks related to the aim and objectives of the study

4.2.1. Aim: To determine the prevalence of dry eye

The aim of this study was to investigate the prevalence of dry eye in a group of diabetic children and adolescents/young adults in eThekwini, South Africa. Diabetes has been shown to be one of the leading systemic risk factors for the development of dry eye. A vast number of studies have reported on the prevalence of dry eye among adults with diabetes.[1] However, sparse literature is available regarding the incidence of the syndrome in children with diabetes. No previous studies have been conducted in sub-Saharan Africa. Data obtained from this study reported that dry eye syndrome is more prevalent within the diabetic paediatric population. Fifteen (40.5%) of the participants from the study group were diagnosed with true dryness compared to just four (10.0%) from the control group, demonstrating statistical significance (p=0.009). The results of the present study strongly correlate with the results of two other paediatric studies which set out to determine dry eye prevalence.[2,3]

4.2.2. Objective 1: – Determine stability of the tear film using Tear Break-up Time (TBUT)

The first objective set out to determine the stability of the tear film by assessing Tear Break-Up Time in diabetic paediatric patients. Evidence has shown reduced TBUT indicating an instability of the tear film in those with diabetes. Mean TBUT results for the diabetic group were 6.94±2.27 seconds and 6.75±1.95 seconds, for the right and left eye respectively. The control group had a TBUT mean of 13.6±2.32 seconds for the right eye and 13.0±2.24 seconds for the left eye. The current study reported tear break-up time values that were significantly lower (p<0.001) in the group with diabetes mellitus as compared to the healthy control group. A strong correlation between the duration of diabetes and TBUT results was established.

4.2.3. Objective 2: – Determine integrity of the lacrimal system using Phenol Red Thread (PRT)

The second objective set out to measure the integrity of the lacrimal system of diabetic paediatric patients by utilizing the PRT test (with anesthetic). Numerous studies have highlighted the fact that diabetes disrupts both tear film function and stability using the Schirmer tests. PRT was favored and used for this study as the fine thread reduced patient discomfort and allowed for shorter testing periods (15 seconds), as compared to the traditional Schirmer tests. The mean PRT value for the right eye of the diabetic group was 24.5±6.32 mm. The mean values for the controls were 29.3±4.55mm and 30.8±5.32mm, for the right and left eye respectively. The outcomes of this objective have suggested that diabetic paediatric patients may present with a lacrimal system functioning at suboptimal levels, as illustrated by the PRT test results. The study also established a moderately significant correlation between duration and PRT values, within the diabetic group.

4.2.4. Objective 3: – Measure tear film osmolarity using the TearLab osmometer

The third objective set out to measure the osmolarity of tears in this population, using the TearLab Osmolarity system. Reduced levels of tear production results in hyperosmolarity which affects the surface of the eye and brings about symptoms of ocular discomfort as well as cause various inflammatory events. Hyperosmolarity of the tear film is known to be the key mechanism in the development of ocular surface abnormalities. The outcomes of this objective showed that tear osmolarity is higher among the diabetic group. This finding is similar to that of Gunay *et al.*[4]

4.2.5. Objective 4 - Compare and document significant findings of two dry eye questionnaires

The final objective of this study was to compare significant findings of two dry eye questionnaires (OSDI and McMonnies) between the study and controls. Previous literature has revealed mixed results; Gunay et al.[4] found that the diabetic group was more symptomatic to the tear film changes,

while a study by Wang *et al.*[3] found that longer duration of diabetes resulted in lower OSDI scores and hence, these patients were considered to be less symptomatic. The current study displayed an insignificant finding in terms of the overall scores of the dry eye questionnaires, for both, the study and control groups, yet the individual results of the McMonnies questionnaire in particular, revealed that the symptoms of dry eye were more prominent in the control group. Chronic hyperglycaemic levels induce numerous metabolic changes which supplement each other via a complex interplay. This results in diabetic neuronal degenerations which ultimately leads to diabetic-related neuropathy.[5] Hence, DM is known to be closely linked to decreased corneal innervation.[6] The questionnaire results of the diabetic group are therefore acceptable. It is of worth noting that a study of this nature has not been previously conducted in a South African population. Two studies were carried out in Ghana – one study[7] investigated ocular change in children and adolescents with DM (type 1) and the other investigated the prevalence of dry eye disease and meibomian gland dysfunction in adults with type 2 DM.[8] A third study carried out in Nigeria, aimed to find a relationship between dry eye and haemoglobin levels; however, the study population consisted of adults with type 2 DM.[9] With regards to TFO testing, a total three studies were conducted within Africa.[10,11,12] However, none of the literature reported on the use of tear osmolarity as parameter for dry eye testing in a diabetic population.

4.3. Limitations

A notable limitation of this study is the cost factor of the TearLab Osmolarity test cards and the fact that these resources are not manufactured and readily available in South Africa, which in turn, resulted in a relatively small sample size. The second limitation was that this research utilized a single center-based case study approach.

4.4. Recommendations

In order to improve the sample size, additional funding should be sought to purchase an adequate number of TearLab Osmolarity test cards. Further research may be expanded to multiple paediatric endocrinology centers, both nationally and internationally.

4.5. Conclusions

The study sought to determine the prevalence of dry eye in a South African diabetic paediatric population. Results emanating from this study showed that dry eye syndrome is significantly higher among children and young adults with DM. Additionally, the study revealed lower TBUT

and PRT values in this population, which demonstrated statistical significance. It was also evident that TFO results were slightly higher in the diabetic group as compared to the controls of the study. The overall findings of this research are novel for the following reasons; (i) to the best of the authors' knowledge, the current study is one of the first to determine the prevalence of dry eye syndrome in a diabetic paediatric population in sub-Saharan Africa, (ii) it is also one of the first studies to comment on ocular surface changes in children and adolescents with diabetes in South Africa, (iii) it is the first African study to use TFO as a parameter for diagnosing diabetes-related dry eye, in a paediatric population.

Evidence has illustrated that the incidence of DM is on the increase, especially in the younger population. Yet, there is a paucity of data on the prevalence of dry eye and tear film changes in DM. This study attempted to fill in the gap in the literature by providing results from a South African perspective. The results of the present study will be beneficial to the healthcare practitioners in South Africa by enhancing physician awareness of dry eye in children and the need to promote early screening and close follow-up of dry eye disease in children with diabetes which should be implemented, especially in children with a long duration of diabetes.

This study showed that the scores of the OSDI and McMonnies questionnaires, were lower in patients diagnosed with diabetes mellitus. Due to the increased glycemic levels, peripheral and sensory neuropathy can occur, reducing the corneal sensitivity of diabetic patients. Hence, these patients appear to be less symptomatic to the tear film alterations, associated with dry eye syndrome, that may be present. Considering that in most instances, dry eye assessments are usually carried out based on the subjective responses of patients, this finding highlights the importance of complete ocular and more specifically, dry eye assessments, within this population. Timeous intervention and management of dry eye syndrome is vital as both the structure and health of the eye may be adversely affected, in the long term. In severe cases of dryness, scarring of the cornea can also occur – leaving patients susceptible to mild-to-severe visual impairment.

4.6. References

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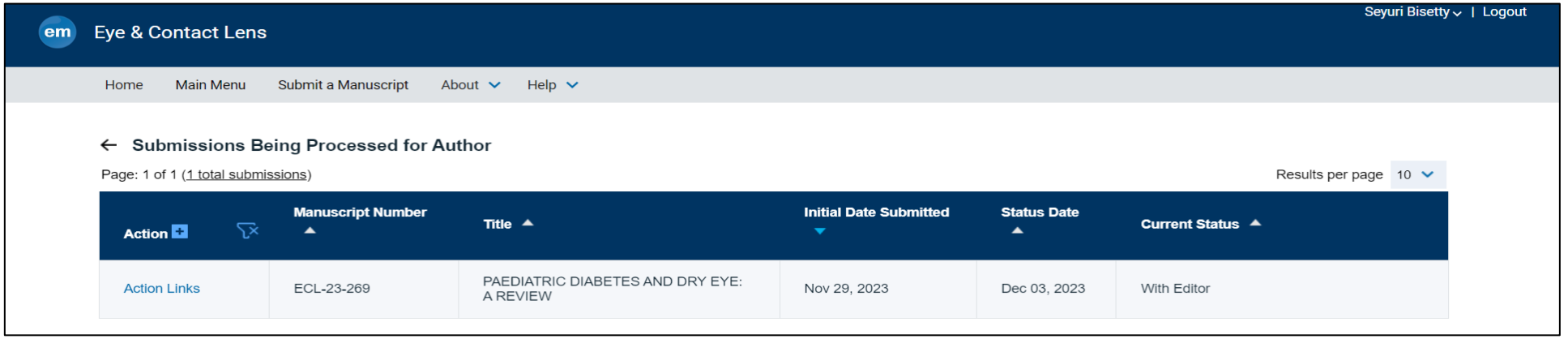
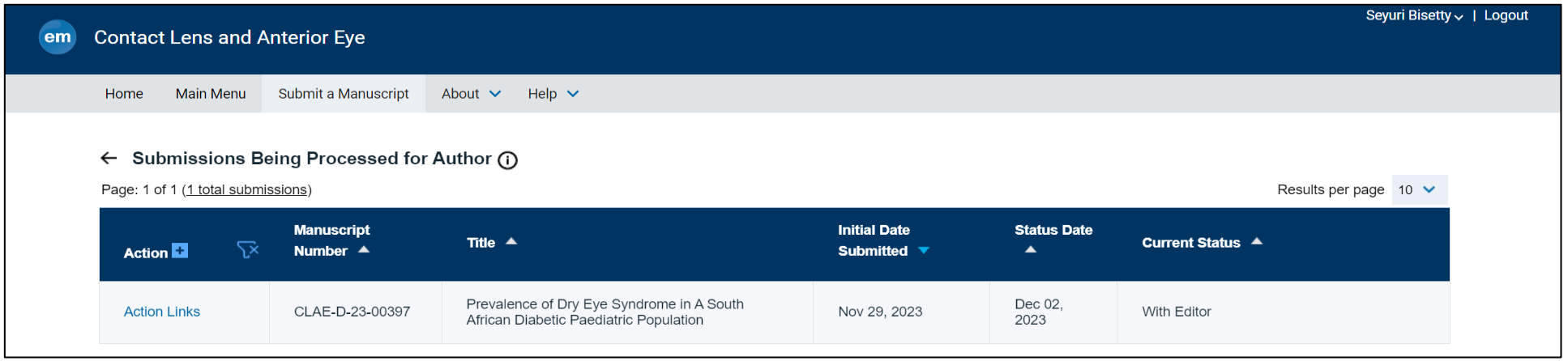
APPENDICES

Appendix A: Journal submission

(1) Manuscript 1



(2) Manuscript 2

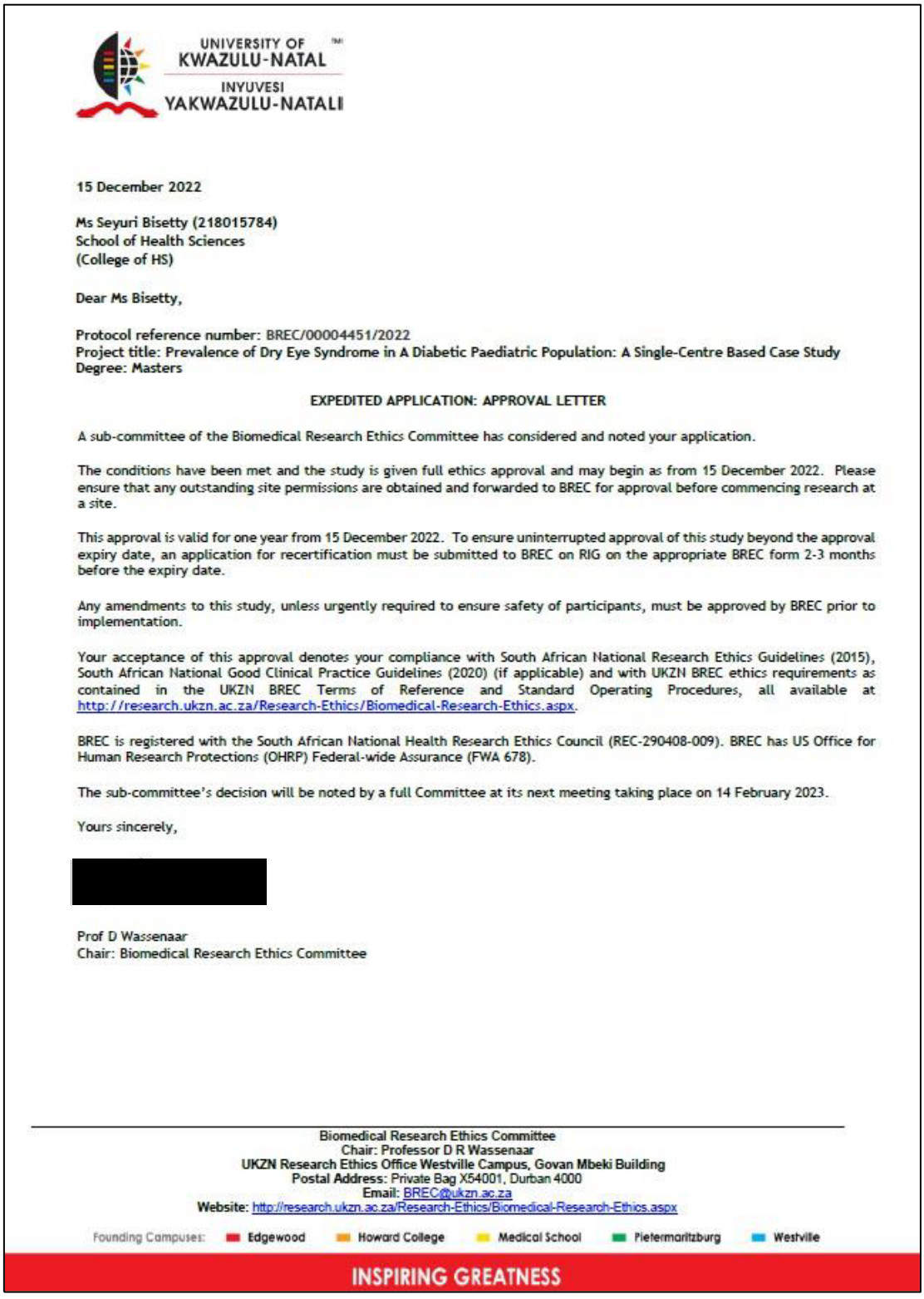


Appendix B: Results

Variable 1	Variable 2	Correlation	P-value
TBUT RE	TBUT LE	0.892	<0.001
Duration in years	**TBUT LE**	**-0.728**	**<0.001**
Duration in years	**TBUT RE**	**-0.717**	**<0.001**
PRT RE	PRT LE	0.541	<0.001
TBUT RE	PRT RE	0.440	<0.001
Duration in years	**PRT LE**	**-0.427**	**<0.001**
TBUT RE	PRT LE	0.409	<0.001
TBUT LE	TFO LE	-0.398	<0.001
TBUT LE	PRT RE	0.390	<0.001
TBUT RE	TFO LE	-0.371	<0.001
Duration in years	**PRT RE**	**-0.368**	**<0.001**
TBUT LE	PRT LE	0.349	0.002
Duration in years	TFO LE	0.224	0.050
PRT LE	TFO RE	-0.191	0.097
PRT RE	TFO RE	-0.155	0.179
Duration in years	TFO RE	0.149	0.197
PRT LE	TFO LE	-0.142	0.218
Total MCMONNIES scores	TFO LE	0.131	0.255
Total OSDI score	TBUT RE	-0.129	0.262
Total OSDI score	PRT RE	-0.128	0.267
TFO RE	TFO LE	0.127	0.269
Duration in years	Total OSDI score	0.125	0.278
Total MCMONNIES scores	TFO RE	0.120	0.297
TBUT RE	TFO RE	-0.119	0.304
Total MCMONNIES scores	PRT RE	0.098	0.399
Total OSDI score	TBUT LE	-0.095	0.411
Total OSDI score	TFO RE	0.089	0.442
TBUT LE	TFO RE	-0.079	0.493
Total OSDI score	TFO LE	0.071	0.537
PRT RE	TFO LE	-0.068	0.558
Duration in years	Total MCMONNIES scores	-0.067	0.561
Total MCMONNIES scores	PRT LE	0.065	0.575
Total MCMONNIES scores	TBUT RE	0.051	0.660
Total MCMONNIES scores	TBUT LE	0.035	0.766
Total OSDI score	PRT LE	-0.014	0.902
Total MCMONNIES scores	Total OSDI score	0.007	0.949

Abbreviations: TBUT= Tear Break-Up Time; PRT= Phenol Red Thread; TFO= Tear Film Osmolarity; RE= Right eye; LE = Left eye; (-) = Correlation, $p<0.05$ = statistically significant

Appendix C: Full ethical approval



UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

15 December 2022

Ms Seyuri Bisetty (218015784)
School of Health Sciences
(College of HS)

Dear Ms Bisetty,

Protocol reference number: BREC/00004451/2022
Project title: Prevalence of Dry Eye Syndrome in A Diabetic Paediatric Population: A Single-Centre Based Case Study
Degree: Masters

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 15 December 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 15 December 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 14 February 2023.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

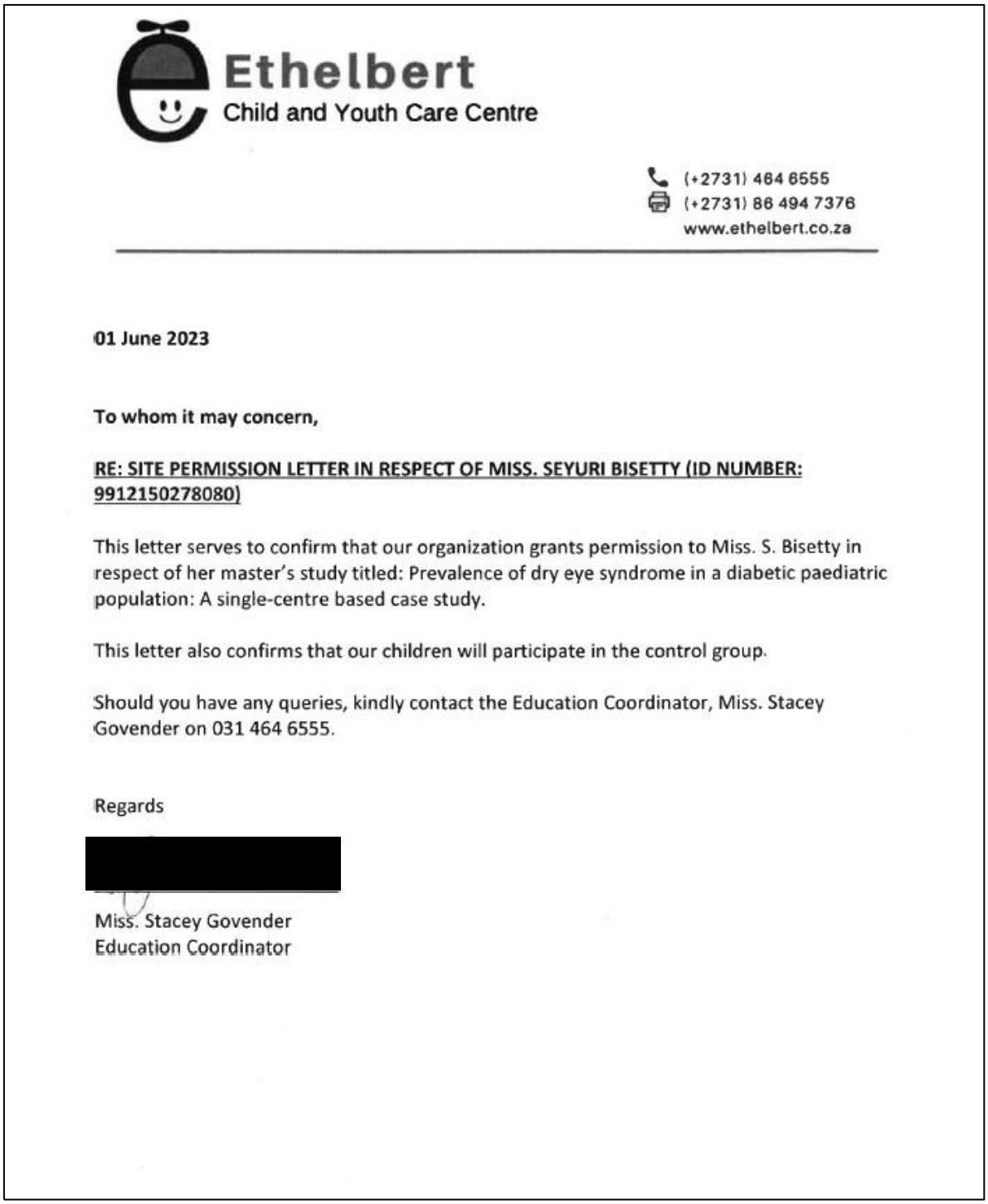
Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

Appendix D: Hospital Gatekeeper permission

Appendix E: Ethelbert Child and Youth Care Centre Gatekeeper permission



Ethelbert
Child and Youth Care Centre

(+2731) 464 6555
(+2731) 86 494 7376
www.ethelbert.co.za

01 June 2023

To whom it may concern,

RE: SITE PERMISSION LETTER IN RESPECT OF MISS. SEYURI BISETTY (ID NUMBER: 9912150278080)

This letter serves to confirm that our organization grants permission to Miss. S. Bisetty in respect of her master's study titled: Prevalence of dry eye syndrome in a diabetic paediatric population: A single-centre based case study.

This letter also confirms that our children will participate in the control group.

Should you have any queries, kindly contact the Education Coordinator, Miss. Stacey Govender on 031 464 6555.

Regards

[redacted]

Miss. Stacey Govender
Education Coordinator

Appendix F: Information and Indemnity (study group – participants)

PREVALENCE OF DRY EYE SYNDROME IN A DIABETIC PAEDIATRIC POPULATION: A SINGLE-CENTRE BASED CASE STUDY

(Information Sheet & Indemnity)

Participants – Study group

April 2022

Dear Potential participants

My name is Ms. Seyuri Bisetty from the Department of Optometry, School of Health Sciences, at the University of KwaZulu-Natal (Cell: 083 229 0454; Email: seyuribisetty15@gmail.com). The present study is for degree purposes (Master of Optometry).

This project will be conducted under the supervision of Dr Naimah Ebrahim Khan (Optometry Academic Leader at the University of KwaZulu-Natal; Email: ebrahimn@ukzn.ac.za)

Invitation

You are being invited to consider participating in a study that involves testing the tear film and investigating the presence of dry eye in children with diabetes. The aim of this study is to determine how common dry eye is among diabetic children in South Africa. There will be **two questionnaires and three tear tests** (explained below). These tests are routinely performed and will not cause any discomfort or pain. The duration of your participation is expected to be between 10 to 15 minutes, should you choose to enroll and remain a part of the study.

Procedure

If you agree to take part in this study, you will be given two sets of short questions which can be answered with help from your parent/guardian. A white light will be used to see your eyelids to ensure good eye health. Thereafter, the three tear tests will be performed:

1. Tear Break-up time

A drop of yellow dye will be put into the eye and post-blink, the eye will be examined using a blue filter light. This test will assess how stable the tear film is.

2. Phenol Red Thread

A thin strand of medical thread will be placed on the lower part of the eye for 15 seconds allowing for wetting of the thread to occur. It is important to note that this thread is extremely fine and you will not feel any pain.

3. Tear Osmolarity

This procedure is similar to testing blood-glucose levels. A strip of paper is used to collect a few tears and is then inserted into a device to gain a reading.

Outcome of the study

The study will enable the researcher to document certain tear function values (the volume of tears and quality of tears) and the presence of dry eye in children and adolescents that have been diagnosed with diabetes, in South Africa.

With the increase in the number of young children being diagnosed with diabetes, the characteristics and risk factors of dry eye disease in this population has become more useful. The results of the questionnaires will be analyzed and one of the questionnaires will be selected a screening tool for medical practitioners working with diabetic children while the clinical results of this research will be used to promote early screening and routine follow-ups of dry eye disease in children with diabetes,

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee **(BREC/00004451/2022)**

In the event of any problems or concerns/questions you may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Voluntary participation

Please note that participation is voluntary, and you, as the participant, can decide to not participate at any stage of the study. You/Your parent or guardian will not have to pay. Your participation will be greatly appreciated.

Confidentiality

All information that will be collected during the study will be kept confidential and will not be given to anyone outside the study. Your name will not appear in any reports.

MINOR ASSENT

I, _____have been informed about the study entitled "Prevalence of Dry Eye Syndrome in a Diabetic Paediatric Population at the ------- Hospital". I understand the purpose and tests of the study.

I have been given a chance to ask questions about the study and the answers were clear and easy to understand. I confirm that my participation in this study is entirely voluntary, and I know that I may change my decision at any time.

I know that I can say no to participating in the study, even if permission has been granted by my parent/guardian.

If I have any further questions related to the study, I understand that I may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

If you want to be in this study, please write your name and sign below.

Check one:

_____I want to be in the study.

_____I do NOT want to be in the study.

Your name: _____

Your signature: _____

Appendix G: Information and Indemnity (study group – parents)

PREVALENCE OF DRY EYE SYNDROME IN A DIABETIC PAEDIATRIC POPULATION: A SINGLE-CENTRE BASED CASE STUDY

(Information Sheet & Indemnity)

Parent/Guardian – Study group

April 2022

Dear Parent/Guardian and potential participants

My name is Ms. Seyuri Bisetty from the Department of Optometry, School of Health Sciences, at the University of KwaZulu-Natal (Cell: 083 229 0454; Email: seyuribisetty15@gmail.com). The present study is for degree purposes (Master of Optometry).

This project will be conducted under the supervision of Dr Naimah Ebrahim Khan (Optometry Academic Leader at the University of KwaZulu-Natal; Email: ebrahimn@ukzn.ac.za)

Invitation

Your child is being invited to participate in a study that involves testing the tear film and investigating the presence of dry eye in children with diabetes. The aim of this study is to determine how common dry eye is among diabetic children in South Africa. This research will include **two questionnaires and three tear tests** (explained below). These tests are routinely performed on patients who want to wear contact lenses to establish that they have a normal tear film in terms of tear quantity and quality. Each procedure minimally invasive but please note that it will, in no manner, cause any discomfort or pain. This will only take between 10 to 15 minutes, should your child choose to remain a part of the study.

Procedure

Upon completion of the consent form, participants will be required to answer two short questionnaires revolving around signs and symptoms as well as factors that may cause dry eye. You, as the parent/guardian may assist in the completion of the questionnaire. The eyelids will be screened with white light to ensure good eye health. Thereafter, the three tear tests will be performed:

1. Tear Break-up time

A drop of sterile yellow dye will be put into the eye and post-blink, the eye will be examined using a blue filter light. This test will assess how stable the tear film is.

2. Phenol Red Thread

A thin strand of medical thread will be placed on the lower part of the eye for 15 seconds allowing for wetting of the thread to occur. It is important to note that this thread is extremely fine and will not cause any pain to the participant.

3. Tear Osmolarity

This procedure is like testing blood-glucose levels. A sterile strip is used to collect a sample of tears and is then inserted into a device to gain a reading.

Outcome of the study

The study will enable the researcher to document certain tear function values (the volume of tears and quality of tears) and the presence of dry eye in children and adolescents that have been diagnosed with diabetes, in South Africa.

With the increase in the number of adolescents and young children being diagnosed with diabetes, the characteristics and risk factors of dry eye disease in this population has become more valuable and of social significance. The results of the questionnaires will be analyzed and one of the questionnaires will be selected a screening tool for medical practitioners working with diabetic children while the clinical results of this research will be used to enhance physician awareness of dry eye in children as well as promote early screening and routine follow-ups of dry eye disease in children with diabetes, which should be implemented, especially in children with a long duration of diabetes. Early intervention is important as scarring of the cornea may occur in some dry eye cases, leading to mild-to-severe visual impairment.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee **(BREC/00004451/2022)**

In the event of any problems or concerns/questions you may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com or the UKZN Biomedical Research Ethics Committee, contact details as follows:

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Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Voluntary participation

Please note that participation is voluntary, and participants may withdraw participation at any stage of the study. In the event of refusal or withdrawal of participation the participants will not incur penalty or loss of treatment or other benefit to which they are normally entitled.

Please note that there will be no payment for participating. Your child's participation will, however, be greatly appreciated.

Confidentiality

All information that will be collected during the study will be kept confidential and will not be given to anyone outside the study. Your child's name will not appear in any reports.

PARENTAL CONSENT:

This consent form is a request for your child's participation in a research study by Ms. Seyuri Bisetty, a master's candidate at the University of KwaZulu-Natal. This research is being conducted under the supervision of Dr Naimah Ebrahim Khan.

I_____have been informed about the study entitled “Prevalence of Dry Eye Syndrome in a Diabetic Paediatric Population at the ----------Hospital”. I understand the purpose and procedures of the study.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that my child’s participation in this study is entirely voluntary and that he/she may withdraw at any time without affecting any treatment or care that he/she would usually be entitled to.

I understand that even if consent is granted on my behalf, my child if free to decline the invite to participate in this study.

If I have any further questions/concerns or queries related to the study, I understand that I may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com

If I have any questions or concerns about my child’s rights as a study participant, or if I am concerned about any aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

_____ _____

Signature of Parent/Guardian Date

_____ _____

Signature of witness (if applicable) Date

Appendix H: Information and indemnity (control group – child)

PREVALENCE OF DRY EYE SYNDROME IN A DIABETIC PAEDIATRIC POPULATION: A SINGLE-CENTRE BASED CASE STUDY

(Information Sheet & Indemnity)

Participants – Control group

April 2022

Dear Potential participants

My name is Ms. Seyuri Bisetty from the Department of Optometry, School of Health Sciences, at the University of KwaZulu-Natal (Cell: 083 229 0454; Email: seyuribisetty15@gmail.com). The present study is for degree purposes (Master of Optometry).

This project will be conducted under the supervision of Dr Naimah Ebrahim Khan (Optometry Academic Leader at the University of KwaZulu-Natal; Email: ebrahimn@ukzn.ac.za)

Invitation

You are being invited to consider participating in a study that involves testing the tear film and investigating the presence of dry eye in children with diabetes. The aim of this study is to determine how common dry eye is among diabetic children in South Africa. **You will be tested for dry eye as part of the control group for this study.** There will be **two questionnaires and three tear tests** (explained below). These tests are routinely performed and will not cause any discomfort or pain. The duration of your participation is expected to be between 10 to 15 minutes, should you choose to enroll and remain a part of the study.

Procedure

If you agree to take part in this study, you will be given two sets of short questions which can be answered with help from your parent/guardian. A white light will be used to see your eyelids to ensure good eye health. Thereafter, the three tear tests will be performed:

5. Tear Break-up time

A drop of yellow dye will be put into the eye and post-blink, the eye will be examined using a blue filter light. This test will assess how stable the tear film is.

6. Phenol Red Thread

A thin strand of medical thread will be placed on the lower part of the eye for 15 seconds allowing for wetting of the thread to occur. It is important to note that this thread is extremely fine and you will not feel any pain.

7. Tear Osmolarity

This procedure is similar to testing blood-glucose levels. A strip of paper is used to collect a few tears and is then inserted into a device to gain a reading.

Outcome of the study

The study will enable the researcher to document certain tear function values (the volume of tears and quality of tears) and the presence of dry eye in children and adolescents that have been diagnosed with diabetes, in South Africa.

With the increase in the number of young children being diagnosed with diabetes, the characteristics and risk factors of dry eye disease in this population has become more useful. The results of the questionnaires will be analyzed and one of the questionnaires will be selected a screening tool for medical practitioners working with diabetic children while the clinical results of this research will be used to promote early screening and routine follow-ups of dry eye disease in children with diabetes,

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee **(BREC/00004451/2022)**

In the event of any problems or concerns/questions you may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Voluntary participation

Please note that participation is voluntary, and you, as the participant, can decide to not participate at any stage of the study. You/Your parent or guardian will not have to pay. Your participation will be greatly appreciated.

Confidentiality

All information that will be collected during the study will be kept confidential and will not be given to anyone outside the study. Your name will not appear in any reports.

MINOR ASSENT

I, _____have been informed about the study entitled "Prevalence of Dry Eye Syndrome in a Diabetic Paediatric Population at the --------- Hospital". I understand the purpose and tests of the study.

I have been given a chance to ask questions about the study and the answers were clear and easy to understand. I confirm that my participation in this study is entirely voluntary, and I know that I may change my decision at any time.

I know that I can say no to participating in the study, even if permission has been granted by my parent/guardian.

If I have any further questions related to the study, I understand that I may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

If you want to be in this study, please write your name and sign below.

Check one:

_____I want to be in the study.

_____I do NOT want to be in the study.

Your name: _____

Your signature: _____

Appendix I: Information and Indemnity (Control group - parent)

PREVALENCE OF DRY EYE SYNDROME IN A DIABETIC PAEDIATRIC POPULATION: A SINGLE-CENTRE BASED CASE STUDY

(Information Sheet & Indemnity)

Parent/Guardian – control group

April 2022

Dear Parent/Guardian and potential participants

My name is Ms. Seyuri Bisetty from the Department of Optometry, School of Health Sciences, at the University of KwaZulu-Natal (Cell: 083 229 0454; Email: seyuribisetty15@gmail.com). The present study is for degree purposes (Master of Optometry).

This project will be conducted under the supervision of Dr Naimah Ebrahim Khan (Optometry Academic Leader at the University of KwaZulu-Natal; Email: ebrahimn@ukzn.ac.za)

Invitation

Your child is being invited to participate in a study that involves testing the tear film and investigating the presence of dry eye in children with diabetes. The aim of this study is to determine how common dry eye is among diabetic children in South Africa. **Your child will be tested for dry eye as part of the control group for the study**. This research will include **two questionnaires and three tear tests** (explained below). These tests are routinely performed on patients who want to wear contact lenses to establish that they have a normal tear film in terms of tear quantity and quality. Each procedure minimally invasive but please note that it will, in no manner, cause any discomfort or pain. This will only take between 10 to 15 minutes, should your child choose to remain a part of the study.

Procedure

Upon completion of the consent form, participants will be required to answer two short questionnaires revolving around signs and symptoms as well as factors that may cause dry eye. You, as the parent/guardian may assist in the completion of the questionnaire. The eyelids will be screened with white light to ensure good eye health. Thereafter, the three tear tests will be performed:

8. Tear Break-up time

A drop of sterile yellow dye will be put into the eye and post-blink, the eye will be examined using a blue filter light. This test will assess how stable the tear film is.

9. Phenol Red Thread

A thin strand of medical thread will be placed on the lower part of the eye for 15 seconds allowing for wetting of the thread to occur. It is important to note that this thread is extremely fine and will not cause any pain to the participant.

10. Tear Osmolarity

This procedure is like testing blood-glucose levels. A sterile strip is used to collect a sample of tears and is then inserted into a device to gain a reading.

Outcome of the study

The study will enable the researcher to document certain tear function values (the volume of tears and quality of tears) and the presence of dry eye in children and adolescents that have been diagnosed with diabetes, in South Africa.

With the increase in the number of adolescents and young children being diagnosed with diabetes, the characteristics and risk factors of dry eye disease in this population has become more valuable and of social significance. The results of the questionnaires will be analyzed and one of the questionnaires will be selected a screening tool for medical practitioners working with diabetic children while the clinical results of this research will be used to enhance physician awareness of dry eye in children as well as promote early screening and routine follow-ups of dry eye disease in children with diabetes, which should be implemented, especially in children with a long duration of diabetes. Early intervention is important as scarring of the cornea may occur in some dry eye cases, leading to mild-to-severe visual impairment.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee **(BREC/00004451/2022)**

In the event of any problems or concerns/questions you may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Voluntary participation

Please note that participation is voluntary, and participants may withdraw participation at any stage of the study.

Please note that there will be no payment for participating. Your child's participation will, however, be greatly appreciated.

Confidentiality

All information that will be collected during the study will be kept confidential and will not be given to anyone outside the study. Your child's name will not appear in any reports.

PARENTAL CONSENT:

This consent form is a request for your child's participation in a research study by Ms. Seyuri Bisetty, a master's candidate at the University of KwaZulu-Natal. This research is being conducted under the supervision of Dr Naimah Ebrahim Khan.

I_____have been informed about the study entitled “Prevalence of Dry Eye Syndrome in a Diabetic Paediatric Population at the ------- Hospital”. I understand the purpose and procedures of the study.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that my child’s participation in this study is entirely voluntary and that he/she may withdraw at any time without affecting any treatment or care that he/she would usually be entitled to.

I understand that even if consent is granted on my behalf, my child if free to decline the invite to participate in this study.

If I have any further questions/concerns or queries related to the study, I understand that I may contact the researcher at 083 229 0454 or seyuribisetty15@gmail.com

If I have any questions or concerns about my child’s rights as a study participant, or if I am concerned about any aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus Govan Mbeki Building

Private Bag X 54001 Durban

4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

_____ _____

Signature of Parent/Guardian Date

_____ _____

Signature of witness (if applicable) Date

Appendix J: Data sheet (sample)

STUDY ID NUMBER:

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

PREVALENCE OF DRY EYE DISEASE IN A SOUTH AFRICAN DIABETIC PAEDIATRIC POPULATION: A SINGLE-CENTRE BASED CASE STUDY

(Data Sheet)

Instructions

Please tick the appropriate response and/or write your answer in the space provided.

SECTION A

SECTION B

- Questionnaire 1
- Questionnaire 2

A. Demographic data

1. Age (years):
2. Gender: Male (1) Female (2)
3. Race:

B. Ocular history

1. Are you currently taking any eye medication/eye drops? Yes (1) No (2)
   If yes, please state the name of medication & dosage (if possible):
2. Do you currently wear spectacles or contact lenses? Yes (1) No (2)
3. Have you previously been diagnosed with dry eye by an eye care practitioner? Yes (1) No (2)
   If yes, what treatment plan was advised:
4. Have you ever had any surgery/injury to the eye? Yes (1) No (2)
   If yes, please indicate details in terms of:
   Surgery – when/ type/complications post-surgery
   Injury – when/where/how/severity

C. Medical History

1. Type of Diabetes (1 or 2)
2. Treatment plan
3. Year of diagnosis

STUDY ID NUMBER:

SECTION B

Questionnaire 1

Please tick or circle the most appropriate answer to the questions below

MODIFIED VERSION OF McMONNIES DRY EYE QUESTIONNAIRE WITH SCORING SCHEME1

1. Have you ever had drops prescribed or other treatment for dry eyes?
Yes (2)/ No (1)/ Uncertain (0)

2. Do you ever experience any of the following dry eye symptoms?
1 Soreness (1) 2 Scratchiness (1) 3 Dryness (1) 4 Grittiness (1) 5 Burning (1)

3. How often do your eyes have these symptoms?
Never (0) Sometimes (1) Often (2) Constantly (3)

4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning, or central heating?
Yes (2) No (0) Sometimes (1)

5. Do your eyes become very red and irritated when swimming?
Not applicable (0) Yes (2) No (0) Sometimes (1)

6. Are your eyes dry and irritated the day after drinking alcohol?
Not applicable (0) Yes (2) No (0) Sometimes (1)

7. Do you take antihistamine tablets (1) or use antihistamine eye drops (1), diuretics (1) (fluid tablets)

8. Do you suffer from arthritis?
Yes (2) No (0) Uncertain (1)

9. Do you experience dryness of the nose, mouth, throat, chest, or vagina?
Never (0) Sometimes (1) Often (2) Constantly (3)

10. Do you suffer from thyroid abnormality?
Yes (2) No (0) Uncertain (1)

11. Are you known to sleep with your eyes partly open?
Yes (2) No (0) Sometimes (1)

12. Do you have eye irritation as you wake from sleep?
Yes (2) No (0) Sometimes (1)

Gender Age Score

Male or Female Under 25 (0)
Male 25-45 (1)
Female 25-45 (3)

STUDY ID NUMBER:

Questionnaire 2

Please tick or circle the most appropriate answer to the questions below

OCULAR SURFACE DISEASE INDEX (OSDI)

1. HAVE YOU EXPERIENCED ANY OF THE FOLLOWING DURING THE LAST WEEK :

	All of the time	Most of the some	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A) ☐

2. HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING DURING THE LAST WEEK:

	All of the time	Most of the some	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B) ☐

3. HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS DURING THE LAST WEEK?

	All of the time	Most of the some	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry) ?	4	3	2	1	0	N/A
12. Areas that are air-conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (C) ☐

Appendix K: Record sheet sample

STUDY ID NUMBER:

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

PREVALENCE OF DRY EYE DISEASE IN A SOUTH AFRICAN DIABETIC PAEDIATRIC POPULATION: A SINGLE-CENTRE BASED CASE STUDY

(Record Sheet)

☐ Information sheet & Indemnity
☐ Data sheet
☐ Record sheet

Date of examination:

1. Slit-lamp Examination

Signs of Meibomian gland dysfunction

YES	NO

2. Tear Break-up time

	OD	OS
1		
2		
Average		

3. Phenol Red Thread test

OD	
OS	

4. Tear Osmolarity test

OD	
OS	

Appendix L: GUIDELINES FOR PRESENTATION OF MASTERS AND PHD DISSERTATIONS/THESES BY RESEARCH

1. Purpose

The purpose of this document is to provide guidance to students and supervisors on how to prepare a dissertation/thesis for Masters by Research and PhD degrees using the manuscript or publication format.

2. Introduction

These guidelines must be read together with the College of Health Sciences (CHS) Handbook as well as the Jacobs documents on examination policies and procedures for PhD degrees. The rules on thesis format are based on modification of point 1 of the definition of terms section in the Jacobs document. In this section a thesis is defined as "the supervised research component of all PhD degrees, whether by supervised research only, or coursework and research, or by papers that are either published or in manuscript form (the supervised research component of the PhD degree by paper(s) comprises the introduction, literature review, account of the methodology, selection of manuscripts, and conclusion)." A dissertation is defined as "the supervised research component of all Masters degrees, whether by supervised research only, or coursework and research, or by papers that are either published or in manuscript form (the supervised research component of the Masters degree by paper(s) comprises the introduction, literature review, account of the methodology, selection of manuscripts, and conclusion)."

2.1 PhD thesis

In the CHS Handbook the rules for a PhD thesis are not in one place; they are stated in DR8 a i & ii, DR9 c and CHS 16. DR8 a i & ii and direct that a thesis be presented in the standard format together with one published paper or an unpublished manuscript that has been submitted to an accredited journal, arising from the doctoral research. CHS16 (thesis by publications states that the thesis may comprise of at least three published papers or in press in accredited journals; such papers must have the student as the prime author. The same CHS16 provides for a thesis by manuscripts that may have at least 3 papers with the student as the prime author that have not yet been published but are in the form of manuscripts; at least two of such papers must constitute original research. In both cases (thesis by publications and manuscripts), there must be introductory and concluding integrative material sections. 60 The standard type thesis is being phased out in many African countries in favour of the other options that originate from the Scandinavian countries. While this format ensures that all details of the work done for the doctoral degree are captured and thoroughly interrogated, they often remain as grey literature which is mainly useful to other students, usually within the same university, although with digitization of theses, such work may become more accessible beyond the source university. Apart from the risk

of losing good work because of it not being on the public domain, as students rarely publish such work after graduating, this approach denies the college additional productivity units (PUs) emanating from publications.

The thesis by publication encourages students to publish key aspects of their doctoral research as they will not graduate if the papers are not published or in press. This approach ensures that the work of the student enters the public domain before the thesis is examined, providing the examiner with some assurance of prior peer review. The thesis must constitute a full study of the magnitude expected of a PhD with the papers providing a sound thread or storyline. Furthermore, the college maximizes the students' work as PUs are awarded for the papers as well as for graduating. However, this approach may negatively affect throughput and frustrate students as they cannot graduate unless all the papers are published or in press, in addition to the synthesis chapter demonstrating the story line of the thesis.

The option of a thesis by manuscripts ensures that students make efforts to start publishing. The risk of not passing because of failure to publish all papers (as in the thesis by publication) does not exist under this option. However, the PUs emanating from publications from the doctoral work are not guaranteed as the submitted papers may eventually be rejected. Thus there is a possibility of the doctoral work remaining on the university library shelves as is the case for the standard thesis format. The standard thesis does have the advantage that more details of the doctoral work are usually included. In view of the above, the best option for the college is that of a thesis by publication. However, in the interim, the attractive option is that of thesis by manuscripts, as it provides the possibility of publication without putting the student at risk of delayed graduation when some of the manuscripts are not published/accepted, which also disadvantages the college in terms of PU earnings. The standard thesis option should ultimately be phased out for the stated reasons and students are not encouraged to present their theses in that format. Consequently this document does not describe the standard thesis.

2.2 MSc dissertation

The rules on presentation of MSc dissertations are presented in CR13 (course work), CHS 14 (course work) and MR9 (research) in the CHS Handbook. CR13 c and MR9 c direct that a dissertation "may comprise one or more papers of which the student is the prime author, published or in press in peer-reviewed journals approved by the relevant college academic affairs board or in manuscripts written in a paper format, accompanied by introductory and concluding integrative material." Such a dissertation should include a detailed description of the student's own distinct contribution to the papers. Both CHS14 and CR13 specify that reviews and other types of papers in addition to original research paper/s may be included, provided they are on the same topic.

3 Length of thesis and dissertation by word count

Table 1 provides a guide of the length of a thesis or dissertation by word count excluding preliminary pages and annexes.

Table 1: Thesis length by word count

Sections	**PhD**		**Masters**	
	Minimum	**Maximum**	**Minimum**	**Maximum**
Introduction	2,700	2,700	2,000	2,000
Chapters	10,000	25,000	6,000	11,000
Synthesis	2,000	2,000	1,700	1,700
Bridging	300	300	300	300
Total	15,000	30,000	10,000	15,000

4. Intention to submit

A written intention to submit a thesis or dissertation should be submitted to the appropriate postgraduate office with endorsement of the supervisor at least three months before the actual date of submission which should be before November if the student intends to graduate in the following year. The actual submission will under normal circumstances require approval of the supervisor.

5. Format for theses/dissertation

There is little variation in the actual format of the PhD thesis and Masters dissertation for the various types described above.

The box below summarise the outline of a thesis/dissertation for the thesis by manuscripts and thesis by publications.

Preliminary pages

i. Title page
ii. Preface and Declaration
iii. Dedication
iv. Acknowledgements
v. Table of contents
vi. List of figures, tables and acronyms (separately presented)
vii. Abstract

Main Text

1. Chapter 1: Introduction
   Introduction including literature review
   Research questions and/or objectives
   Brief overview of general methodology including study design
2. Chapter 2
   First manuscript/publication
3. Chapter 3
   Second manuscript/publication
4. Chapter n
   Final manuscript/publication
5. Chapter n+1: Synthesis
   Synthesis
   Conclusions
   Recommendations
6. References Appendices

NB. Between the manuscripts or publications there must be a 1 page (maximum) bridging text to demonstrate the link between them

NB. Between the manuscripts or publications there must be a 1 page (maximum) bridging text to demonstrate the link between them

6. Details for thesis/dissertation subheadings

This section summarizes what is expected under each subheading shown in Boxes 1 and indicates where there might be variations between a Masters Dissertation and PhD Thesis.

6.1 Title Page

The officially approved title that is concise (Fewest words that adequately describe the contents of the thesis/dissertation – usually 15 or fewer words) is presented at the top. This should be followed by the candidate's name in a new line. At the bottom the thesis statement should be presented. The thesis statement may be stated as "Submitted in fulfilment of the requirements for the degree of in the School of, University of KwaZulu-Natal" for a PhD/Masters by Research thesis. In the case of a Masters Dissertation it should be stated as "Submitted as the dissertation

component in partial fulfilment (% stated) for the degree of in the School of, University of KwaZulu-Natal". For both Masters and PhD the date of submission must be stated.

6.2 Preface (Optional)

The preface merely states the reason (motivating factors) why the study was conducted without getting into details of what was investigated.

6.3 Declaration

This must be structured as follows:

I, Dr/Mr, declare as follows:

1. That the work described in this thesis has not been submitted to UKZN or other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.

Where a colleague has indeed prepared a thesis based on related work essentially derived from the same project, this must be stated here, accompanied by the name, the degree for which submitted, the University, the year submitted (or in preparation) and a concise description of the work covered by that thesis such that the examiner can be assured that a single body of work is not being used to justify more than one degree.

2. That my contribution to the project was as follows:

This is followed by a concise description of the candidate's personal involvement in and contribution to the project, in sufficient detail that the examiner is in no doubt as to the extent of their contribution.

That the contributions of others to the project were as follows:

This is followed by a list of all others who contributed intellectually to the project, each accompanied by a concise description of their contribution. This does not include people who ordinarily would be "acknowledged" as opposed to considered for authorship.

Signed _____ Date _____

6.4 Dedication

This is an optional section. Should it be included it must be very brief merely indicating to whom the work is dedicated. Avoid anything too flowery

6.5 Acknowledgements

This section acknowledges all individuals, groups of people or institutions that the candidate feels indebted to for the support they rendered. The funding source for the work should also be acknowledged.

6.6 Table of contents

Table of contents must be inserted after the preliminary sections and must capture all major sections of the thesis at the various levels (primary, secondary, tertiary subheadings). It should be electronically generated and should be able to take the reader to specific headings in the thesis.

6.7 Lists of figures, tables, and acronyms

These lists must be presented separately. All titles of figures presented in the thesis/dissertation must be listed indicating on what page they appear. Similarly for tables the titles must be presented indicating on what page they appear. In the case of acronyms, the acronym is stated and all the words describing the acronym are presented. Only key acronyms should be stated. In some cases they may not be listed as long as full text is presented whenever the acronym is used for the first time.

6.8 Abstract

The abstract should summarize the thesis mainly stating the purpose of the study, highlights of chapters and the new knowledge contributed by the thesis. The abstract must be approved by the supervisor of the thesis and should not be more than 350 words in length.

6.9 Introduction

The introductory chapter for both types of thesis is similar. The section should include literature review and have the following information. Headings are used as appropriate and need not correspond exactly to the following.

i. Background and the context of the study

ii. Description of the core research problem and its significance

iii. A comprehensive, critical, coherent overview of the relevant literature leading to clearly defined knowledge gaps

iv. A coherent problem statement highlighting the nature and magnitude of the problem, the discrepancy, knowledge gaps therein and possible factors influencing the problem.

v. Clear and SMART research questions, objectives, and hypothesis and/or theoretical framework

vi. A conceptual framework (optional)

vii. Description of the study area and general methodology (in a standard thesis this should be a stand-alone section)

viii. Layout of the thesis (thesis structure) indicating what chapters are presented in the thesis and how they address the objectives.

6.10 Literature review

This section is subsumed in the introduction within the stipulated word count for a thesis or dissertation.

6.11 Methodology

A standalone section is not needed as the methods are adequately described in each manuscript/publication.

6.12 Data chapters/manuscripts/publications

The full published paper or manuscript submitted for publication should be presented as published or submitted to the journal. The actual published paper should be scanned and inserted in the chapter. There should be a separator page between chapters that has text linking the previous chapter to the next and providing details of the next manuscript/publication indicating publication status.

6.13 General discussion/Synthesis chapter

This is a general discussion that demonstrates the logical thread that runs across the various manuscripts/publications (synthesis). There should be no doubt that the manuscripts/publications complement each other and address the original objectives stated in the general introduction of the thesis. The general discussion/synthesis chapter should end with a conclusion and recommendations where necessary.

6.14 References

Only references cited in the introduction and synthesis chapters should be listed as all other references should be within the manuscripts presented under data chapters.

6.15 Annexes

All information (questionnaires, diagrams, ethics certificates, etc) considered important but not essential for inclusion in the actual thesis is put in this section as reference material. In addition papers that emanated from the work but not directly contributing to the thesis may be included.

7. Thesis formatting

For standardisation of thesis the following formatting specifications should be followed.

7.1 Font

Times New Roman 11pt should be used throughout the thesis. However, major headings may be made bigger (12pt) but using the same font type

7.2 Paper size and margins

A4 (297 x 210 mm) should be used and in the final thesis both sides of the paper should be used. However, the loose bound copy submitted for examination should be printed on only one side. The recommended margins are 30mm for all the left, right, top, and bottom margins.

7.3 Line spacing

The copy submitted for examination should have 1.5 line spacing but the final copy should have single line spacing. Paragraphs should be separated by a blank line. Published or submitted

manuscripts should remain in their original format in all aspects as they are inserted in their published format in appropriate places.

7.4 Headings

A consistent numbering system and captions should be maintained with first level being in CAPS and centred, second level being normal bold font and third level being italics bold. If there is need for 4th level it should be normal italics.

7.7 Pagination

Page numbers should be centred at the bottom of the page. All preliminary pages should be numbered in lower case Roman numerals and subsequent pages should be numbered as indicated in the Box The title page should not be numbered. The body of the thesis (chapter 1 onwards) should be numbered consecutively with Arabic numerals. The numbers should continue consecutively from the introduction through the through the publications or submitted manuscripts and subsequent sections. The published papers will therefore bear two numbers: a set specific to the manuscript (it is recommended to place these in the upper right hand corner) or published paper, as well as the consecutive numbers belonging to the thesis as a whole. Care must be taken to distinguish these in terms of position and font.

7.8 Referencing

Supervisors have the freedom to decide the type of citation of references but there must be consistency. This is mainly applicable to the standard type of thesis. In the case of thesis by manuscripts or publications, individual papers will maintain the reference system of the journal but the supervisor can decide on the type of referencing for the introductory and synthesis chapters.

8. Final thesis submission

The thesis should be submitted for examination in a loose bound form accompanied by a PDF copy. After the examination process the final version PDF copy of the thesis must be submitted to PG office for onward submission to the library. It is not a requirement to submit a copy fully bound in leather cloth or similar material.

Appendix M: Turnitin report

Masters Thesis - S. Bisetty

ORIGINALITY REPORT

8%	5%	6%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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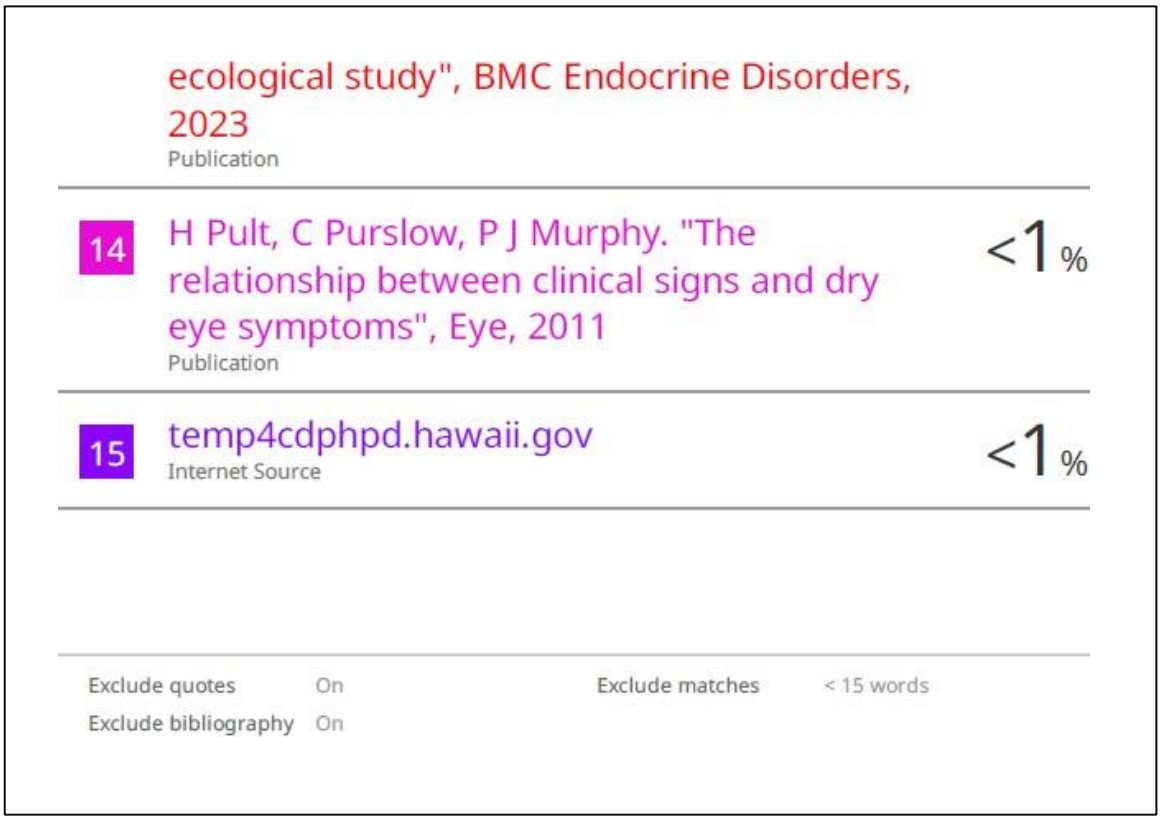
ecological study", BMC Endocrine Disorders, 2023
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