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Optic Nerve Head Structural Response to IOP Elevation in Patients with Keratoconus

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Study Intervention: In-vivo investigation of ocular structure under elevated intraocular pressure using OCT in keratoconus

IRB Number: 17-01360

List of Abbreviations

AMD – Age related macular degeneration
FDA – Food and drug administration
IOP – Intraocular Pressure
NYU – New York University
OCT – Optical coherence tomography
ODM- Ophthalmodynamometer
ONH – Optic Nerve Head
ORA – Ocular Response Analyzer
UPMC – University of Pittsburgh medical center
VF – Visual field

Study Summary

Title	Optic Nerve Head Structural Response to IOP Elevation in Patients with Keratoconus
Short Title	Keratoconus and IOP elevation Study
IRB Number	17-01360
Study Type	Human study
Study Design	Prospective experimental study
Study Intervention	In-vivo investigation of ocular structure in eyes with keratoconus under elevated intraocular pressure
Study Duration	Indefinite
Study Location(s)	NYU Department of Ophthalmology: Faculty Group Practice
Primary Objective	To examine in-vivo how lamina cribrosa in subjects with keratoconus respond to increasing intraocular pressure
Sample Size	230 subjects
Diagnosis and Main Inclusion Criteria	Subjects diagnosed with keratoconus or glaucoma
Control / Comparison	None
Statistical Methodology	Mixed effect models for the comparison between keratoconus and glaucomatous eyes

1. Introduction

This study will be conducted in compliance with the protocol approved by the IRB, GCP guidelines, and applicable NYUMC and federal regulatory requirements.

Background

Glaucoma is a leading cause of blindness worldwide and its prevalence tends to increase (1). Intraocular pressure (IOP) is the primary risk factor for the development and progression of glaucoma, however the mechanisms of damage on tissues of the eye remain unclear (2). The optic nerve head (ONH) was proposed to be a biomechanical structure where the influence of IOP-related connective tissue stress and strain plays a central role in the pathophysiology of glaucoma acting on the ONH connective tissues including the lamina cribrosa (LC), on its axons and on its cellular components (3). Some eyes have characteristics that may render them sensitive to IOP and more likely to develop glaucoma and other eyes present more resilient to IOP and more prone to present with hypertension only (4).

Keratoconus is a frequently occurring asymmetric non-inflammatory disease of the cornea characterized by thinning and ectasia. Its etiology is unknown and it affects mainly the central cornea (5). Histopathological findings of keratoconus explants may explain biomechanical abnormalities such as decreased elastic strength and abnormal shear behavior (6-8). The biomechanical properties of the cornea are currently accessed with the ocular response analyzer (ORA) that is based on a dynamic bidirectional applanation process. This device measures the corneal hysteresis (CH) and the corneal resistance factor (CRF). Studies show that keratoconus has decreased CH and CRF (5, 9).

Optical coherence tomography (OCT) enables tissue pathology to be imaged in situ and in real time with a resolution approaching that of conventional histopathology, but without the need for excising and processing specimens. Over the course of the years, we and other groups have demonstrated the excellent diagnostic ability of OCT, and the technology has become the cornerstone of clinical management in ophthalmology worldwide and the number of publications using this technology has soared exponentially in recent years (10, 11). OCT has been approved by the Food and Drug Administration for use in ophthalmology. The device provides accurate and reproducible measurements of tissues of interest in the eye (12). These properties enable improved diagnosis and longitudinal assessment for ocular disease such as glaucoma, age related macular degeneration (AMD), diabetic retinopathy (DR) and macular edema (13-16). Extensive studies have been performed with OCT examining both cross-sectional as well as longitudinal patient populations (17). Our group has published more than 100 peer-reviewed manuscripts focusing on the use of this technology in ocular diseases (18, 19).

Considering that the cornea and the LC are predominantly composed by collagen and elastin fibers, the defective corneal properties might also affect the LC reflected by abnormal response to biomechanical modulation. In the present project, our objective is to evaluate with OCT of the optic nerve head the response to IOP elevation in eyes with keratoconus, with glaucoma and in controls using commercial and prototype ophthalmic OCT imaging instruments in order

to assess the biomechanical properties of the ONH structures including the LC. This project complements our ongoing research on the LC response to pressure modulation in healthy and glaucoma (IRB protocol under review) and in animal models.

Study Rationale

The mechanism by which vision loss in glaucoma occurs is still unknown, but it is clear that increased IOP is a major risk factor. It is also thought that the LC is a site of primary damage during the pathogenesis of the disease. We would like to determine the in-vivo mechanical response to IOP modulation at the level of the ONH and LC. Subjects with keratoconus exhibit abnormal collagen properties that can impair their LC behavior. By evaluating their lamina biomechanical response we can advance our understanding on the role of the lamina in glaucoma pathogenesis. A better understanding of the process will ultimately lead to improved detection and management of glaucoma.

The study design involves a short increase in IOP and imaging with prototype OCT devices to examine the response of the LC to elevated pressure. These devices adhere to all American National Standards Institute safety requirements and do not pose any risk to the participants. The length and magnitude of the pressure elevation in our study design has been previously used, and did not cause any short or long- term damage.

2. Study Objectives

To study the differences in optic nerve microstructure and biomechanical features between keratoconus and glaucomatous eyes. We hypothesize that subjects with keratoconus have an abnormal biomechanical response of the lamina cribrosa in response to IOP modulation.

3. Study Design

This is a prospective, non-randomized, consecutive, experimental study.

4. Participant Selection, Enrollment, and Withdrawal

Study Population

We aim to enroll 230 subjects including subjects diagnosed with keratoconus or glaucoma (115 in each cohort). There will be no enrollment restrictions based on gender, ethnic origin or HIV status and the study population will reflect the demographics of NYU Department of Ophthalmology.

Inclusion Criteria

Candidates must meet the following inclusion criteria in order to participate in the study.

- Ages 18 and older
- Ability to provide informed consent and to understand the study procedures

And have a diagnosis of either:

Keratoconus:

- Clinical diagnosis of keratoconus
- Central thinning of the cornea
- Abnormal posterior ectasia.

Or:

Glaucoma:

- Glaucomatous ONH abnormality: rim thinning, notching, undermining (excavation) or diffuse or localized RNFL defects that are characteristic of glaucoma.
- Two consecutive abnormal SITA standard perimetry tests with GHT outside normal limits.

Exclusion Criteria

Candidates that meet any of the exclusion criteria at baseline will be excluded from study participation.

- Media opacity (e.g. lens, vitreous, cornea).
- Strabismus, nystagmus or a condition that would prevent fixation.
- Diabetes with evidence of retinopathy.
- Previous intraocular surgery or ocular trauma.
- Neurological and non-glaucomatous causes for visual field damage.
- Any intraocular non-glaucomatous ocular disorders.

Participant Recruitment, Screening and Enrollment

Subjects will be enrolled consecutively from NYU Department of Ophthalmology from the investigator's and the research team's clinics. Eligibility will be determined based on the results of a patient's eye examination, and all qualified subjects will be offered to participate in the study. Study team members will approach participants during their routine examinations at NYU Department of Ophthalmology. To maximize recruitment, eligible subjects may also be contacted via IRB-approved messaging through the NYULH MyChart portal in Epic.

The consent will be obtained after thorough explanation of the study to the participant by the clinician and/or study team member. The participant will be encouraged to ask questions and offered to spend as much time as needed to review the consent with the guidance of the study team member. We will emphasize that participation is voluntary. Documentation of the informed consent process will be used to ensure that the appropriate questions have been asked to the perspective participant. Only study personnel will conduct the consenting process. For candidates who are not fluent in English, NYU translation service will be used to ensure that the candidate fully understands the study and the consent. While the short form will be used with an interpreter, if we encounter a subject who meets inclusion criteria and speaks a language other than English, we will ensure that if more than 10% of prospective subjects per language speak a language other than English, we will amend the submission to include a consent form translated to that particular language.

The site will enroll NYU employees, including those working within the Department of Ophthalmology. Employees listed on the delegation log as study team members will not be enrolled into the research study.

The study assessments/procedures will take place at the NYU Langone Eye Center.

To minimize undue inducement, IRB approved advertisements will be distributed and displayed at IRB approved locations. Interested employees will approach the study team to discuss the study and if they are interested, the informed consent process will take place prior to any study related procedures. The study team member will emphasize that participation is voluntary. The person obtaining consent will also emphasize that the volunteer's decision will not affect their employment within NYU Langone Health and/or NYU School of Medicine.

Participation in the study and data collection will be possible only after subjects have signed consent.

Early Withdrawal of Participants
There are no anticipated circumstances that would lead to discontinuing a subject's participation in this research study.

Subjects may withdraw their consent for participation in this research study at any time. Any identifiable research or medical information recorded for, or resulting from, subject participation in this research study prior to the date that subject formally withdrew consent may continue to be used and disclosed by the investigators for the purposes described above.

5. Study Intervention
Participants will be examined by an ophthalmologist using conventional techniques. The eye examination (which is standard of care) includes recording medical and family history, visual acuity testing, axial length, intraocular pressure and central corneal thickness measurements, slit lamp examination, dilated slit lamp examination with stereo biomicroscopy of the optic nerve head and nerve fiber layer, indirect ophthalmoscopy, and visual field testing. This is followed by imaging of the cornea with Pentacam, hysteresis evaluation with ORA, stereophotography of the optic nerve head, macula and nerve fiber layer optical coherence tomography (OCT) and anterior segment OCT (ASOCT) imaging with FDA approved and non-FDA approved devices (see below). The estimated time for this step is approximately two hours and will occur during a single visit.

The Department of Ophthalmology at NYU includes Pentacam and OCT as part of standard ophthalmic work-up. Every subject with keratoconus routinely undergoes scanning with Pentacam, and they will also have the hysteresis accessed with ORA, both are FDA approved and used as per their approved indication. Subjects with glaucoma routinely undergo imaging with OCT. OCT images will be acquired using commercial OCT instruments (FDA approved devices), and non-commercial instruments that have not been approved by the FDA. More information on the later devices are provided in the appendixes.

These devices are designed using all safety requirements as defined by American National Standards Institute's regulations. The non-FDA approved devices will be used to obtain physiological data, and are non-investigational in the context of this study.

As part of the routine examination, pupils will be dilated using dilating drops (tropicamide and/or phenylephrine hyrdrochloride). As part of routine clinical IOP measurement, numbing drops (proparacaine) will be used. In cases where the clinical evaluation did not include pupil dilation and pupil size prevents ocular imaging, dilating drops might be used for the purpose of imaging in the study.

All procedures will be performed by clinical or research staff.

Experimental procedure: The IOP will be measured with the Goldman applanation tonometer, and then the IOP will be increased using an ODM. Proparacaine drops, which are widely used during routine eye examinations, will be used during this procedure to numb the eye while the IOP is measured. ODM is an FDA approved device that allows an increase of force on the eye in a controlled fashion and is routinely used as part of neurophthalmic evaluation. Forces will be imposed on the eye while Goldman tonometry is used to measure the IOP to reach the target IOP between 20-35 mmHg. The procedure will take five minutes.

OCT scanning will be obtained at baseline and with increased IOP. The IOP elevation will last no longer than two minutes, during which scans will be acquired by the imaging device. This stage will take 10 minutes.

The subject will be tested by clinical or research staff under the direct supervision and direction of the principal investigator or co-investigators. All devices in this study are FDA-approved with the exception of the investigational OCT devices and multi-modal adaptive optics system; see Appendix). None of the systems in this study are considered investigational, nor do any of the devices produce harmful radiation.

Devices

1. Ophthalmodynamometer
The ODM (Baillart ophthlmodynamometer, W. Koch Optik, Zurich, Switzerland) is a disc attached to a piston that induces a controlled force on a fixed area. The device will be used to apply a pressure within the range of 20 mmHg - 35 mmHg 4 times to each eye. Each increase of pressure will last approximately 30 seconds. The device is FDA approved and will be used as routinely used in clinical practice.

2. Goldmann Applanation Tonometer
The Goldmann applanation tonometer (Haag-Streit, Basel, Switzerland) measures the IOP after the eye is numbed with a drop of anesthetic (proparacaine), which is approved by the FDA. Proparacaine is part of routine patient care using a tonometer regardless of participation in this study. The instrument's tip lightly touches the surface of the cornea and the IOP is measured. The device is FDA approved is routinely used in clinical practice.

3. Pentacam

This device (Pentacam HR; Oculus Optikgerate GmbH, Wetzlar, Germany) maps the cornea and provides pachymetry, topography and corneal aberration maps. The device is FDA approved and routinely used in clinical practice.

4. ORA
ORA (Reichert Corp, Buffalo NY) is an air puff tonometer that applies controlled force to flattens the cornea and provides the corneal hysteresis and corneal resistance factor. The device is FDA approved and routinely used in clinical practice.

5. Optical Coherence Tomography (OCT)
OCT is a non-contact, real-time, high resolution, and reproducible imaging modality that provides in-vivo optical cross-sectional scanning of the retina, the ONH and of the anterior segment structures including the cornea. Some are FDA approved and used for their approved indications. The other OCT systems and the multi-modal adaptive optics system used in this study have not been approved by the FDA, but are not being used in a way that would cause significant risk to subjects. Their use is for obtaining physiologic data, not for clinical investigation. Clinical staff will perform subject testing, not research coordinators. Information about these non-FDA approved OCTs and the multi-modal adaptive optics system can be found in appendices. With all devices, the participant sits in a slit lamp like frame. A low power laser light is projected toward the back of their eyes while the subject fixates on a target. None of the systems produce harmful radioactive radiation.

6. Statistical Plan
The data will be divided into two groups according to the clinical diagnosis: subjects with keratoconus and with glaucoma. Baseline ONH location and shape will be compared to IOP stressed location and shape by mixed effect models.

Based on unpublished pilot data, an increase in cup depth of approximately 13µm in response to acute IOP elevation is anticipated. To detect a difference of 13µm in cup depth with an experimental error of 0.07µm, a sample of 230 subjects with keratoconus and glaucoma has a power of 80% (5% level of significance).

Analysis Methods
The ONH and peripapillary region scans by OCT will be evaluated for tissue deformation, decrease in the rim area, increase in cup depth and changes in the lamina cribrosa structure. . Outcome measures will evaluate the aforementioned expected deformations of the LC in microns. These micron measurements will be obtained from in vivio OCT images.
Cornea will be evaluated for anterior and posterior curvatures, aberrations, pachymetry and hysteresis.

Mixed effect models will be used for longitudinal analysis accounting for the use of information from both eyes for some subjects. Custom analysis techniques will be utilized to measure differences in ocular structures, especially the LC, under different pressure conditions.

7. Safety and Adverse Events

Risks and Discomforts

There is a risk of blurred vision and difficulty in near vision operation (e.g., reading and writing), which is common, due to the use of dilating drops (tropicamide and/or phenylephrine hyrdrochloride). The effects of these drops will disappear within 3-4 hours after instillation. The participant may be asked to remain in the clinic in the event that they experience blurred vision and do not have an accompanying person.

Pupil dilation may cause an increase in eye pressure or the possibility of an angle-closure event, which happens in a rare configuration of eyes. All subjects will be examined clinically before dilating drops are instilled to identify eyes at risk, in which case no dilation drops will be used. If either of these risks should occur, the subject will be treated immediately with eye drops at no cost. There is a rare risk of an allergic reaction to the drops, as with any drug or medication.

Ophthalmologic OCT imaging is performed in a non-contact fashion, so there is minimal risk of infection to the participant. To reduce the possibility of eye infection, all exposed surfaces near the eye, as well as the chin rest and forehead rest of the instrument, will be cleaned with alcohol before participants are examined. The risk of infection is low.

Imaging will be performed using commercial (FDA approved) and non-commercial (non-FDA approved) imaging instruments. All devices are subject to standard medical regulatory and safety requirements and adhere to the American National Standards Institute safety standards for the use and exposure to lasers. There is no known cumulative risk for repeating OCT scans multiple times on the same day or on different days.

Infrequent risks from the IOP elevation using the ODM include corneal abrasion. However, the ODM is designed with a smooth surface to minimize this risk. While increasing IOP causes neural loss, the length and magnitude of the pressure elevation in our study design was previously used and have been shown to not cause any short or long-term damage.

Adverse Event

The IRB and participants will be notified immediately of any new information learned in regards to this study. Expected and serious adverse events that occur will be reported to the IRB. Fatal or life threatening adverse events with research intervention will be reported to the IRB within 24 hours of notice. If there is a major unresolved dispute between the research investigator and a research subject or between research investigators, a letter will be submitted to the IRB describing the dispute and identifying the parties involved.

All adverse events occurring during the study period will be recorded. At each contact with the participant, the research team members will seek information on adverse events by specific questioning and examination. Information on all adverse events will be recorded in the patient file immediately. The clinical course of each event will be followed by the PI and research team members until resolution, stabilization or until it has been determined that participation in the

study is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed to determine the final outcome.

A review of the outcome and adverse event data will be monitored by the PI and clinical coordinators to determine whether the study should be continued, changed or terminated. A copy of the review will be submitted to the DSMB and to the IRB at the time of renewal.

The PI will ultimately be responsible for the data safety monitoring of the overall study. The DSMB will include the PI and clinical coordinators, who will meet every other week to monitor data, recruitment, retention, confidentiality and adherence to the study protocol. At the time of obtaining renewal approval from the IRB, a report indicating the PI's evaluation of whether there is any change in the risk benefit considerations of the study will be submitted. A licensed medically qualified sub-investigator will be responsible for reviewing and assessing adverse events. There are no predetermined stopping criteria.

Adverse events will be reported immediately to the DSMB for further evaluation. Annual reports will be provided regularly to the DSMB by each of the sub-sites. If the DSMB or IRB conclude that changes should be made to the study protocol, all sites will be informed in writing by the PI. There are no direct benefits to subjects who participate in this study.

8. Data Management and Record Keeping

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). In accordance with these regulations, participants will sign authorization of the following:

- The protected health information (PHI) that will be collected
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI

In the event that a participant revokes authorization to collect or use PHI, the investigator retains the ability to use all information collected prior to the revocation of authorization.

Data will be collected after the participant has signed an informed consent form and completed their visit. The collected data will include demographics, clinical information and testing results. Data management will include steps that will ensure confidentiality and security of the data. Data will be collected only by members of the research team and stored in accordance with Federal and University regulations. The data will be de-identified prior to any analysis and the key will be accessible only by study personnel. Research related materials will be retained and stored following NYU policy (a minimum of seven years following study completion). ICF's will also be retained for seven years. Paper-based records and external hard drives containing data will be kept in a secure location within a double locked room and only be accessible to personnel involved in the study. Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, granted prior to

access to any study-related information residing within NYU firewall. Identifiable health information will not be reused or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study. Records will only be destroyed after confirmation from sponsor and IRB.

The project is funded by the NIH, who may have access to de-identified data. Our research results are published in scientific journals and deposited in PubMed in a timely manner, as required. We willingly distribute the reprints of our publications to those who are interested but do not have access to these journals. Additionally, our group has a long history of successful collaborations with interested investigators. We share de-identified data and our analytical tools with collaborators in accord with New York University and NIH policies. Although this study is not designed for data collection of genome wide association study (GWAS), we would contribute data from some of our well-characterized participants to multi-center GWAS studies.

Study Monitoring, Auditing, and Inspecting

Study Monitoring Plan

The study will be routinely monitored by the PI and the coordinator during their regular DSMB meetings. The following aspects will be specifically monitored: enrollment and retention, data collection, confidentiality, breaches from the study protocol or any adverse event. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. diagnostic tests), and has adequate space to conduct the monitoring visit.

The investigator(s) and study team will meet bi-weekly to discuss recruitment, retention and breaches in confidentiality and any adverse events that may have occurred. A summary report of the DSMB and multi-centered DSMB will be submitted with annual review. All adverse events that occur including expected and serious will be reported to the IRB as outlined in Chapters 3 of the IRB Reference Manual.

Both the IRB and the participants will be notified immediately of any new information that is learned in regards to this study. Any adverse event that occurs during this research study will be reported to the IRB, as reported in the adverse events section of this protocol.

Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the funding sponsor, and University compliance and quality assurance groups of all study related documents. The investigator will also ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10. Ethical Considerations

This study will be conducted in compliance with the protocol approved by the IRB, GCP guidelines, and applicable NYU Langone Health and federal regulatory requirements. No deviation from the protocol will be implemented without prior review and approval of the IRB, except where it may be necessary to eliminate an immediate risk to a participant. In such case, the deviation will be reported to the IRB according to its policies and procedures.

This protocol and any amendments will be submitted to an IRB in agreement with local legal prescriptions, for formal approval of study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All participants will be provided with a consent form describing the study and providing sufficient information for them to make an informed decision about their participation. See attachment for a copy of the Participant Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a participant, using the IRB-approved consent form, will be obtained before that participant undergoes any study procedure. The participant must sign the consent form, and only the investigator-designated research personnel may obtain the consent.

11. Study Finances

Funding Source

Charges will be billed only for procedures performed as part of the subject's routine clinical care. All other costs will be charged to the grant funded by the NIH R01-EY013178.

Conflict of Interest

The PI Chaim Gadi Wollstein and three of the co-investigators, Dr. Sperber, Dr. Schuman, and Dr. Ishikawa, have a potential conflict of interest with this project. The NYU COI committee has established a management plan that will be implemented for this project.

Participant Stipends or Payments

Subjects will receive $30 at the completion of study procedures to compensate them for their participation in this research study.

12. Publication Plan

All publications resulting from this project will cite funding from NIH R01-EY013178.

The results of the study, complete or partial, carried out under this protocol will not be published or passed on to any third party without the consent of the PI or primary responsible party. Any investigators involved with this study will be obligated to provide the PI or primary responsible party with complete test results and all data derived from the study.

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