Comparison of corneal morphological characteristics between diabetic and non- diabetic population

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Abstract

The International Diabetes Federation reported that in 2019 there exist 463 million persons living with diabetes globally, with 48 million, 11.1%, living in North America and the Caribbean[3]. In Trinidad and Tobago, Diabetes is one of the most common diagnosed systemic diseases in individuals, where Trinidad and Tobago was ranked as the third country with the highest reported number of deaths due to diabetes in 2018[2]. Diabetes is known to affect the eye and its effects are variable throughout the entire eye from the front, the cornea to the back, the retina. This study was granted permission by the Optometry Unit and the UWI Ethics Committee, to investigate if there exists any corneal morphological differences between the diabetic and non-diabetic population. This research study design was originally that of a case-control, analytical, prospective and quasi-experimental study design, but, due to the COVID-19 pandemic that has taken place the study design is now qualitative where expected results are simulated. Based on previous studies which allowed simulated expected result that related to this study, it can be concluded that there does exist corneal morphological differences between the diabetic and non-diabetic population. However, it is noted that results are variable and inconsistent, due to statistical analysis of data being either significant or insignificant although observables changes may be recorded.

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Definition of terms

- Incidence – the frequency of new cases of a disease in a population over a particular time period.
- Morphology – the particular form, shape, size and structure of identifying an object.
- Cornea – the clear front surface of the eye which is directly anterior to the pupil and the iris.
- Cornea endothelium- a layer of cells of the inner surface of the cornea at the interface of the cornea and anterior chamber.
- Cornea epithelium- outer most layer of the cornea, composed of stratified squamous cells which form tight junctions to act as a barrier against loss of fluids from within the cornea and the protection of pathogens trying to invade inside the eye.
- Polymegathism – variation in cell size within the corneal endothelial single cell layer.
- Pleomorphism – variation in cell shape within the corneal endothelial monolayer
- Corneal hysteresis – the ability of the cornea to absorb and release energy
- Visual acuity – the ability to perceive detail and shape in one's vision
- Topography – test which maps out the corneal curvature, to asses any irregularities and inconsistency in the cornea surface
- Pachymetry – the ability of measuring the corneal thickness.
- Specular microscopy- in vivo assessment of the corneal endothelium to determine cell loss, polymegathism and pleomorphism.

- Keratometry – a measurement of corneal curvature, which determines the power of the cornea.
- Oxidative stress – an abnormality caused by the imbalance between formation and aggregation of oxygen reactive species (ROS) in cells and tissues and the potential for biological system to detoxify the reactive products.
- Osmotic stress - physiologic impaired functionality caused by an abrupt change in the solute concentration of the cells environment, resulting in a rapid change in the transition of water molecules across its cell membrane.
- Polyol pathway- the conversion of glucose to sorbitol by use of aldose reductase and then converting sorbitol to fructose by use of sorbitol dehydrogenase, done in a two-step process.

Chapter 1 Introduction

1.1 Background of study

Internationally, it has been shown that corneal morphological changes exist between diabetic and non-diabetic population. One such research study conducted by Qamar Ul Islam et al in 2017[1] showed that diabetic patients presented with 'decreased corneal endothelial cell density, decreased endothelial cell size, and other morphological changes', when compared to non-diabetic patients. In Trinidad and Tobago, Diabetes is one of the most common diagnosed systemic diseases in individuals, where Trinidad and Tobago was ranked as the third country with the highest reported number of deaths due to diabetes in 2018[2]. The International Diabetes Federation reported that in 2019 there exist 463 million persons living with diabetes globally, with 48 million, 11.1%, living in North America and the Caribbean[3].

1.2 Statement of the Problem or Rationale of study

Although, there are 48 million people living with diabetes in North America and the Caribbean as of 2019, currently, there exists a porosity of data on the corneal morphological changes between diabetic and non-diabetic population in the region. This research study will like to investigate if there are any corneal morphological changes between diabetic and non-diabetic population given the increase in the incidence of diabetic persons in the country where diabetes is listed as one of the leading causes of blindness.

1.3 Aim of the study

To investigate if there exists any corneal morphological differences between the diabetic and non-diabetic population.

1.4 (a) Objectives of the study

To observe if there are any differences in corneal morphology between the diabetic and non-diabetic population.

To compare corneal morphological differences between the diabetic and non-diabetic population.

To identify any significant differences in morphology between the corneal epithelial and endothelial layers between the controlled and uncontrolled diabetic population.

1.5 (b) Research questions

1. Is there a difference in corneal morphology (particularly in the epithelial and endothelial layer) between diabetic and non-diabetic population?

2. Is there a significant difference in morphology between the corneal epithelial and endothelial layer between controlled and uncontrolled diabetic population?

1.4 (c) Hypothesis

There exist differences in corneal morphology, particularly the epithelial and endothelial layers, between diabetic and non-diabetic population.

1.5 Significance of the study

The International Diabetes Federation believes that there will be a 33% increase in the number of diabetic person in North America and the Caribbean by 2045, i.e., by 2045 it is expected to have at least 63 million people living with diabetes. Due to the expected rise in the diabetic population and the lack of research regionally, which links the effects of diabetes to the cornea, this research can be used as the foundation for future research to be done regionally and locally with a larger sample size. It can also create a means of greater preventative methods to be enforced as the knowledge of the detrimental effects it can have on the eyes is discussed.

Chapter 2 Literature Review

A variety of online resources were used which showed that internationally this research study was done over a period of time by different researchers but unfortunately, it failed to show any research studies done locally.

In an online research article published in 2017 titled 'Comparison of corneal morphological characteristics between diabetic and non-diabetic population' by Dr. Qamar Ul Islam et al. [1], results showed that 'the mean cell endothelial density was lesser among diabetics compared to the control group.' However, statistically, the researchers reported that there were 'no significant changes between the two groups with respect to coefficient variation of cell size and hexagonality as compared to other studies.'

This research was conducted on 298 eyes from 298 subjects at the PNS Shifa, Karachi Hospital which is located in Pakistan in Southern Asia. The 298 subjects consisted of 149 diabetic patients and 149 patients being the control/normal/healthy group. The general age range was 30-80 years and the subjects were age-matched as this aimed to lessen any age bias that may have arisen. The duration of the diabetic population was categorized into those with diabetes for less than or more than 10 years and the study mentioned the effect patients with diabetes for more than 10 years experienced in relation to the results obtained. It revealed that subjects who had diabetes for more than 10 years had notably larger average cell size and lower cell endothelial density. Furthermore, it was noted that all the patients underwent a full eye exam, which consisted of visual acuity test, auto-refraction, slit lamp bio-microscopy and non-contact tonometry and the morphological changes in the cornea to be investigated, such as the average cell size and endothelial density, were assessed using SP-3000 Specular Microscope.

This article remarkably relates to this present research study as it assessed the endothelial layer of the cornea which this study also aimed to assess as well. It revealed that this present study hypothesis may be proven as false. In addition, it provided results on the correlation among the duration of one's diabetic status and the effects it has on the average cell size, and cell endothelial density. Thus it can be assumed for the present study that the duration of one's diabetic status affects the corneal morphological findings.

Another research article, done in 2015, titled, 'A comparative study of corneal endothelial structure between diabetes and non-diabetes,' by Leelawongtawun W et al [4], supported the above online resource as the research concluded that 'there exists no statistically significant difference in the endothelial layer between the two groups although findings did show changes between the two groups[4].' This research was conducted on a smaller sample size than the one above at the Thammasat University in Thailand which is southeastern of Asia, where 180 subjects were used which consisted of, 90 diabetic patients with an estimated history of diabetes for 6 years and 90 non diabetic patients. Both groups had subjects who were between the ages of 40-91 years. All the subjects endothelial layer was assessed using Confoscan4 (CS4) Specular Microscope.

Based on this study, it further showed that the duration of one's diabetes is another main factor in the decreased findings of the endothelial layer of the cornea with respect to the hexagonal cell size and polymegathism as the disease progressed. It also concluded that there exists no difference in the endothelial cell density as the disease progressed. This article relates to this present study as it also assessed the endothelial layer of the test subjects providing added information on the effects the duration of diabetes has on the findings.

The following article below, not only focused on the endothelium layer as the previous articles did but also investigated the epithelium layer, by assessing central corneal thickness changes. The

research article titled ‘Corneal endothelium and central corneal thickness changes in type 2 diabetes mellitus’ was conducted by El-Agamy A and Alsubaie S and was published in 2017’ [5] This study consisted of 102 patients in total, with 57 patients with type-II diabetes (27 males and 30 females) and 45 controlled patients (22 males and 23 females). The age ranged between 40-80 years. This research study was conducted at the Sulaiman Al Habib Hospital in Saudi Arabia, in southwestern Asia.

The results obtained provided the assumption that the sample size is not a main factor in determining statistically significant results given that in this study there were statistically significant changes between the endothelial layer in the diabetic and non-diabetic patients among the 102 subjects assessed. The decreased endothelial cell density and increased polymegathism of endothelial cells were statistically significantly. With respect to the epithelium layer, the central corneal thickness was thicker in diabetics compared to non-diabetic patients. However, the statistical analysis of the results showed that the change was not statistically significant to be considered, in addition to decreased hexagonal endothelial cells[5]. This article relates to the present study as it is focused not only on the endothelium layer of the cornea as the preceding articles but also the epithelium layer, which is also one of the primary focuses of the present study.

Another article, entitled ‘Corneal endothelial morphology and central thickness in patients with type II diabetes mellitus’ by Allan Storr-Paulsen et al[6], concluded that there existed statistically significant increased central corneal thickness in diabetics compared to non-diabetics. However, it also concluded that there were observable changes in the corneal endothelial morphology, such as reduced endothelial cell density and increased polymegathism but similar to other research studies, these findings were insignificant statistically.

This research study was conducted at Frederiksberg University Hospital in Denmark which is located in northern Europe. 235 subjects were tested, 107 subjects were type II diabetics and 128 subjects were non-diabetic. Corneal endothelial morphology which consisted of the endothelial cell density, the variation in endothelial cell size (CV) and the percentage of hexagonal cells were measured using a SP 2000P Topcon Specular Microscope. This study did investigate HbA1 values in the subjects and revealed that increased values in diabetic patients, which were four times the non-diabetic values correlated to decreased endothelial cell counts, though not statistically significantly. Other variables which were included such as age, gender, visual acuity and intraocular pressures of the subjects showed no significant differences between the groups and there were also no correlations of these variables to the findings of the study's topic. This study further discussed similar studies from 1996 to 2008 which showed statistically significant changes in the corneal endothelial layer and central corneal thickness between diabetics and non-diabetics and others which expressed that there were no statistically significant changes in the findings between the two groups. These studies mentioned had differing sample sizes which alludes that sample size is not necessarily an important factor in these research findings. This article relates to the present study as it also focused not only on the endothelium layer of the cornea but also the epithelium layer, which are the primary focuses of the present study.

The variability in the different articles aforementioned showed that though structural changes are observed, whether on the epithelial or endothelial layer, statistically it may not be significant. These studies showed that there are inconsistencies in the results findings of this research and thus there exists no one standard expected result to statistically reason if corneal morphological changes exists between diabetic and non-diabetic patients significantly.

These studies further showed that assessment of different factors such as HbA1c values and duration of one's diabetic status should be considered in future research.

Chapter 3 Methodology

3.1 Research design

This research study design was originally that of a case-control, analytical, prospective and quasi-experimental study design, used to investigate if there exists any corneal morphological differences between the diabetic and non-diabetic population at the UWI Optometry Clinic. Quantitative data was thus expected to be collected throughout the time frame of this project in the form of a questionnaire and through different tests conducted at the clinic.

However, due to the COVID-19 pandemic that has taken place the study design is now qualitative where expected results are simulated.

3.2 Study population

The study population was expected to consist of adult, patients and/or students of the UWI Optometry Clinic, Trinidad, West Indies.

3.2.1 Area of study

This study was expected to be conducted at the UWI Optometry Clinic, located at the Couva Hospital and Multi Training Facility in Preysal, Couva. This area is multiracial and multi-religious similar to most parts of Trinidad. However, it consists of approximately 57% of East Indians. The country's main language is English, which is also the language of persons in Couva. In 2016, Couva was referred to as the third largest region out of nine in Trinidad and Tobago with an estimated population of over 170,000 inhabitants. This area was generally known for its cocoa and sugar production but its production has lessened drastically over the years[7].

Although the area of study is in Preysal, Couva, the study population is not only subjected to persons from this area as the clinic is open and easily accessible to all persons of Trinidad and Tobago.

3.2.2 Inclusion criteria

This was expected to consist of the study or test group and the control group.

The study group entailed subjects with: type 1 or type 2 diabetes, between the ages of 18 to 90 years old. All ethnicities and gender are accepted. These subjects would have been patients who attend UWI Optometry Clinic.

The control group entailed subjects who do not have diabetes, between the ages of 18 to 90 years old. All ethnicities and gender are accepted. These subjects would also have been patients or students who attend UWI Optometry Clinic.

3.2.3 Exclusion criteria

Subjects screened at the clinic would have been excluded from the sample size if they showed any of the following for the given groups.

Study group: Pregnant women, subjects with any history of eye surgeries or trauma, contact lens users, subjects with keratoconus and subjects with astigmatism greater than -0.75 DC.

Control group: Pregnant women, subjects with any history of eye surgeries or trauma, contact lens users, subjects with keratoconus and subjects with astigmatism greater than -0.75 DC.

3.3 Sample size and sampling technique

3.3.1 Sample size determination

Raosoft sample size calculator was used to determine the estimated sample size. A population size of 2000 subjects in total from the clinic was used; along with a confidence level of 95% and a 5% margin of error, this produced a recommended sample size of 323 subjects. The minimum sample size calculated is 239 subjects and the maximum sample size is 499 subjects. The estimated number of subjects to be screened is 323. However, to cater for drop-outs and subjects that do not meet the inclusion criteria, 400 subjects would have been screened. 300 subjects were expected to be enrolled.

3.3.2 Sampling technique

It was expected that subjects will be recruited based on appointments at UWI Optometry Clinic only. Given that the clinic sees approximately 340 patients per month, it was feasible enough at the time to screen 400 patients during an estimated two to three months period, catering for drop outs or uninterested persons. Out of the patients screened, a sample size of 300 subjects would have been enrolled once they fit the inclusion criteria, where 150 subjects will be recruited as the control group and another 150 subjects as the study group. Also, because most of the students showed characteristics of the inclusion criteria, it was also expected that most of the students would have possibly volunteered to assist in the study. During the appointments, if the patient fit the inclusion criteria they would be asked after their appointment is completed if they will like to participate in the project.

It would have been crucial to ask them after their appointment rather than before so that they do not think that by saying 'no' their appointment would be jeopardize in anyway. Given that most of the tests would have been completed during the eye exam, the subjects would have been asked if they are willing to complete an additional test that is not standard procedure but experimental. Once agreed, the consent form will be given to them.

3.4 Ethical consideration

Firstly, the co-investigators were given permission to conduct a research on the topic mentioned by the Optometry Unit and a supervisor/principal investigator was assigned. From here, the co-investigators and the principal investigator under one form applied for ethical approval to the UWI ethics committee. The UWI ethic committee granted the investigators permission to conduct the research on December 9th 2019. An approval letter was provided (see Appendix, Image 4) in addition to the patients' consent form to participate, as well as an experimental subjects' right document. (See Appendix, Image 5 to 8)

In addition, all standard test results for each participant will be provided immediately to them upon completion of the eye examinations.

Due to the nature of the study, there existed low potential risks and these would have been possibly visual discomfort due to bright lights from the various testing methods. In respect to this, if subjects did experience visual discomfort, they would have been permitted breaks from the light source between various tests.

If any an adverse event occurs were to occur for unknown reasons, standard medical care for Optometry will be followed, although it is highly unlikely that any adverse effects were to occur.

In addition, to ensure patients' confidentiality during the duration of the experiment, the names of patients recruited would have been kept separate from the patients' record numbers. The patients' record number would have been an assigned unique identifier number which will be entered on the data collection sheet to prevent bias during the analysis of data. The data from the data collection sheets would have been stored on a password encrypted, protected, computer of the principal investigator and would have been accessed only by the investigators in the study. The paper based copies used for collection of data will be stored in a locked storage cabinet belonging to the principal investigator for a minimum of five years after which materials will be destroyed.

3.5 Tests and instrument/equipment

The tests and instrument/equipment that would have been used in this study is as follows:

- visual acuity testing of distance and near vision using Snellen charts

  This test would have been done to determine how well the subjects can distinguish letters at both near and far, thus determining their visual status in each eye. The results from this test would then be analyzed to mainly observe whether the patient's diabetic status affects their visual acuity or not, which in turn either affected their corneal structure or not. Also, based on results from the questionnaire it could have also shown if there is correlation between the above and the duration of the patients' diabetic status.

- autorefraction of the subjects' prescription using the autorefractor machine

  This test is done to obtain an automatic reading of patients' prescription, as there is an exclusion criteria of subjects' prescriptions with astigmatism greater than -0.75 DC.

  The results from this test would then be analyzed to observe whether the patient's diabetic status affects their prescription or not which in turn affects their corneal structure or not.

Also, based on results from the questionnaire it could have also shown if there is a correlation between the above and the duration of the patients' diabetic status.

- glucose monitoring test using a glucometer kit to record the subjects' glycemic index

  This test would have been done to evaluate the blood sugar levels of the non-diabetics, the controlled and poorly controlled diabetic patients. The results from this test would then be analyzed to observe whether the patient's diabetic status affects their corneal structure or not. Also, based on results from the questionnaire it could have also shown if there is a correlation between the above and the duration of the patients' diabetic status.

- blood pressure monitoring using an automatic, digital sphygmomanometer

  This test would have been done to evaluate the blood pressure levels of the non-diabetic and the diabetic patients. The results from this test would then be analyzed to observe whether the patient's blood pressure level in the diabetic subjects is affected by their diabetic status which in turn affects their corneal structure or not. This would have been tested as it assumed that diabetic patients may also suffer with hypertensive conditions.

- intraocular pressure (IOP) test using the non-contact ocular response analyzer (ORA) machine

  This test would have been done to measure the intraocular pressures of the eyes as a buildup of glucose in the blood can lead to the obstruction of blood vessels in the eye, which can result in detrimental changes to the eye.

  Thus the results would have enabled us to analyze if there is a trend between the test and control groups. In addition to that, the results analyzed would have allowed us to observe whether the intraocular pressure in the diabetic subjects affects their diabetic status or vice versa which in turn may affect their corneal structure or not. Also, based on results from the questionnaire it could have also shown if there is a correlation between the above and the duration of the patients' diabetic status.

- non-contact topography using the Topographer machine to assess corneal curvatures

  This test would have been done to assess if there is any structural changes to the epithelium layer of the cornea. It would have further allowed analysis of any trends that may or may not exist between the subject and control groups. In addition, one would be able to decipher among the subject group if there is a correlation between the above and the duration of the patients' diabetic status based on results from the questionnaires as well.

- pachymetry using the optical coherence tomography (OCT) to assess corneal thickness

  This test would have been done to assess if there is any changes to the central corneal thickness between the two groups.

The findings of test would have also been used in the analysis of the diabetic group to determine if there is an effect between the duration of diabetes and the central corneal thickness.

- specular microscopy using a specular microscope CEM-530 to assess the corneal endothelium layer.

  This test will be done to assess the endothelial layer of the cornea between the two groups. The corneal endothelial layer of diabetics and non-diabetic patients would be analysed based on endothelial cell density, hexagonal cell percentage, average cell size and coefficient variation of cell size. The findings of this test would have also been used in the analysis of the diabetic group to determine if there is an effect between the duration of diabetes and the corneal endothelium layer.

- Patient record cards, questionnaire forms and data collection sheet would have been used as well

3.6 Data collection procedure

If data would have been collected, the following procedure would be followed.

Once the patient consented to participate in the research study after filling out the consent form, and after completing the questionnaire, the results would have been obtained by transferring the needed information from the standard procedure results from the patient record cards followed by completion of the experimental procedures which in this study would have been Specular microscopy.

The visual acuities would have been recorded during the case history section as well as the glycemic index and blood pressure levels. After these, the IOP readings using the ORA would have been measured followed by use of the AR machine given that these equipments are in the same room. Pachymetry measurements would have been recorded followed by the Topography readings, as these equipment are also in the same room. These accounts for the standard procedure of every eye examination. Specular microscopy would have then been conducted.

3.7 Data analysis

If data were collected, the data would have been analyzed using the Statistical Package for Social Sciences (SPSS) software version 24.0 for windows. Descriptive statistics would then be used to generate descriptive analysis of continuous variables and frequencies for nominal variables. Contingency chi-square test would be used to assess the association and t-test for continuous variables. If a p-value of less than 0.05 was obtained this would have indicated a significance level at a 95% confidence interval (CI) and this would have proven the hypothesis.

Chapter 4 Results

Analysis of results has been subjected to change, to the assessment of results from previous studies that relates to the changes of the corneal morphology between diabetics and non-diabetics. In this study a series of test were listed to assess corneal topography, corneal thickness, visual acuity, corneal endothelium cell density, endothelial cell size variation and endothelial cell hexagonality readings. Studies done in the past were therefore used to simulate this study expected results which would aid in determining if any trends or patterns were likely to be observed. These trends that would have been identified would help determine if there is a difference in corneal epithelial and endothelium morphology of diabetics who may have controlled or uncontrolled diabetes and also non-diabetics.

Expected results

Best case scenario will look at findings that would support this study hypothesis whereas worst case scenario would have disproved this study hypothesis.

Expectation 1: Topography Readings

Best case scenario

Diabetic patients would be observed to have higher K values and thus steeper corneas than the control, non-diabetic group, with an estimate of 7.62 mm in diabetics and 7.65 mm in the control group. There would also be a correlation with an expected reduction in visual acuity.

Worst case

No research has been conducted to disprove that corneal curvature is not affected by diabetes, therefore providing lack of results that would contradict the hypothesis.

Expectation 2: Specular microscopy readings

Best case scenario

It would be expected that in diabetics there would be a decrease in corneal cell density with an increase in cell hexagonality and cell shape. There can also be no expected change in cell density with an increase in cell hexagonality and variation in cell size. It would also be expected to observe an increase in cell variation for patients with a higher diabetic status than for those with a shorter duration of diabetic status.

Worst case scenario

Previous studies were able to correlate no change in endothelial cell density, hexagonality and pleophormism between diabetics and the control group, this disproves the hypothesis that there are corneal morphological changes between diabetics and non-diabetics as there were no significant observable changes.

Expectation 3: Pachymetry readings

Best case scenario

Previous studies have shown a correlation between central corneal thickness with duration of diabetic diagnosis and also the diabetic status of the patients. Thus, there would be an expected increase in central corneal thickness for patients with a longer duration of diabetes, with an estimated increase of 4% in diabetics compared to the control group. Diabetics with poorly controlled blood glucose levels would also be expected to have a 2.1% increase when compared to the controlled group of diabetics.

Worst case scenario

Studies have been proven to contradict the research questions displaying that no observable change is noticed on the effect of diabetes severity, the subjects' duration of diabetes and the central corneal thickness. Thus there will be no expected increase and observable changes in the corneal thickness when the test and control groups are compared.

Expectation 4: IOP findings using the ORA

Best case scenario

It is expected to observe an increase in intraocular pressure of the diabetic population when compared to the control group. It is expected that there would also be a direct proportional increase of corneal endothelium damage to visual acuity. Increased corneal thickness would also correlate with an increased IOP reading.

Worst case scenario

It can be expected that there would be no observable correlation between corneal thickness, corneal endothelial morphology and IOP readings. In addition, there would be no recorded differences in intraocular pressure values between the test and control groups.

Expectation 5: Visual acuity values

Best case scenario

It is expected that a correlation would exist between a decreased visual acuity with the test group with poorly controlled blood sugar levels.

It is expected a correlation would be observed with an increased corneal endothelium cell changes in the diabetic group to an increase in intraocular pressure with approximately 2% decrease in endothelium cell density.

It is expected that a correlation would exist between the test group with an observable increased in central corneal thickness value and reduced visual acuity.

Worst case scenario

There are no studies to prove that diabetic changes in corneal shape do not affect one's visual acuity. Hence it can be assumed that there would not be a correlation between the test group visual acuity and corneal morphological changes.

Expectation 6: Blood sugar level

Best case scenario

It is expected that with poorly controlled blood sugar levels, IOP levels and central corneal thickness would be increased[8].

Worst case scenario

Studies have shown that there were no changes in corneal morphology between controlled blood sugar levels in diabetic patients and poorly controlled blood sugar levels in diabetic patients[9].

Chapter 5

5.1 Discussion

Diabetes is a systemic disease that causes a variable list of structural changes to the human's corneal morphology. The effective changes diabetes can incur on the cornea is known as diabetic keratopathy and it can be associated with the permanent loss of vision which is secondary to recurrent corneal erosion, persistent epithelial defects, scarring, long standing cornea swelling and keratoconjunctivitis sicca (KCS)[10]. Though these changes can occur there exist many more changes that can occur specifically to the corneal endothelial layer. The design of this study was constructed to investigate and compare any changes observed between diabetic and non-diabetic population with specific attention paid to the corneal epithelial and endothelial layer. There are observable changes in the monolayer of the corneal endothelium associated with a reduced cell density, cell shape and cell size[1, 4, 5, 6].

The observable changes that would have been recorded, would have been used to evaluate the research objectives which would have answered the research questions.

In previous studies conducted where the keratometry readings of diabetic and nondiabetic patients were assessed, it can be observed that diabetic patients had steeper corneas with higher keratometry readings[11, 12]. Therefore, in expectation 1: Topography readings, it can be suspected that expected k values of the diabetic population would be higher than those of non-diabetics population. This would have been observed as a significant difference of corneal shape on the topographical map of the cornea of the subjects, where a steeper cornea in diabetics would be observed due to the ability of diabetes to affect corneal aspherity[11].

Corneal endothelium changes were expected to be discovered between the diabetic and the non-diabetic population, where previous studies have aided in the determination of factors which needed to be assessed when comparing the endothelium morphology. These parameters were the cell density, the average cell size, the coefficient variation size and cells' hexagonality[1,4,5,6]. The effect diabetes has on the corneal endothelium is said to be due to oxidative and osmotic stress from over activation and accumulation of broken down glucose to sorbitol in the polyol pathway[13].

In Expectation 2: Specular Microscopy, in diabetic patients, it would have been expected to observe a statistically significant decrease in cell density and hexagonality with an increase in irregular cell size[14]. This would have been expected as there exists a wide variety of studies which expressed corneal endothelium morphology changes due to diabetes and this would have been taken into consideration if the study had been continued. However, in the worst case scenario, it is also expected that changes in cell density would have been observed but it could have been statistically insignificant as previous studies also expressed that there were decreased cell hexagonality and polymegathism[4], and also statistically insignificant differences in cell density, polymorphism or polymegathism and increased polymegathism between the non-diabetic controls and diabetic populations, but lastly, it was insignificant statistically[1]. Therefore, the best case scenario would have proven the hypothesis, thus answering yes to the research questions whereas the worst case scenario would have disproved the hypothesis, answering no to the research questions. In previous studies it was also expressed that patients with diabetic duration of over 10 years had more corneal endothelial morphological abnormalities, mainly the coefficient of variation in cell size, compared with the control subjects.

In expectation 3: Pachymetry readings, increased central corneal thickness would have been expected in diabetics as diabetes causes damage to the corneal endothelial pump due to a reduction

of adenosine triphosphate concentration produced by the Krebs cycle in the diabetic patient's cornea. These changes in morphology would therefore have resulted in swelling of the cornea and increased central corneal thickness[12]. Relating the best case scenario expected pachymetry results of the diabetic patients to their expected specular microscopy results, it can be assumed that there is no correlation. This can be considered from previous studies shown that evaluated the severity of the diabetic status of the patient and the duration of the disease which revealed significant changes in the central corneal thickness but not necessarily the corneal endothelial morphology. However, the central corneal thickness was significantly correlated with the diabetic duration of the patients[14].

This can be linked to the blood sugar level (BSL), expectation 6, where a poorly controlled blood glucose level leads to increased blood sugar levels and this damages the corneal endothelium resulting in increased central corneal thickness[8,9]. This expectation can help prove the hypothesis, which states there is a change in the cornea between controlled and uncontrolled diabetics, as increased corneal central thickness would comply with poorly controlled BSL levels. However to disprove the hypothesis studies have been conducted to show that there has been no effect of diabetes, its severity and duration, on the corneal central thickness[15,16].

The intraocular pressure was also assessed and was not initially suspected to provide a great difference to corneal morphological changes between the test and the control groups but it can be noted that changes in corneal hysteresis due to diabetes, would result in diabetic patient's experiencing a higher IOP reading when matched to the control group of non-diabetics, independent of central corneal thickness[17].

Previous studies show that there exists a correlation among IOP, specular microscopy and pachymetry readings, where an increase in IOP can lead to a decrease in corneal endothelial cell density and in return results in an increase in central corneal thickness[18].

Damage to the integrity of the corneal endothelium leads to reduce visual acuity, due to increase influx of liquid into the cornea and to a greater extent formation of bullous keratopathy, this assists in the observation of a significant difference in the corneal shape of diabetic patients and the control group and also it showed that due to this change patient vision can be affected as well as their ocular health[19].

Poor visual prognosis is a result of poorly controlled blood sugar levels, where the crystalline lens is affected and under osmotic properties swelling of the lens occurs and results in poor visual acuity[20]. This previous study have proven that diabetes changes the optical properties of the eye which relates to the cornea, tear film, lens and vitreous, which in turn gives rise to poor visual outcomes changes that correlates with visual acuity[21]. Changes in corneal morphology in the diabetic population can also be due to further changes of the corneal epithelium basement membrane and endothelium membrane which results in an increase in corneal hydration. These corneal changes in long term diabetic patients relates to an increase in corneal optical density and subsequent decrease in corneal transparency[22]. A decline in corneal transparency over a duration is due to degeneration of corneal collagen fibers which lead to greater corneal optical density. As individuals age the fibers become glycosylated and it gets thicker and harder. In poorly controlled blood sugar levels, advanced glycation end products known as AGE, is concentrated in the epithelial basement membrane of the cornea's matrix. Damage of the cells structures are subsequent to the abnormal protein production by the decemet membrane, which results in local incrassation, multiple stratification and discontinuity.

Therefore the long duration of diabetes on the cornea leads to decreased corneal transparency and reduced visual acuity[22]. There are no studies which have been proven that diabetes has no effects on the visual outcomes of patients.

The factors assessed determined that diabetes do influence the corneal morphology to a variable extent of ways. It can also prove to show that there is a difference in corneal morphology between diabetics and non-diabetics. Also, previous studies helped indicate that diabetes can also have no effect on patient's corneal morphology, and it can be presented in individuals in the non-diabetic, control population. It can also be highlighted that assessment of the corneal morphology of diabetics should be regularly assessed as diabetes have multifaceted effects on patients' corneas, some of which can lead to detrimental effects in patients ocular and general health.

5.2 Conclusion

In this research study, the design was originally that of a case-control, analytical, prospective and quasi-experimental study design, used to investigate if there exists any corneal morphological differences between the diabetic and non-diabetic population at the UWI Optometry Clinic. However due to unprecedented circumstances of the pandemic COVID-19 no data was possibly ascertain, therefore research of previous studies relevant to the topic was used to aid in simulating expected results. The assets of the simulated results were then used to correlate findings to the research topic, the research questions and the research objectives. The simulated results determined that diabetes affects the cornea morphology of diabetics and non-diabetic controls in a best case scenario. It was seen that diabetes can increase the corneal steepness of diabetics and also increase central corneal thickness in those with a greater number of years of their diabetic status. The epithelium curvature would increase, and the endothelial cell density reduces along with or without the increase of cell polymegathism and pleomorphism. The diabetic population would have experienced a reduction in visual acuity when compared to the non-diabetics due to changes in the corneal morphology of diabetics. The epithelium and endothelium layers of diabetics are also observed to show a difference when compared to control and poorly controlled diabetic population. Other factors which affected the cornea also lead to the assistance of achieving the research objectives. Significant changes in corneal morphology such as increased central corneal thickness were also observed in diabetics with a poorly controlled blood sugar level. It is acceptable to imply based on research statistics of previous studies that corneal morphology in diabetics do show a variety of differences when compared to control, non-diabetic subjects.

5.3 Limitation of the study

This research study was limited due to the COVID-19 pandemic that is currently taking place and as such, the UWI Optometry Clinic is temporary closed and collection of data was ceased. Therefore, our results section was based on assumptions as to what would have occurred if data was collected. This made the project less scientifically sound in nature as there were no data and no statistical analysis of the data that would have proven whether the research hypothesis was accepted or denied.

In addition, if data was collected the results would have been limited as the test group consisted of diabetics who may have suffered from other systemic conditions as well such as hypertension. If this were the case, it would have been difficult to decipher if the corneal morphological changes observed were specifically from increased blood glucose level, from increased blood pressure levels or from both the conditions.

Furthermore, if majority of the corneal morphological changes were to occur among the older age groups, respectively 45 years and more, it would have been difficult to decipher if the corneal morphological changes observed were specifically from increased blood glucose level, from increased blood pressure levels or from both the conditions or in this case from age-related conditions. There are studies which have shown that corneal morphological changes that are expected to occur in diabetic patients, sometimes occur in older, healthy/normal patients[6]. This factor thus further limits the expected results.

Lack of local research studies on this topic is another limitation of this study. There were also lack of literature on correlation between corneal curvatures and diabetic patients.

There was however, literature that provided other corneal epithelial changes in the diabetic population such as decreased wound healing and decreased corneal sensitivity. Hence, this study was limited in its data collection method as slit lamp bio-microscopy was not included and thus a factor such as decreased corneal sensitivity was not investigated.

5.4 Recommendations

-Optometric practices should pay more attention to the cornea of diabetics as it can also become severely affected by increased blood glucose levels.

-The ministry of health can implement further preventative measures to reduce the incidence of type II diabetes in the country.

-Further research can be done in future where data collection and data analysis are conducted.

-Senior researchers or Optometric establishments can conduct this same research using a stricter sample size, i.e. diabetic patients without hypertensive conditions or any other systemic diseases in order to determine the exact correlation between diabetic patients and cornea morphological changes.

-Another group of senior researchers or another Optometric establishment can also conduct this research project using another sample size such as younger individuals diagnosed with diabetes between the ages of 18-35 years. This will determine whether corneal morphological changes observed in other studies correlated to the diabetic status of the patient or if it was due to age-related changes.

- Another group of senior researchers or another Optometric establishment can also conduct this research project, this time investigating if corneal morphological changes differ from diabetics with Type I or Type II diabetes.

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Appendix

Figure 1 below shows a copy of the data collection sheet for this study.

Comparison of corneal morphological characteristics between diabetic and non-diabetic population

DATA COLLECTION SHEET

Unique Identifier Number: **Date:**

Visual Acuity

	OD	OS	OU
DISTANCE	**20/**	**20/**	**20/**
NEAR	**20/**	**20/**	**20/**
ADD			

AUTO REFRACTOR (Rx) OD: **OS:**

GLYCEMIC INDEX

_____ mg/dL
Time (AST) (am/pm): _____

BLOOD PRESSURE:

Systolic pressure: _____

Diastolic pressure: _____

Pulse/min: _____

ORA
OD: _____

OS: _____

Time (AST) (am/pm): _____

TOPOGRAPHY
(With attached copy of topographical map of cornea)
K's
OD: _____
OS: _____

PACHYMETRY

OD CCT: _____
OS CCT: _____

SPECULAR MICROSCOPY

	OD	OS	Comments
Corneal endothelial cell density cells/mm^2			
Average cell size (micrometer^2)			
CV of size (%)			
Hexagonality (%)			

Comparison of corneal morphological characteristics between diabetic and non-diabetic population

Unique Identifier Number:

Please ensure you have read the consent form first before filling out this form.

This questionnaire serves as means of data collection on research of the corneal morphological changes between diabetic and non-diabetic population.
This research is overseen by The UWI Optometry Clinic and lead by year 3 research candidates. Below are questions that are critical to the present study and your honest answers to these questions will be greatly appreciated.
Your answers are strictly confidential, and at no given point in time is your name required.

Please return this questionnaire to any of the researchers upon completion.

For each question, different options would be given, please choose only one response by circling your answer.

1. Age
   - 20-29 years
   - 30-39 years
   - 40-49 years
   - 50-59 years
   - 60-69 years
   - 70-79 years
   - 80-90 years
   - Other: _____

2. Gender
   - Male
   - Female

3. Ethnicity
   - Indo-Trinidadian
   - Afro-Trinidadian
   - Caucasian
   - Mixed (Dougla)
   - Chinese
   - Other: _____

Image 1 above shows page 1 of the questionnaire.

Comparison of corneal morphological characteristics between diabetic and non-diabetic population

4. General Residing Area (e.g. Curepe, Cunupia):

_____

_____

5. Are you on any medication/eye drops?
- o No
- o Yes

If yes, please state the medications you are on?

_____ _____

_____ _____

_____ _____

6. How often do you get your eyes examined?

- o Every 1- 6 months
- o Every 6 months
- o Annually
- o Every 2 years
- o Once every 3 years or more

7. What is your educational level?
- o Primary School
- o Secondary School
- o Tertiary Level
- o Other _____

8. Are you currently diagnosed with diabetes?
(If no then proceed to question 13.)
- o Yes
- o No

Image 2 above shows page 2 of the questionnaire.

Comparison of corneal morphological characteristics between diabetic and non-diabetic population

10. Do you know what type of diabetes you have?
- o Type 1
- o Type 2
- o Not sure

11. How long have you been diagnosed with diabetes?
- o Less than 1 year
- o 1-3 years
- o 4-6 years
- o 7-9 years
- o 10 or more years

12. What would you say is your average (random) blood sugar level on a daily basis?
- o 79–140 mg/dL
- o 141 – 200 mg/dL
- o 201 mg/dL or more

13. Do you have a family history of diabetes?
- o Yes
- o No

If yes to the above question please tick your relation with said family member.

☐ Mother	☐ Son	☐ Other
☐ Father	☐ Sister	
☐ Daughter	☐ Brother	

You have now come to the end of the questionnaire.
Thank you for your time and cooperation!

Image 3 above shows page 3 of the questionnaire.

THE UNIVERSITY OF THE WEST INDIES
ST AUGUSTINE, TRINIDAD AND TOBAGO, WEST INDIES
CAMPUS RESEARCH ETHICS COMMITTEE
TEL.: (1-868) 662-2002 ext. 82755 E-mail: campusethics@sta.uwi.edu

December 9 2019

Mr. Niall Farnon (Josiah Ambris,Khachielle Farmer)
UWI Optometry Clinic, Gordon Street, St.Augustine
Email: niall.farnon@sta.uwi.edu

Dear Mr. Niall Farnon,

Ref: CREC-SA.0069/10/2019

Title: comparison of corneal morphological characteristics between diabetic and non-diabetic population

I am pleased to advise that your application for research on the above captioned topic has been approved on behalf of Campus Research Ethics Committee, St. Augustine.

Sincerely,

Surendra Arjoon (Prof.)
Chairman
Ethics Committee

Digitally generated by UWIScholar

Image 4 above shows a copy of the approval letter by the ethics committee.

THE UNIVERSITY OF THE WEST INDIES
ST AUGUSTINE, TRINIDAD AND TOBAGO, WEST INDIES
CAMPUS RESEARCH ETHICS COMMITTEE
TEL: (1-868) 662-2002 ext. 82755 E-mail: campusethics@sta.uwi.edu

CONSENT TO PARTICIPATE IN RESEARCH

Complete Protocol Title: comparison of corneal morphological characteristics between diabetic and non- diabetic population

Principal Investigator: Mr. Niall Farnon

Co Investigator(s): Josiah Ambris,Khachielle Farmer

Research Sites: EyeNet Limited,Uwi Optometry Clinic

Sponsors: There are no sponsors for this research study.

Why is this research being done?

This research is being done so as to understand the effects diabetes has on the front of the eyes due to the rapid increase in the diabetic population in Trinidad and Tobago.

What is the duration of taking part in the study (for each subject)?

You will be here for one (1) hour whether you are in either group.

What will happen to me?

You will undergo a series of routine eye examination tests that are non-invasive.

What is in in for me?

Your cooperation in this study will provide the researchers with results that will benefit future patients that are at risk for diabetes or those already diagnosed with it, as better management of diabetic patients can be implemented.

What will happen if I drop out of the study early?

Nothing will happen to you.

What are my responsibilities if I join and what about confidentiality?

You are responsible for answering any questions asked honestly. Your confidentiality will not be breached as you will be given a number that is unique to you that only the researchers can identify you by, as your name will not be recorded on the data collection sheet and

Image 5 above shows page 1 of the consent form.

questionnaire.

What if I get hurt in the study?

You will not get hurt, however if an emergency arises there are trained lecturers who will be present for each measurement taken to assist if the need be.

CONSENT

I have read and understood this explanation. The researcher has also explained the study to me. I have had a chance to ask questions and have them answered to my satisfaction. I agree to take part in this study. I have not been forced or made to feel like I had to take part.

I have read the attached experimental Subject's Rights, which contain some important information about research studies. I have also read the Authorisation to use my Private Health Information. **I must sign this Consent Form, the Experimental Subject's Rights and the Authorisation to use my Private Health Information. I will be given a signed copy of each to keep**.

Print Name of Subject

_____

Signature of Subject Date

_____ _____

Signature of Person conducting the informed consent discussion Date

_____ _____

Role of person named above in the research project

_____

Signature of Second Witness Date

_____ _____

Image 6 above shows page 2 of the consent form.

By Chairman:

This document was approved by Campus Ethics Committee on:
December 9 2019
This document expires on:
2020-05-30

EXPERIMENTAL SUBJECT'S RIGHTS

If I am asked to consent to participate as a subject in a research study involving a medical experiment, or if I am asked to consent for someone else, I have the right to:

1. Learn the nature and purpose of the experiment (also called "study" or "clinical trial").
2. Receive an explanation of the procedures to be followed in the study, and any drug or device used.
3. Receive a description of any discomforts and risks that I could experience from the study.
4. Receive an explanation of any benefits I might expect form the study.
5. Learn about the risks and benefits of any other available procedures, drugs or devices that might be helpful to me.
6. Learn what medical treatment will be made available to me if I should be injured as a result of this study.
7. Ask any questions about the study or the procedures involved.
8. Quit the study at any time, and my decision will not be used as an excuse to withhold necessary medical treatment.
9. Receive a copy of the signed and dated consent form.
10. Decide to consent or not to consent to a study without feeling forced or obligated.

If I have questions about a research study, I can call the contact person listed on the consent form. If I have concerns about the research staff, or need more information about my rights as a subject, I can contact the Principal Investigator, The University of the West Indies at: niall.farnon@sta.uwi.edu, 2251016.

By signing this document, I agree that I have ready and received a copy of this document.

Image 7 above shows page 1 of the experimental subject's right.

Signature of Subject or Legal Representative | Date

REQUEST FOR PERMISSION TO USE AN INDIVIDUAL'S PRIVATE HEALTH INFORMATION

Name of Study: comparison of corneal morphological characteristics between diabetic and non-diabetic population

Investigators: Mr. Niall Farnon, Josiah Ambris,Khachielle Farmer

What is private health information?

Private health information is any information that can be traced back to you. We need your permission to use your private health information in this research study. The type of private health information that will be used and shared for this study includes:

- Your past and present physical and mental health information
- Information that can be used to contact you
- Results of your medical tests and DNA
- Questionnaires and information on your drug/alcohol usage and that of your family.

Who else will see my information?

Only the researchers, principal and co-investigators, will view your information.

How long will the investigators use and share my information?

For five years or until the information is published.

What if I change my mind about sharing my research information?

Your information will not be published.

Do I have the right to see and copy my research information?

Yes you do.

If you agree to share your information, you should sign this form below. You will receive a copy of this form.

I agree to share my information as described in this form

Print Name | Signature | Date

If you have questions or concerns about your privacy and the use of your personal medical information, please contact the investigator at the telephone number listed in the consent form.

Image 8 above shows page 2 of the experimental subject's right.