REMISIÓN DICTAMEN PERICIAL || DTE. SEBASTÍAN GIRÓN ARCILA || RAD. 2022-00194-00 || DMMN/ VS

Darling Mz <darlingmarcela1@gmail.com>

Vie 5/05/2023 15:15

Para: Juzgado 02 Civil Circuito - Valle Del Cauca - Tulua <j02cctulua@cendoj.ramajudicial.gov.co>

CC: rmpequipoconsultor <rmpequipoconsultor@gmail.com>;giron.arcila.sebasan97@gmail.com <giron.arcila.sebasan97@gmail.com>;sanacionyvidaips@gmail.com <sanacionyvidaips@gmail.com>;stellia-ms@hotmail.com <stellia-ms@hotmail.com>;Secretaria General <secretaria.general@nuevaeps.com.co>;noficacionesjudiciales@suramericana.com.co <noficacionesjudiciales@suramericana.com.co>;anniecanabal@gmail.com <anniecanabal@gmail.com>;tatacoa612@hotmail.com <tatacoa612@hotmail.com>;abaron@gha.com.co <abaron@gha.com.co>;Darlyn Marcela Muñoz Nieves <dmunoz@gha.com.co>;vsanclemente@gha.com.co <vsanclemente@gha.com.co>

1 archivos adjuntos (10 MB)

Dictamen pericial_Sebastían Girón.pdf;

Señores
JUZGADO SEGUNDO (2°) CIVIL DEL CIRCUITO DE TULUÁ, VALLE DEL CAUCA
j02cctulua@cendoj.ramajudicial.gov.co
E. S. D.

PROCESO: **VERBAL RESPONSABILIDAD CIVIL**
DEMANDANTE: **SEBASTÍAN GIRÓN ARCILA**
DEMANDADOS: **CLÍNICA OFTALMOLÓGICA DE PALMIRA S.A.S. Y OTROS**
RADICACIÓN: **76-834-31-03-002-2022-00194-00**

DARLYN MARCELA MUÑOZ NIEVES, mayor de edad y domiciliada en la ciudad de Cali, identificada con cédula de ciudadanía No. 1.061.751.492, abogada titulada y en ejercicio portadora de la T.P. No. 263.335 del Consejo Superior de la Judicatura, obrando en calidad de apoderada sustituta de **LA CLÍNICA OFTALMOLÓGICA DE PALMIRA S.A.S.**, encontrándome dentro del término procesal oportuno doy cumplimiento al auto No. C0216 del 14 de marzo de 2023 notificado por estados el 16 de marzo de la misma anualidad y aporto el dictamen pericial anunciado junto con la contestación de la demanda, solicitando el mismo sea dotado de pleno valor probatorio en relación al trámite de la referencia.

Cordialmente,

DARLYN MARCELA MUÑOZ NIEVES
C.C. No. 1.061.751.492
T.P. 263.335 del C.S. de la Jra.

Dirigido al Juzgado segundo civil del circuito de Tuluá, Valle del Cauca

DICTAMEN PERICIAL DE CONTRADICCIÓN

Elaborado por Carlos Eduardo Rivera Hoyos
C.C. 79.599.124
R.M. 03.547

Demandante: Sebastián Girón Arcila

Demandados: Clínica Oftalmológica de palmira S.A.S. Nueva Empresa Promotora de Salud S.A.

Documento elaborado en el trámite de responsabilidad civil médica en proceso con radicado76-834-31-03-002-2022-00194-00

Fecha de elaboración: 27 de abril de 2023

COLLECTIVE INNOVATIONS
Carlos E. Rivera H.
Director Medico y Científico
+032 332 22 22 ext 113
316 522 59 61
carlos.rivera@collectiveinnovations.co
crivera@grupogsr.co
grupogsr.co
mcwilliamscollective.co
Cr 100 # 11 - 60, C.C Holguines Trade Center, Oficina 201, T Farallones, Cali - Colombia
McWILLIAMS COLLECTIVE
GSR INTERNATIONAL CORPORATION

1. INFORMACION PERSONAL

NOMBRE: Carlos Eduardo Rivera Hoyos
PROFESION: Médico Cirujano
Oftalmólogo - Glaucomatólogo
Master in Business Administration (MBA)

UNIVERSIDAD: Pontificia Universidad Javeriana - Bogotá, 1995
FECHA DE NACIMIENTO: marzo 4 de 1972, en Bogotá
ESTADO CIVIL Casado
CEDULA DE CIUDADANIA 79599124
REGISTRO MEDICO 03547
DIR. Y TEL. CONSULTORIO Centro Comercial Holguines local 236 Gsr centro medico
DIR. Y TEL: RESIDENCIA calle 16 121 a – 97 Cali, Valle del Cauca
Cel.3165225961

2. ESTUDIOS REALIZADOS

PRIMARIA: Colegio San Luis Gonzaga, Manizales
SECUNDARIA: Colegio Mayor de San Bartolomé- Bogotá
UNIVERSITARIOS: Pontificia Universidad Javeriana- Bogotá. Médico y Cirujano.1995
Pontificia universidad Javeriana. Oftalmólogo. 2000
Fellowship en Glaucoma, 2005 Fundación oftalmológica de Santander
MBA Eude Business School, 2016
AÑO RURAL: Anapoima, Cundinamarca. 1996

3. EXPERIENCIA PROFESIONAL

GSR centro médico y Ópticas. Director Médico. 2020 a la actualidad
Clínica Farallones: Practica Privada, 2009 – 2020
Centro Médico Imbanaco: Oftalmólogo, Practica Privada. 2006 – 2009
Fundación Valle de Lili: Oftalmólogo, Practica institucional 2002 – 2004
Aruba Eye Institute: Oftalmólogo, Practica institucional, 2000 – 2002

4. DOCENCIA

Profesor Adscrito, Universidad Javeriana Cali, 2021 a la actualidad.

5. SOCIEDADES OFTALMOLÓGICAS

Glaucoma Colombia, miembro activo desde 2006
Sociedad Colombiana de Oftalmología, miembro activo desde 2000

6. PUBLICACIONES

- Blood pressure, ocular perfusion pressure and open-angle glaucoma in patients with systemic hypertension

  Cantor, E., Méndez, F., Rivera, C., Castillo, A., & Martínez-Blanco, A. (2018). Blood pressure, ocular perfusion pressure and open-angle glaucoma in patients with systemic hypertension. Clinical Ophthalmology, 1511-1517.

- Low-level expression of SOD1 in peripheral blood samples of patients diagnosed with primary open-angle glaucoma

  Canizales, L., Rodriguez, L., Rivera, C., Martinez, A., Méndez, F., & Castillo, A. (2016). Low-level expression of SOD1 in peripheral blood samples of patients diagnosed with primary open-angle glaucoma. Biomarkers in medicine, 10(12), 1218-1223.

- Prevalence of primary open angle glaucoma among patients with diagnosis of systemic hypertension and diabetes mellitus: The Colombian Glaucoma Study

  Rivera, C. E., Cantor, E., Castillo, A., Martinez, A., Newball, L., Rueda, J. C., ... & Mendez, F. (2020). prevalence of primary open angle glaucoma among patients with diagnosis of systemic hypertension and diabetes mellitus: The Colombian Glaucoma Study. Open Journal of Ophthalmology, 10(2), 99-114.

- Relationship between Optic Disc Hemorrhage and Glaucoma among patients diagnosed with Systemic Hypertension and Diabetes Mellitus: The Colombian Glaucoma Study:

  Seth, A., Rivera, C. E., Ferreria, M. C., Libreros-Peña, L., Shah, M. A., Aristizabal, J. C., ... & Burbano-Montenegro, G. (2022). Relationship between Optic Disc Hemorrhage and Glaucoma among patients diagnosed with Systemic Hypertension and Diabetes Mellitus: The Colombian Glaucoma Study. Iberoamerican Journal of Medicine, 4(4), 220-228.

- Utility of the ganglion cell complex thickness map in glaucoma: the presence of raphe sign CE Rivera, MC Ferreira, JC Aristizabal, E Muñoz, A Seth:

Rivera, C. E., Ferreira, M. C., Aristizabal, J. C., Muñoz, E., & Seth, A. (2022). Utility of the ganglion cell complex thickness map in glaucoma: the presence of raphe sign. Ophthalmology Journal, 7, 35-41.

- Ultra biomicroscopy findings in goniotomy-assisted transluminal trabeculotomy—a case report

  Ferreira, C., Rivera, C. E., Aristizabal, J. C., Seth, A., & Muñoz, E. (2021). Ultra biomicroscopy findings in goniotomy-assisted transluminal trabeculotomy—a case report. Ophthalmology Journal, 6, 178-183.

- Retinal detachment with a giant bleeding cyst, simulating a uveal melanoma—a case report C Ferreira, CE Rivera, E Muñoz, A Seth, JC Aristizábal

  Ferreira, C., Rivera, C. E., Muñoz, E., Seth, A., & Aristizabal, J. C. (2021). Retinal detachment with a giant bleeding cyst, simulating a uveal melanoma—a case report. Ophthalmology Journal, 6, 199-205.

- Optical coherence tomography findings in compressive optic neuropathy and pre-existing glaucoma

  Rivera, C. E., Ferreira, C., Aristizabal, J. C., Muñoz, E., & Seth, A. (2021). Optical coherence tomography findings in compressive optic neuropathy and pre-existing glaucoma. Ophthalmology Journal, 6, 249-254.

- Retinal nerve fiber layer defects in the presence of a physiological cup to disc ratio—a case series

  Rivera, C. E., Aristizabal, J. C., Muñoz, E., & Seth, A. (2021). Retinal nerve fiber layer defects in the presence of a physiological cup to disc ratio—a case series. Ophthalmology Journal, 6, 258-264.

7. IMPEDIMENTOS LEGALES, MANIFESTACION JURAMENTADA

Me permito manifestar bajo juramento, que se entiende prestado con la firma de este documento, que no me encuentro incurso en ninguna de las causales de impedimento e inhabilidades contempladas en el artículo 50 del C.G.P. o en el artículo 219 de la ley 1437 de 2011 que vicien mi actuar como perito en el presente proceso. Acepto el régimen jurídico del auxiliar de la justicia; poseo la formación académica y experticia profesional para rendir esta opinión pericial del caso asignado.

No tengo grado de consanguinidad o parentesco con las partes inmersas en este proceso. Tampoco tengo interés económico con el resultado del asunto en litigio, dependencia u otra razón que me ligue con las partes procesales. De igual forma manifiesto bajo juramento que he actuado con lealtad y fidelidad en el desempeño de esta labor, que la opinión pericial que rindo corresponde a mi real convicción profesional, que en su elaboración he invocado la experiencia obtenida como especialista en oftalmología, en su confección y redacción he actuado con la mayor objetividad e imparcialidad, sin injerencia de ninguna de las partes implicadas en el proceso y con la observancia de las guías, protocolos y la literatura médica que rigen el caso analizado.

Adicionalmente manifiesto que no he sido designado como perito en los últimos 4 años y en todo caso, esta es la primera experticia que rindo a solicitud de la apoderada o de la Clínica Oftalmológica de Palmira S.A.S.

8. OBJETO DE EXPERTICIA

Como glaucomatólogo este dictamen de contradicción de la experticia presentada por el Dr. Jorge Augusto Zambrano, tiene por objeto indicar, con base en la historia clínica suministrada, cual fue el curso de la enfermedad padecida por el señor Sebastián Girón Arcila, los factores de riesgo, manejo y atención de las partes involucradas, particularmente de la Clínica Oftalmológica de Palmira S.A.S.

9. DOCUMENTOS RECIBIDOS Y ANALIZADOS

Historia clínica completa del señor Sebastián Girón Arcila relacionada en el expediente de este proceso.

10. METODOLOGÍA

La metodología empleada para la realización de esta experticia consistió en el análisis de la historia clínica del señor Sebastián Girón Arcila en concordancia con la literatura médica en la materia y la experiencia con que cuento en el campo de la medicina, enfocada particularmente en la especialidad de oftalmología y glaucoma.

Los métodos, exámenes, experimentos y/o investigaciones realizadas para la elaboración de esta experticia son similares a los empleados en curso del ejercicio de mi profesión como médico especialista es oftalmología y subespecialista en glaucoma y son los mismos que se emplean en el ejercicio regular de mi profesión.

11.ANÁLISIS DE LA HISTORIA CLÍNICA

Paciente de 25 años quien consulta a medicina general en Tuluá el 1 de febrero de 2020 por presentar disminución de agudeza visual por el ojo izquierdo y cefalea, para lo cual es remitido a oftalmología 7 meses después es valorado por optometría en agosto 2020 que evidencia 20 / 20 en ambos ojos y remite a oftalmología.

El 26 de agosto 2020 la Dra. Annie Canabal examina al paciente presentando una agudeza visual de 20 / 25 en ambos ojos, pio de 12 mmhg (rango normal) evidenciando en el ojo izquierdo una excavación amplia, probable edema de papila para lo cual solicita una tomografía óptica coherente del nervio óptico, potenciales visuales evocados y valoración por Neurooftalmología.

El 3 de septiembre consulta de manera particular donde el Dr. Carlos Lozano en Tuluá por presentar disminución de agudeza visual por el ojo izquierdo, la agudeza visual en esa consulta era de 20 /25 en ojo derecho y movimiento de manos en el ojo izquierdo, la presión del ojo era de 34 mmhg en ojo derecho y 54 mm hg en ojo izquierdo, en el ojo izquierdo se observó una excavación de 0.9. Se hace un diagnóstico de hipertensión ocular severa por lo cual el paciente es remitido a clínica de oftalmología en Cali, donde el Dr. Edgar Lozano (Glaucomatólogo) confirma anteriores hallazgos y programa una trabeculectomia el 1 de octubre de 2020.

Los controles posoperatorios del 2 de octubre al 18 de diciembre se observa una agudeza visual del ojo derecho de 20 / 20 y ojo izquierdo de 20 / 70 y presiones intraoculares estables de 12 en el ojo derecho y 9 en ojo izquierdo.

En febrero 2021, se observa una elevación de la presión del ojo derecho a 54 por lo cual el Dr. Edgar Lozano realiza trabeculectomia en ese ojo. Los controles posoperatorios inmediatos y tardíos mostraron un adecuado control de la presión del ojo.

Para el año 2022 el paciente presenta 2 controles en marzo evidenciando agudez visual de 20 / 40 en ojo derecho y 20 / 50 ojo izquierdo. La presión ocular derecha estaba 13 y 9 en en el ojo izquierdo.

9. CONTRADICCIÓN DE DICTAMEN PERICIAL APORTADO POR EL DEMANDANTE.

El Dr. Zambrano, afirma que se trata de un paciente joven con un glaucoma probablemente de varios meses de evolución, lo cual es difícil de establecer sin contar con exámenes complementarios que confirmen las fechas con mayor exactitud. El día de la consulta realizada por la Dra. Cannabal, se realiza de manera oportuna la toma de agudeza visual la cual era normal para esa fecha, presión intra ocular, la cual era normal y evidencio una alteración del nervio óptico para lo cual solicito exámenes y remitió a Neurooftalmología, siendo esta la conducta adecuada.

10. ANALISIS DEL CASO Y CONCLUSIONES

Por la edad del paciente y el cuadro severo de elevación de presión intraocular considero que se trata de un cuadro de glaucoma juvenil temprano de difícil control, el cual requirió de trabeculectomia en ambos ojos, logrando un control adecuado de la presión intraocular.

La agudeza visual del último control reportado en marzo 2022 se observa una estabilidad de 20 / 40 en ojo derecho y 20 / 50 en ojo izquierdo, similar a los controles anteriores del 2021 y finales del 2020. Con base en la historia clínica, el día del examen de la Dra. Canabal se tomó la agudeza visual y la presión intraocular que son las bases del diagnóstico de glaucoma, los cuales eran normales en el momento, se sospecha una alteración del nervio óptico, para lo cual solicito los exámenes pertinentes. Desafortunadamente el paciente no regreso a control con los resultados. El paciente consulta a los 8 días a oftalmólogo particular donde se evidencio la elevación de la presión ocular, se remite a un especialista en glaucoma y el paciente es operado de manera oportuna.

11. BIBLIOGRAFÍA

Wiggs, J. L., Damji, K. F., Haines, J. L., Pericak-Vance, M. A., & Allingham, R. R. (1996). The distinction between juvenile and adult-onset primary open-angle glaucoma. American journal of human genetics, 58(1), 243.

12.ANEXOS

Se relacionan como anexos toda la documentación que da cuenta de mi formación profesional, las publicaciones literarias que he realizado y la bibliografía consultada para la atención de este caso.

Atentamente,

_____

Carlos Eduardo Rivera Hoyos
C.C. 79.599.124
R.M. 03.547

República de Colombia

FUNDACION OFTALMOLOGICA DE SANTANDER

Clínica Carlos Ardila Lülle

FOSCAL

Institución Docente-Asistencial

Certifica que el Doctor:

Carlos Eduardo Rivera Hoyos

Médico Especialista en Oftalmología

Ha completado satisfactoriamente su:

Fellowship en Glaucoma

En el periodo comprendido entre el 10 de Enero de 2005 y el 9 de Enero de 2006
de acuerdo con el Programa de la Fundación Oftalmológica de Santander.

Dr. Juan Carlos Mantilla Suárez
Director Médico FOSCAL

Dr. Augusto Gómez Durán
Director Dpto. de Oftalmología FOSCAL

Dr. Juan Camilo Parra Restrepo
Departamento de Glaucoma

Dr. Juan Carlos Rueda Galvis
Departamento de Glaucoma

EN ATENCION A QUE

CARLOS EDUARDO RIVERA HOYOS

C. C. 79.519.124 BOGOTA

HA CURSADO TODOS LOS ESTUDIOS Y CUMPLIDO LOS REQUISITOS ESTABLECIDOS POR LA UNIVERSIDAD Y LAS DISPOSICIONES LEGALES PARA UN GRADO UNIVERSITARIO

EN LA FACULTAD DE MEDICINA

LE OTORGA

EN NOMBRE DE LA REPUBLICA DE COLOMBIA

Y POR AUTORIZACION DEL MINISTERIO DE EDUCACION NACIONAL

EL TITULO DE MEDICO Y CIRUJANO

EN FE DE LO CUAL FIRMAMOS Y SELLAMOS ESTE [illegible]

NOSOTROS EL RECTOR LOS DECANOS Y EL SECRETARIO GENERAL DE LA UNIVERSIDAD

EXPEDIDO EN STA. FE DE BOGOTA A LOS 1 DIAS DEL MES DE DICIEMBRE DE 1995

24 ENE 2005

RECTOR

SECRETARIO GENERAL

DECANO ACADEMICO

DECANO FACULTAD

Nº 462

141 C

LA PONTIFICIA UNIVERSIDAD JAVERIANA

PERSONERIA JURIDICA: RES 73-12 DE DICIEMBRE 1933 - MINGOBIERNO

EN ATENCION A QUE

CARLOS EDUARDO RIVERA HOYOS

C.C. No. 79.594.124 DE BOGOTA

HA CURSADO TODOS LOS ESTUDIOS Y CUMPLIDO LOS REQUISITOS ESTABLECIDOS POR LA UNIVERSIDAD Y LAS DISPOSICIONES LEGALES PARA UN GRADO UNIVERSITARIO

EN LA FACULTAD DE MEDICINA

LE OTORGA

EN NOMBRE DE LA REPUBLICA DE COLOMBIA

Y POR AUTORIZACION DEL MINISTERIO DE EDUCACION NACIONAL

EL TITULO DE ESPECIALISTA EN OFTALMOLOGIA

EN FE DE LO CUAL FIRMAMOS Y SELLAMOS ESTE DIPLOMA

NOSOTROS EL RECTOR LOS DECANOS Y EL SECRETARIO GENERAL DE LA UNIVERSIDAD

EXPEDIDO EN BOGOTA, D.C A LOS 21 DIAS DEL MES DE SEPTIEMBRE

RECTOR

SECRETARIO GENERAL

DECANO ACADEMICO

DECANO DEL MEDIO UNIVERSITARIO

Nº2332

MARIA SOL SINISTERRA
NOTARIA CATORCE DE CALI
18 JUL 2003
Es fiel copia del original que he tenido a la vista

MARIA SOL SINISTERRA
NOTARIA CATORCE DE CALI
24 ENE 2005
Esta fotocopia es copia fiel y exacta del original que ha tenido a la vista

CARMEN STELLA OSSA BOLDAN
NOTARIA ENCARGADA

REPÚBLICA DE COLOMBIA

MINISTERIO DE SALUD Y PROTECCIÓN SOCIAL

DISTINTIVO DE HABILITACIÓN DE SERVICIOS

Código y Nombre del Prestador	**7600107416 - CARLOS EDUARDO RIVERA HOYOS**				
Código y Nombre de la Sede	**760010741601-CARLOS EDUARDO RIVERA HOYOS**				
Departamento	**VALLE DEL CAUCA**	**Municipio**	**CALI**	**Dirección**	**CARRERA 100 No. 11-60 LOCAL 236 - 237**
Grupo del Servicio	**Consulta Externa**				

335 - OFTALMOLOGÍA

Número Único del Distintivo de Habilitación de Servicios: ***DHSS0073722***

Verifique la información de este documento, ingresando a: https://prestadores.minsalud.gov.co/habilitacion/consultadistintivo_dhss.aspx y posteriormente digitando el Número Único del Distintivo de Habilitación de Servicios:DHSS0073722

En caso de cualquier inquietud con el DISTINTIVO DE HABILITACIÓN DE SERVICIOS comuníquese con la SECRETARIA DEPARTAMENTAL DE SALUD DEL VALLE - Dirección:Carrera 6 entre calles 9 y 10 Edificio Palacio de San Francisco - Telefono(s):3128151109 3128151109 - Correo Electronico:reps@valledelcauca.gov.co

Fecha de apertura del servicio: 30 - 04 - 2009 (DD-MM-AAAA).

Fecha de impresión: martes 11 de mayo de 2021 (10:54 p. m.).

El presente documento se expide de conformidad con lo previsto en la Parte 5, Título 1, Capítulo 1 del Decreto 780 de 2016 y la Resolución 3100 de 2019, o las normas que la modifiquen o sustituyan.

Código interno MinSalud_PS:-765498409

Versión 3.0.

es de todos

COLOMBIANO
CMC

IDENTIFICACIÓN ÚNICA DEL TALENTO HUMANO EN SALUD

CARLOS EDUARDO RIVERA HOYOS

C.C. 79599124

MÉDICO

Pontificia Universidad Javeriana

Bogotá D.C.

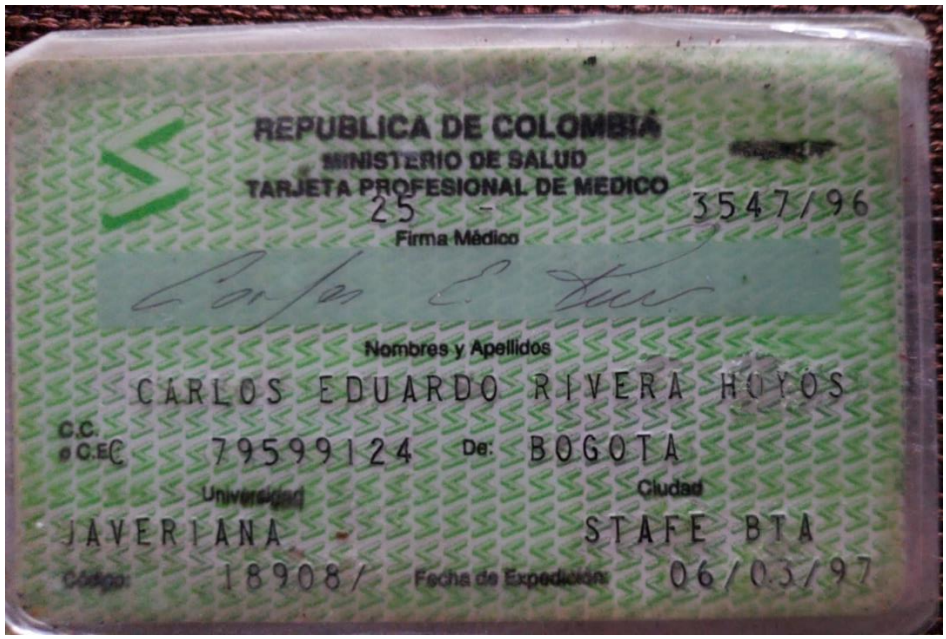
Grado: 01/12/1995

Rethus: 20/12/1996

ESPECIALIZACIÓN EN OFTALMOLOGÍA

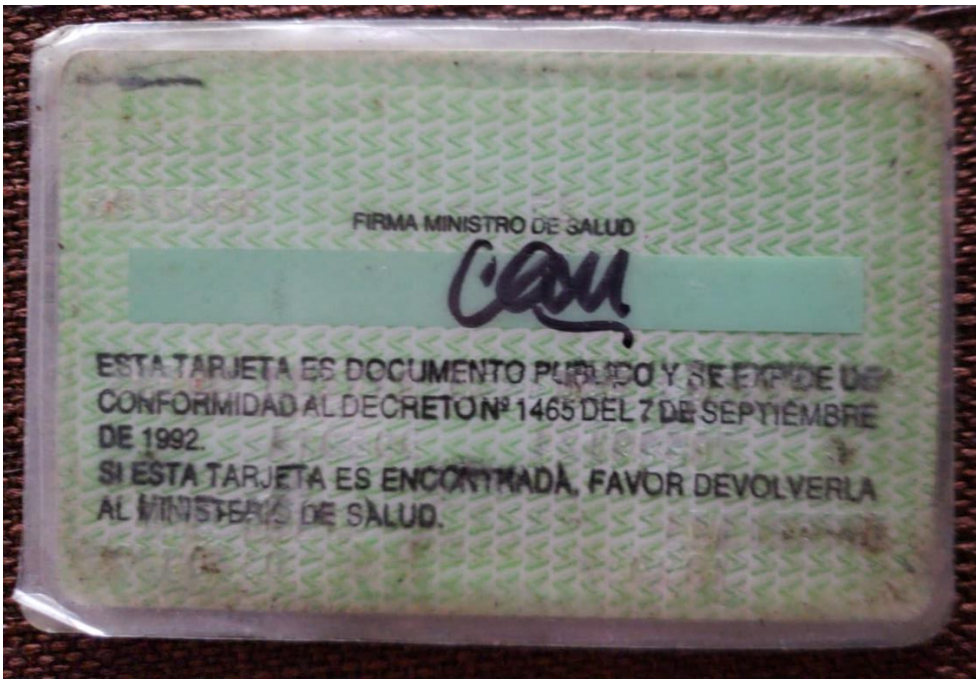
Esta tarjeta es un documento público que se expide de conformidad con la ley 1164 de 2007 y el decreto 4192de 2010.Si esta tarjeta es encontrada, favor devolver al colegio medico colombiano Av. Carrera 15 # 100-43 Oficina 501 - Edificio Avenida 15 PH.
Info@colegiomedicocolombiano.org

Firma Representante Colegio Medico Colombiano



REPUBLICA DE COLOMBIA
MINISTERIO DE SALUD
TARJETA PROFESIONAL DE MEDICO
25 - 3547/96
Firma Médico

Nombres y Apellidos
CARLOS EDUARDO RIVERA HOYOS
C.C. o C.E.C 79599124 De: BOGOTA
Universidad Ciudad
JAVERIANA STAFE BTA
Código: 18908/ Fecha de Expedición: 06/03/97



FIRMA MINISTRO DE SALUD

ESTA TARJETA ES DOCUMENTO PUBLICO Y SE EXPIDE DE CONFORMIDAD AL DECRETO Nº 1465 DEL 7 DE SEPTIEMBRE DE 1992.
SI ESTA TARJETA ES ENCONTRADA, FAVOR DEVOLVERLA AL MINISTERIO DE SALUD.

Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Blood pressure, ocular perfusion pressure and open-angle glaucoma in patients with systemic hypertension

This article was published in the following Dove Press journal:
Clinical Ophthalmology

Erika Cantor[1]
Fabián Méndez[2]
Carlos Rivera[3]
Andrés Castillo[4]
Alexander Martínez-Blanco[5]

[1]Research Institute, Centro Médico Imbanaco, Cali, Colombia; [2]School of Public Health, GESP Group, Universidad del Valle, Cali, Colombia; [3]Centro Medico Farallones, Fundación Oftalmológica del Valle, Cali, Colombia; [4]Department of Biology, Faculty of Natural and Exact Sciences, Universidad del Valle, Cali, Colombia; [5]Department of Ophtalmology, Universidad del Valle, Research Institute, Centro Médico Imbanaco, Cali, Colombia

Background: The aim of the study was to evaluate the relationship between blood pressure (BP), ocular perfusion pressure (OPP) and occurrence of primary open-angle glaucoma (POAG) among patients with systemic hypertension.

Participants and methods: A cross-sectional study of hypertensive patients was conducted in six cities in Colombia. The participants underwent a complete ophthalmological examination. The intraocular pressure measurement was obtained by Goldmann tonometry. The diagnosis of glaucoma was confirmed by visual field and optic nerve photos. Interviews and questionnaires were used to evaluate participants' lifestyle and other health conditions. A multinomial logistic regression was used to assess the relationship between BP, OPP and presence of suspected or confirmed POAG.

Results: A total of 1,272 individuals were included in this study; 131 (10.3%) were diagnosed with suspected glaucoma and 65 (5.1%) with confirmed glaucoma. High values of diastolic BP (>90 mmHg) and low values of OPP (<40 mmHg) were associated to an increased risk of confirmed POAG. The type of antihypertensive treatment did not modify these relationships.

Conclusion: This study suggests that there is a close relationship between OPP and confirmed glaucoma in hypertensive patients, providing further evidence of the vascular mechanism in glaucoma pathogenesis.

Keywords: open angle-glaucoma, blood pressure, ocular perfusion pressure, hypertension, ocular blood flow

Introduction

Glaucoma is considered an optic neuropathy that results in vision loss, and it tends to remain asymptomatic until advanced stages have been reached. It is estimated that over 76 million people will have glaucoma in 2020 increasing to 111.8 million in 2040. Primary open-angle glaucoma (POAG) is the most common form of glaucoma and represents approximately 60%–70% of all cases.[1]

Systemic hypertension has been related to increased intraocular pressure (IOP) and a higher risk of POAG.[2] Although the physiopathology of glaucoma is still not completely understood, IOP is the main modifiable risk factor due to its direct mechanical effect on the optic nerve head (ONH). Nevertheless, evidence suggests that damage to the optic nerve axons occurs due to microvascular injury and low perfusion.[3,4] Among vascular factors associated with glaucoma, blood pressure (BP) is the most studied, because it is related to microvascular blood flow and IOP, the two main elements that determine the ocular perfusion pressure (OPP).[2] Several studies have shown a positive correlation between IOP and BP,[5–7] which makes difficult the understanding

Correspondence: Erika Cantor
Research Institute, Centro Médico Imbanaco, Carrera 38 BIS No 5B2-04, Cali, Colombia
Tel +57 682 1000
Email erika.cantor@imbanaco.com.co

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OPTH.S165747

of the complex role that IOP, BP and OPP may have in the prevalence and progression of POAG.

Recently, a bimodal relationship was described between BP and the risk of glaucoma, indicating that patients with either high or low BP have a higher risk of developing POAG.[8,9] The OPP could be reduced during the decrease or elevation of BP, and this may result in ischemic injury of the retinal ganglion cells in the absence of an adequate mechanism of autoregulation.[2] Additionally, in patients with systemic hypertension and glaucoma, vascular dysfunction does not allow the activation of ocular blood flow autoregulation mechanisms, increasing susceptibility to POAG.[10–12]

The objective of this study was to evaluate the relationship between the BP, OPP and POAG in patients with systemic hypertension in a cross-sectional study, the Colombian Glaucoma Study (ECG, from the initials in Spanish).

Participants and methods

Design and study population

ECG is a cross-sectional study of hypertensive and diabetic patients from six cities in Colombia, conducted from September 2014 to October 2015. All participants were selected from the hypertension control programs. At enrollment, individuals were ≥50 years of age and were treated with antihypertensive medications for at least 1 year before the beginning of the study. Subjects with previous intraocular surgery (trauma retinal detachment, complicated cataract surgery, macular degeneration or maculopathy), congenital ocular pathology (eg, coloboma) or severe associated comorbidities (renal failure, congestive heart failure, sleep apnea, autoimmune diseases with biological therapy) were excluded. A total of 1,591 individuals were initially selected, but participants with diagnosis of angle-closure glaucoma and other types of glaucoma (n=57), unconfirmed diagnosis of systemic hypertension (n=168), prior diagnosis of POAG (n=51) and incomplete records (n=43) were excluded. Finally, a total of 1,272 patients were included in the analysis. The Universidad del Valle Review Board approved this study (Approval Code 030-014), and all participants signed informed consent.

The ECG participants underwent a complete ophthalmological examination, including visual acuity measurement, refraction, slit lamp examination, IOP and pachymetry measurement. The IOP measurement was obtained from the average of three values by Goldmann tonometry. The POAG diagnosis was confirmed using visual field (VF) test with the 24-2 Swedish Interactive Threshold Algorithm (Humphry; Carl Zeiss Meditec, Inc) and optic nerve photos; these procedures were only performed in the suspected cases. Trained glaucomatologists performed the examinations using standardized protocols. Interviews and questionnaires were used to evaluate participants' lifestyle and other health conditions.

Diagnosis of glaucoma

Suspected and confirmed cases of glaucoma were defined according to the criteria specified by Foster et al.[13] Confirmed glaucoma was defined as structural and functional evidence of glaucomatous damage in at least one eye that met the following criteria: 1) horizontal or vertical cup-disc ratio >0.7 (97.5th percentile), focal glaucomatous disc change (disc hemorrhage, notch of the neuroretinal rim, marked sloping of rim tissue, narrowest remaining rim of 0.1 disc diameter or less), cup/disc asymmetry >0.2 (97.5th percentile), associated with a glaucomatous VF defect; 2) horizontal or vertical cup-disc ratio >0.8 (99.5th percentile), focal glaucomatous disc change, asymmetry >0.3 (99.5th percentile) with absence of functional evidence of glaucomatous damage (if the subject could not satisfactorily complete the VF examination). Cases that did not meet all criteria were classified as suspected glaucoma. In addition, VF defects that were not explained by any other disease, like asymmetry across the horizontal midline, visual defects located in the mid-periphery or clustered in neighboring test points, were defined as compatible with the disease.[14] Figure 1 shows the VF and optic nerve photos for a confirmed case of POAG.

Measurement of BP and OPP

BP was measured in sitting position after 5 minutes of rest, using a sphygmomanometer. The cutoff values of BP were defined according to the guidelines for the management of arterial hypertension of European Society of Hypertension.[15] High BP was defined as systolic BP (SBP) >140 mmHg or diastolic BP (DBP) >90 mmHg. Low BP was defined as SBP <90 mmHg and DBP <60 mmHg. Mean arterial BP (MABP) was calculated as 1/3 SBP + 2/3 DBP. The OPP was defined as 2/3 MABP minus IOP, while diastolic OPP (DPP) and systolic OPP (SPP) were defined as DBP or SBP minus IOP, respectively. The highest IOP value between the two eyes was used to calculate OPP.

Statistical analysis

Suspected and confirmed cases of glaucoma were included in data analysis. The BP values were classified according to the high and low values of SBP and DBP. Comparisons were made using a SBP cutoff value of 110 mmHg due to the small

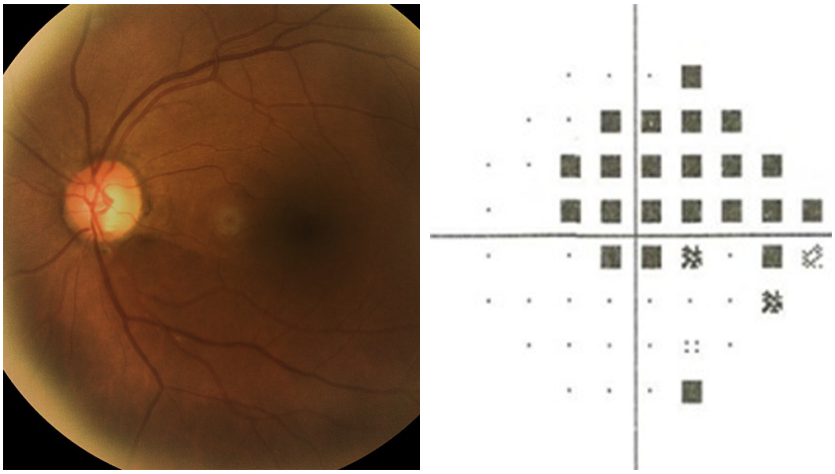


Figure 1 Example of a case of POAG with inferior retinal nerve fiber layer defect characterized with a superior arcuate defect on VF.
Abbreviations: POAG, primary open-angle glaucoma; VF, visual field.

number of participants in the study with SBP <90 mmHg in this group of hypertensive patients. The SPP, DPP and OPP were categorized into groups of 10 mmHg.

The dependent variable had three categories: confirmed glaucoma, suspected glaucoma and no glaucoma, as reference category. Therefore, we applied a multinomial logistic regression model to evaluate the relationships with main independent variables, namely BP and OPP, adjusted by age, sex, diabetes, type of antihypertensive drug used (B-blockers, angiotensin-converting enzyme inhibitors [ACE-I] and angiotensin II AT_1 receptor antagonists [ARBs]), time since diagnosis and IOP. The ORs were calculated with 95% confidence interval, and goodness-of-fit was evaluated using a likelihood ratio test and the model deviance. All analyses were carried out using Stata 13 (STATA Corp, College Station, TX, USA).

Results

From 1,272 individuals who met the selection criteria, 131 (10.3%) were diagnosed with suspected glaucoma and 65 (5.1%) with confirmed glaucoma. Sixty percent of the individuals had been diagnosed with hypertension for more than 5 years and 32.4% (412) were diabetic. The percentage of cases with high SBP >140 mmHg and DBP >90 mmHg were 9.4% and 5.3%, respectively.

The demographic and clinical characteristics of participants are described in Table 1. Males had a higher risk of confirmed glaucoma than women (OR: 2.2; 95% CI: 1.3–3.8). No statistically significant relationship was found between age and suspected diagnosis. However, data suggest that the proportion of confirmed POAG was 2-fold higher in the 70–79 years age group (OR: 2.1; 95% CI: 1.0–4.1) when compared to the youngest age group (50–59 years). The number of persons with diabetes mellitus was lower in the confirmed POAG group (confirmed: 21.5% vs suspected: 32.8%). There was a higher proportion of B-blocker consumption in confirmed POAG (50.0%). ARB consumption was more common in suspected and no POAG cases. The proportion of IOP ≥21 mmHg was 1.7% among the patients without glaucoma, 5.3% in the group with suspected POAG and 15.4% in the one with confirmed POAG. Figure 2 shows the distribution of IOP according to POAG diagnosis.

Table 1 Demographic and clinical characteristics by presence of POAG

	Confirmed POAG N (%)	Suspected POAG N (%)	No POAG N (%)
Age (years)			
50–59	14 (21.5)	44 (33.6)	322 (30.1)
60–69	20 (30.8)	49 (37.4)	422 (39.4)
70–79	26 (40.0)	29 (22.1)	261 (24.4)
>80	5 (7.7)	9 (6.9)	66 (6.2)
Sex			
Female	31 (47.7)	89 (67.9)	709 (65.9)
Male	34 (52.3)	42 (32.1)	367 (34.1)
DM	14 (21.5)	43 (32.8)	355 (33.0)
Antihypertensive drug			
B-blockers	32 (50.0)	42 (33.6)	413 (39.0)
ACE-I	22 (34.9)	30 (24.6)	243 (23.5)
ARBs	20 (31.7)	75 (61.5)	514 (49.7)
DBP, mmHg (mean ± SD)	75.9±13.6	77.1±10.8	76.9±10.7
SBP, mmHg (mean ± SD)	127.3±18.1	125.8±15.2	125.8±15.0
IOP, mmHg (mean ± SD)	15.8±5.0	15.3±2.9	14.3±2.7
OPP, mmHg (mean ± SD)	46.2±10.1	46.8±7.2	47.9±7.8

Abbreviations: POAG, primary open-angle glaucoma; DM, diabetes mellitus; ACE-I, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II AT_1 receptor antagonists; DBP, diastolic blood pressure; SBP, systolic blood pressure; IOP, intraocular pressure; OPP, ocular perfusion pressure.

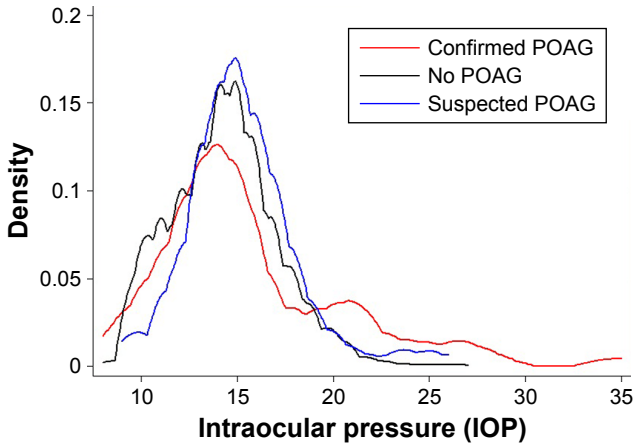


Figure 2 Curve of intraocular pressure according to POAG diagnosis.
Abbreviation: POAG, primary open-angle glaucoma.

Relationship between POAG and BP

After adjusting for age, sex, diabetes, type of antihypertensive drug used and time since diagnosis and IOP, there was no direct relationship between values of SBP or MABP and occurrence of glaucoma. However, an increase of confirmed POAG probability was observed among patients with DBP >90 mmHg; patients with DBP values higher than 90 mmHg were 2.2 times more likely to have confirmed POAG (*p*-value: 0.08) (Table 2). The type of antihypertensive treatment did not modify the relationship between BP and POAG. In addition, a suggested association between POAG and ARB consumption was not conclusive due to an increase of suspected glaucoma probability (OR: 1.7 [95% CI: 1.1–2.5]) but a decrease of confirmed glaucoma probability (OR: 0.6 [IC 95% 0.3–1.0]) with ARB treatment.

Relationship between POAG and OPP

Low values of OPP and DPP were associated with an increased risk of confirmed POAG. Those with DPP ≤50 mmHg were 2.2 times more likely to have confirmed POAG when compared with those with DPP values between 61 and 70 mmHg. The relationship between suspected glaucoma and OPP was not statistically significant. We also found that those with OPP of 40 mmHg or less were two times more likely to have confirmed POAG than those with OPP between 41 and 50 mmHg. Figure 3 shows a higher percentage of confirmed glaucoma in low (<40 mmHg) and high (>60 mmHg) OPP values with a prevalence of 6.4%, decreasing when the OPP was between 41 and 60 mmHg. Additionally, high SPP was significantly associated with a higher risk of confirmed glaucoma; those with SPP higher than 130 mmHg had a higher probability of confirmed POAG than those with SPP between 111 and 120 mmHg (Table 3).

Discussion

In this program-based study of hypertensive subjects, results suggest that there is no relationship between BP and suspected or confirmed POAG. However, OPP was associated with confirmed glaucoma.

Based on our knowledge, this is the first study that evaluates the cross-sectional relationship between BP, OPP and POAG in hypertensive patients. However, the relationship found with OPP was similar to the findings reported in other populations.[9,16,17] We did find a similar report, the Rotterdam Eye Study, which is a sub-analysis carried out only in patients undergoing antihypertensive treatment, wherein

Table 2 Distribution and relationship between POAG diagnoses according to the blood pressure level

Blood pressure	Confirmed POAG N (%)	Suspected POAG N (%)	No POAG N (%)	OR (95% CI) confirmed/ no GPAA[a]	OR (95% CI) suspected/ no GPAA[a]
SBP, mmHg					
<110	16 (24.6)	29 (22.1)	202 (18.8)	1.6 (0.7–3.3)	1.5 (0.8–2.5)
111–120	17 (26.1)	37 (28.2)	355 (33.0)	1	1
121–140	21 (32.3)	52 (39.7)	424 (39.4)	0.9 (0.5–1.9)	1.2 (0.7–1.9)
>140	11 (16.9)	13 (9.9)	95 (8.8)	2.0 (0.8–4.5)	1.2 (0.6–2.4)
DBP, mmHg					
<60	11 (16.9)	19 (14.5)	121 (11.2)	1.3 (0.6–2.7)	1.6 (0.9–2.8)
61–80	40 (61.5)	81 (61.8)	735 (68.3)	1	1
81–90	7 (10.8)	27 (20.6)	164 (15.2)	0.6 (0.2–1.6)	1.3 (0.8–2.2)
>90	7 (10.8)	4 (3.0)	56 (5.2)	2.2 (0.9–5.5)*	0.5 (0.1–1.5)
MABP, mmHg					
<80	11 (16.9)	18 (13.7)	117 (10.9)	1.2 (0.6–2.7)	1.3 (0.7–2.5)
81–90	20 (30.8)	36 (27.5)	302 (28.1)	1	1
91–100	18 (27.7)	41 (31.3)	451 (41.9)	0.6 (0.3–1.1)	0.7 (0.4–1.1)
>100	16 (24.6)	36 (27.5)	206 (19.1)	1.0 (0.5–2.2)	1.3 (0.8–2.1)

Notes: *p-value <0.10, [a]multinomial logistic regression adjusted by age, sex, diabetes, type of antihypertensive drug and IOP.
Abbreviations: POAG, primary open-angle glaucoma; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean blood pressure; IOP, intraocular pressure.

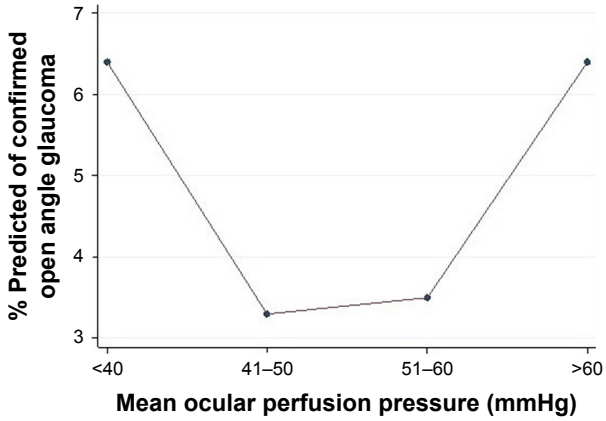


Figure 3 Relationship between OPP and confirmed POAG.
Abbreviations: OPP, ocular perfusion pressure; POAG, primary open-angle glaucoma.

an increase of normal tension glaucoma risk in high values of DBP (>85 mmHg) and an increase of high-tension glaucoma risk in low values of DPP (<50 mmHg) were found. Nevertheless, this study was not conclusive in a relationship between BP and POAG in all population.[18]

Although our data did not reveal a relationship between BP and POAG, the characteristics of the population included in the analysis could explain this result. In particular, all patients in the study were undergoing hypertensive treatment, which could decrease the probability of hypotension or hypertension events. These events have been associated with the POAG risk in general population.[2,8] For example, the LALES Study found an increase in POAG risk in high and low values of BP, suggesting that the relationship between BP and glaucoma is bimodal and "U" shaped. In high values of BP, the risk of development of arteriosclerosis may increase and lead to a reduction of perfusion of the ONH. The events of hypotension when coinciding with an increase of IOP may exacerbate the damage to the ONH due to the reduction of OPP.[2,8]

The relationship found between the OPP and POAG in hypertensive patients is similar to the findings reported in other observational studies.[9,16,18–20] Therefore, our results suggest that in hypertensive patients, the glaucomatous damage may occur due to the ischemia of the optic nerve or the retinal ganglion cells because of the reduction of the perfusion pressure. These structural changes may induce the development of POAG. Although ocular blood flow is an autoregulated process to ensure the adequate irrigation of ocular tissues, vascular dysfunction processes can disturb it. In patients with systemic hypertension, there have been findings that suggest an alteration in the production of endothelin-1 levels, which is related to the dysfunction processes in the endothelial regulation, reducing the ocular blood flow in patients with glaucoma.[10–12]

On the other hand, there was no relationship between age and diagnosis of suspected POAG. This finding disagrees with those reported in other populations.[19,21] Confirmed POAG was more frequent among males, which is consistent with the data from Latin population.[21]

The consumption of ARBs was related with a decreased risk of confirmed POAG. However, its consumption was also identified as a risk factor for the presence of suspected POAG.

Table 3 Distribution and relationship between POAG diagnosis according to the OPP

Ocular perfusion pressure	Confirmed POAG N (%)	Suspected POAG N (%)	No POAG N (%)	OR (95% CI) confirmed/ no GPAA[a]	OR (95% CI) suspected/ no GPAA[a]
SPP, mmHg					
<100	22 (33.8)	31 (23.7)	229 (21.3)	1.7 (0.8–3.6)	0.9 (0.6–1.7)
101–110	14 (21.5)	36 (27.5)	347 (32.2)	0.9 (0.4–1.9)	0.7 (0.4–1.2)
111–120	14 (21.5)	42 (32.1)	295 (27.4)	1	1
121–130	4 (6.1)	11 (8.4)	120 (11.1)	0.7 (0.2–2.3)	0.7 (0.4–1.5)
>130	11 (16.9)	11 (8.4)	85 (7.9)	2.7 (1.1–6.4)**	0.8 (0.4–1.7)
DPP, mmHg					
<50	14 (21.5)	19 (14.5)	132 (12.3)	2.2 (1.0–5.1)**	1.4 (0.8–2.5)
51–60	24 (36.9)	38 (29.0)	334 (31.0)	1.7 (0.8–3.4)	1.0 (0.6–1.6)
61–70	15 (23.1)	49 (37.4)	402 (37.4)	1	1
>70	12 (18.5)	25 (19.1)	208 (19.3)	1.7 (0.8–3.8)	1.0 (0.6–1.7)
OPP, mmHg					
<40	18 (27.7)	23 (17.6)	149 (13.8)	2.1 (1.1–4.1)**	1.4 (0.8–2.3)
41–50	26 (40.0)	62 (47.3)	525 (48.8)	1	1
51–60	16 (24.6)	43 (32.8)	346 (32.2)	1.1 (0.5–2.1)	1.0 (0.6–1.5)
>60	5 (7.7)	3 (3.3)	56 (5.2)	1.8 (0.6–5.2)	0.1 (0.1–1.6)

Notes: **p-value <0.05; [a]multinomial logistic regression adjusted for age, sex, diabetes, type of antihypertensive drug and IOP.
Abbreviations: POAG, primary open-angle glaucoma; SPP, systolic perfusion pressure; DPP, diastolic perfusion pressure; OPP, ocular perfusion pressure; IOP, intraocular pressure.

These findings may be considered paradoxical, but it could be explained, in part, by several confounding factors such as the degree of adherence to treatment, time of drug intake and doses received. Although our results suggest a relationship between ARBs and POAG, these have not been documented in the literature. However, other authors have found that the consumption of ACE-I may be related to a higher risk of POAG, and B-blocker consumption could decrease the risk of development of glaucoma.[22,23]

This study used a standardized protocol and a universal definition of glaucoma, which allows the comparison with other studies. Our main limitation is the use of a single measurement of BP, which may be biased by the variability of BP in patients with hypertension. Therefore, this generates uncertainty about the association found between BP values and POAG. Another limitation is the lack of control characterization of baseline condition of the participants (antihypertensive medication, time of drug intake and doses consumption). This information could help to identify if there are differences between controlled and uncontrolled hypertensive patients.

Conclusion

The findings of our cross-sectional study in hypertensive patients suggest that there is a close relationship between OPP values and confirmed POAG, providing further evidence of the vascular mechanism in glaucoma pathogenesis. Complementary studies are needed to evaluate the influence of the types of antihypertensive drug in the ocular blood flow.

Acknowledgments

The authors would like to thank Tecnoquimicas SA for their financial support for this study. The funder had no role in the design of the study and collection, analysis and interpretation of data, and writing the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014; 121(11):2081–2090.
2. Caprioli J, Coleman AL; Blood Flow in Glaucoma Discussion. Blood pressure, perfusion pressure, and glaucoma. *Am J Ophthalmol*. 2010; 149(5):704–712.
3. Yanagi M, Kawasaki R, Wang JJ, Wong TY, Crowston J, Kiuchi Y. Vascular risk factors in glaucoma: a review. *Clin Exp Ophthalmol*. 2011;39(3):252–258.
4. Harris A, Werne A, Cantor LB. Vascular abnormalities in glaucoma: from population-based studies to the clinic? *Am J Ophthalmol*. 2008; 145(4):595–597.
5. Memarzadeh F, Ying-Lai M, Azen SP, Varma R; Los Angeles Latino Eye Study Group. Associations with intraocular pressure in Latinos: the Los Angeles Latino Eye Study. *Am J Ophthalmol*. 2008;146(1):69–76.
6. Klein BEK, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. *Br J Ophthalmol*. 2005;89(3):284–287.
7. Chan MPY, Grossi CM, Khawaja AP, et al; UK Biobank Eye and Vision Consortium. Associations with intraocular pressure in a large cohort: results from the UK Biobank. *Ophthalmology*. 2016;123(4):771–782.
8. Chung HJ, Hwang HB, Lee NY. The association between primary open-angle glaucoma and blood pressure: two aspects of hypertension and hypotension. *Biomed Res Int*. 2015;2015:827516.
9. Memarzadeh F, Ying-Lai M, Chung J, Azen SP, Varma R; Los Angeles Latino Eye Study Group. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51(6):2872–2877.
10. Resch H, Garhofer G, Fuchsjäger-Mayrl G, Hommer A, Schmetterer L. Endothelial dysfunction in glaucoma. *Acta Ophthalmol*. 2009;87(1): 4–12.
11. He Z, Vingrys AJ, Armitage JA, Bui BV. The role of blood pressure in glaucoma. *Clin Exp Optom*. 2011;94(2):133–149.
12. Moore D, Harris A, Wudunn D, Kheradiya N, Siesky B. Dysfunctional regulation of ocular blood flow: a risk factor for glaucoma? *Clin Ophthalmol*. 2008;2(4):849–861.
13. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol*. 2002;86(2):238–242.
14. Broadway DC. Visual field testing for glaucoma – a practical guide. *Community Eye Health*. 2012;25(79–80):66–70.
15. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159–2219.
16. Zheng Y, Wong TY, Mitchell P, Friedman DS, He M, Aung T. Distribution of ocular perfusion pressure and its relationship with open-angle glaucoma: the singapore malay eye study. *Investig Ophthalmol Vis Sci*. 2010;51(7):3399–3404.
17. Tham YC, Lim SH, Gupta P, Aung T, Wong TY, Cheng CY. Inter-relationship between ocular perfusion pressure, blood pressure, intraocular pressure profiles and primary open-angle glaucoma: the Singapore Epidemiology of Eye Diseases study. *Br J Ophthalmol*. Epub 2018 Jan 13.
18. Hulsman C, Vingerling JR, Hofman A, Witteman JC, de Jong PT. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. *Arch Ophthalmol*. 2007;125(6):805–812.
19. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: proyecto VER. *Arch Ophthalmol*. 2001;119(12):1819–1826.
20. Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B; BESs Study Group. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. *Ophthalmology*. 2008;115(1):85–93.
21. Doshi V, Ying-Lai M, Azen SP, Varma R; Los Angeles Latino Eye Study Group. Sociodemographic, family history, and lifestyle risk factors for open-angle glaucoma and ocular hypertension. The Los Angeles Latino Eye Study. *Ophthalmology*. 2008;115(4):639.e2–647.e2.
22. Owen CG, Carey IM, Shah S, et al. Hypotensive medication, statins, and the risk of glaucoma. *Invest Ophthalmol Vis Sci*. 2010;51(7): 3524–3530.
23. Müskens RP, de Voogd S, Wolfs RC, et al. Systemic antihypertensive medication and incident open-angle glaucoma. *Ophthalmology*. 2007; 114(12):2221–2226.

Short Communication

For reprint orders, please contact: reprints@futuremedicine.com

Biomarkers in Medicine

Low-level expression of *SOD1* in peripheral blood samples of patients diagnosed with primary open-angle glaucoma

Aim: Glaucoma is a multifactorial disease of retinal ganglion cells, with low prognosis. For that reason, the identification of biomarkers in peripheral blood samples for diagnostics and treatment of the disease is needed. To establish mRNA expression level of several oxidative stress biomarkers reported in aqueous humor of patients with primary open-angle glaucoma (POAG). **Materials & methods:** The mRNA expression levels of eight genes from 15 patients diagnosed with POAG and 11 control subjects were analyzed using an RT^2 Custom Profiler PCR Array. **Results:** mRNA expression level of superoxide dismutase 1 (SOD1) showed a significant downregulation in patients diagnosed with POAG in respect to control subjects. The low expression of SOD1 found in blood is consistent with the reported proteomic levels in aqueous humor. **Conclusion:** SOD1 may be a useful biomarker in the peripheral blood of patients diagnosed with POAG.

First draft submitted: 11 June 2016; Accepted for publication: 27 September 2016; Published online: 7 December 2016

Keywords: antioxidant defense • biomarkers • glaucoma • mRNA • oxidative stress • PCR array • SOD1 • trabecular meshwork

Licelly Canizales[1], Laura Rodriguez[2], Carlos Rivera[3], Alexander Martinez[4], Fabián Mendez[5] & Andres Castillo*[,2]

[1]Department of Biology, Faculty of Natural Sciences, Universidad ICESI, Calle 18 No. 122–135, Cali - Colombia

[2]Department of Biology, Faculty of Natural & Exact Sciences, Universidad del Valle, Calle 13 No. 100–00, Cali - Colombia

[3]Centro Medico Farallones, Fundacion Oftalmologica del Valle, Calle 9 c 50–25 cons 400, Cali - Colombia

[4]Ophthalmology Residency Program, Universidad del Valle & Centro Medico Imbanaco, Carrera 38 A No. 5A 100, Cali - Colombia

[5]School of Public Health, GESP Group, Universidad del Valle, Calle 4B No. 36A-140, Cali - Colombia

*Author for correspondence: andres.castillo.g@correounivalle.edu.co

Glaucoma is a multifactorial disease that results in the apoptosis of retinal ganglion cells [1]. Apoptosis is induced by the inhibition of cell survival, and involves many components and metabolites, and concerns the whole nerve pathway from the retina reaching the calcarine sulcus.

Glaucoma is the leading cause of irreversible blindness worldwide and the status of intraocular pressure (IOP) as a defining characteristic of glaucoma has evolved over time [2]. When the optic nerve tissue is significantly damaged, patients develop a reduction in the visual field and even before clinical detection, they may lose a significant amount of optic nerve tissue. For this reason, early diagnosis is important to anticipate visual loss. The risk of glaucoma increases with age [3]. Other risk factors for the development and evolution of glaucoma are family history, high blood pressure and diabetes mellitus [4]. Likewise, African Americans have an increased risk of developing the disease [5].

The most common type of glaucoma is primary open-angle glaucoma (POAG), involving 60–70% of all cases. POAG is a chronic, asymptomatic and slow progression disease. Diagnosis is delayed and frequently performed when the patient has already lost 40–50% of the optic nerve fibers, and the visual damage is significant [6]. The relationship between high IOP and glaucomatous lesions of the optic nerve is evident, but the existence of a type of glaucoma with normal IOP (Normotensive glaucoma) indicates that other factors must play a significant role in glaucoma pathogenesis [7].

In 2012, proteomic expression level in the aqueous humor of patients with POAG versus control subjects was reported [8]. In this study, the results suggested that several

Future Medicine part of fsg

oxidative stress enzymes may be useful biomarkers of glaucomatous patients, such as glutamine synthase, nitric oxide (NO) synthase, superoxide dismutase (SOD) and glutathione transferase.

The aim of this study was to develop a noninvasive peripheral blood-based method to investigate the expression level of several oxidative stress biomarkers reported by proteomic levels in aqueous humor of patients with POAG.

Materials & methods

Study design

We evaluated the mRNA expression levels of eight oxidative stress genes, from peripheral blood samples of 26 participants over 50 years of age, using an RT^2 Custom Profiler PCR Array. Fifteen patients diagnosed with POAG and 11 control subjects were included in the present study.

As inclusion criteria, all participants voluntarily agreed to participate in the study by signing the informed consent document (#05–014 granted by the Humans Ethics Committee of the Universidad Del Valle, Cali - Colombia), had received a clinical diagnosis of POAG and were over 50 years of age. As exclusion criteria, they had no associated co-morbidities, severe renal failure, congestive heart failure, sleep apnea, autoimmune diseases with biological therapy, previous intraocular eye surgery such as complicated cataract surgery, trauma, retinal detachment, disease macular degeneration or congenital eye diseases such as coloboma.

Peripheral blood sample

2.5 ml of peripheral blood samples was collected and stored in Vacutainers® Plus K2 EDTA tubes. Participants who had a recent blood transfusion (<30 days) were also excluded.

mRNA isolation & cDNA conversion

Total RNA isolation was performed using PAXgene Blood RNA Kit (Qiagen, catalog number 762174). RNA concentrations were quantified using a Nanodrop spectrophotometer machine. The mRNAs were converted to cDNA using the RT^2 First Strand Kit (Qiagen, # 330401).

PCR arrays for differential expression genes

The samples were evaluated using RT^2 Custom Profiler PCR Array (Qiagen, # 330131CAPA9612–12) built with genes associated with oxidative stress (Table 1) and SYBR Green Master Mix (Qiagen, 330502 catalog number). A Bio-Rad CFX96 thermal cycler was used. Gene expression profiles were established using

Table 1. Genes associated with oxidative stress processes used in PCR array.

Gene names	Abbreviations	Function
Angiotensin I converting enzyme	ACE	The enzyme involved in the conversion of angiotensin I into a physiologically active peptide angiotensin II. Angiotensin II is a potent vasopressor and aldosterone-stimulating peptide that controls blood pressure and fluid-electrolyte balance.
Angiotensin II converting enzyme	ACE2	Enzyme involves the cleavage of angiotensin I into angiotensin 1–9, and angiotensin II into the vasodilator angiotensin 1–7.
Angiotensin II receptor, type 1	AGTR1	Receptor for angiotensin II. Mediates its action by association with G proteins that active a phosphatidylinositol-calcium second messenger system.
Glutathione peroxidase 1	GPX1	Glutathione peroxidase functions in the detoxification of hydrogen peroxide and is one of the most important antioxidant enzymes in humans.
Glutathione reductase	GSR	It is a central enzyme of cellular antioxidant defense and reduces oxidized glutathione disulfide (GSSG) to the sulfhydryl form, which is an important cellular antioxidant.
Superoxide dismutase 1	SOD1	Enzyme responsible for destroying free superoxide radicals in the body.
Superoxide dismutase 2	SOD2	This mitochondrial protein binds to the superoxide byproducts of oxidative phosphorylation and converts them to hydrogen peroxide and diatomic oxygen.
Glyceraldehyde-3-phosphate dehydrogenase	GAPDH	Used as a reference gene for normalization of mRNA expression.

Table 2. Expression of genes associated with oxidative stress present in apparently healthy participants (control) versus patients diagnosed with primary open-angle glaucoma.

Genes	Control (n = 11) rank sum/expected	Glaucoma (n = 15) rank sum/expected	p-value
ACE	10/6.5	68/71.5	0.30
ACE2	29/24	91/96	0.46
AGTR1	30/34	106/102	0.62
GPX1	97.5/148.5	253.5/202.5	0.01**
GSR	48/60	142/130	0.29
SOD1	187.5/148.5	163.5/202.5	0.04*
SOD2	109.5/148.5	241.5/202.5	0.04*

*$p < 0.05$.
**$p < 0.001$.
ACE: Angiotensin I converting enzyme; ACE2: Angiotensin II converting enzyme; AGTR1: Angiotensin II receptor, type 1; GPX1: Glutathione peroxidase 1; GSR: Glutathione reductase; SOD1: Superoxide dismutase 1; SOD2: Superoxide dismutase 2.

the $2^{-\Delta\Delta CT}$ method. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has been used as an endogenous control for gene expression.

Statistical analysis

Gene expression profiles were analyzed by Stata 11.0 software. Raw data from PCR arrays were transformed and normalized, taking GAPDH as a reference gene. Gene expression differences between groups were analyzed using the sum of ranks of Wilcoxon (Mann–Whitney) test.

Results & discussion

Differential expression genes associated with oxidative stress in patients diagnosed with POAG versus control subjects showed significant differences for glutathione peroxidase 1 (GPX1; p = 0.01), SOD1 (p = 0.04) and SOD2 (p = 0.04), as shown in Table 2.

Currently, information regarding oxidative stress effects on glaucoma development is limited. A mechanistic hypothesis proposed that the loss of antioxidant defenses linked with the decrease in antioxidant levels could influence disease development, due to the increase of reactive oxygen species in cells. Specifically, its increasing levels could damage the plasma membrane of cells through the lipid peroxidation pathway [9]. Usually, lipid peroxidation level is linked to the degree of cellular damage, which means that a high peroxidation due to increased interaction between lipid and reactive species could cause lysis of the plasma membrane, leading to death by necrosis. In the present study, we found that GPX1 and SOD2 gene expression were higher in POAG patients than in subjects of the control group. In contrast, the expression of SOD1 was lower in POAG group than the control group. Our results correlate with the decrease in SOD1 protein expression reported in 2012 by two independent studies, both in the aqueous humor of POAG patients [8,10]. SOD1 is an enzyme that plays an essential role in the antioxidant defense for humans [11]. The lower expression of SOD1 found in peripheral blood samples could be proposed as an important noninvasive biomarker for POAG diagnosis.

Oxidative stress must not be the only factor considered for glaucoma development. The nitrosamine stress could be produced principally by NO action and the presence of toxic nitrogen species that have the capability to cause damage at cellular and tissue levels and could be related to glaucoma disease. NO has a considerable importance in the organism for its active participation in multiple processes linked to blood pressure regulation. In abnormal levels, NO behaves as a free radical, and in the presence of oxygen or other reactive species, it generates toxic forms inducing damage to lipids, proteins and nucleic acids [9]. The results of this study suggest that the oxidative stress has an impact on POAG. Decreasing expression of SOD1 could be promoting an increase of reactive species, like anion superoxide ($O2^{\bullet}$). This species reacts with NO, resulting in cytotoxic peroxynitrite anion formation, which could lead to damage in endothelial cells of the trabecular meshwork (TM) in the eye, which are highly sensitive to oxidative damage. The TM is the most important anterior chamber structure in the development of glaucoma because it allows the path of aqueous humor to the schlemm canal. Unfortunately, the TM is more sensitive to oxidative damage than other tissues that compose the anterior chamber, so the development and progression of glaucoma are accompanied by accumulation of oxidative damage in this tissue [6]. We could indicate that a continuous accumulation of damage at this level is an important pathogenic factor for the IOP increase [8], which consequently induces the development of glaucoma. However, we could not find a cor-

relation between SOD1 levels and an IOP increasing. This could be because IOP increasing is just one risk factor for POAG. We lack information about other genes that could be playing an important role in the pathway involved in the TM damage and subsequent disease pathology.

Several authors agree that a glutamate increase could cause the opening of calcium channels and as a result, promote an intracellular overload of calcium [12,13]. The increase in the intracellular calcium activates the NO synthase inducing an increment of NO levels. As we previously discuss, an excess of NO will divert the production of peroxynitrite compounds, which is highly toxic to the organism, inducing cell death by apoptosis in retinal photoreceptor cells.

Conclusion

Low expression levels of SOD1 in peripheral blood is consistent with the reported proteomic levels in aqueous humor [8]. Therefore, SOD1 may be a useful biomarker in the peripheral blood of patients diagnosed with POAG. This finding raises the need for population studies to validate SOD1 as a biomarker using this noninvasive peripheral blood method in patients diagnosed with POAG.

Future perspective

The use of molecular techniques to detect molecular entities such as SOD1 in peripheral blood samples may be useful as a potential tool to personalize the diagnosis and treatment of glaucoma. Indeed, SOD1 could indirectly reflect the oxidative stress level present in the aqueous humor of glaucoma patients. At the same time, SOD1 may be a useful biomarker in the peripheral blood of patients diagnosed with POAG. Due to the asymptomatic nature of the disease, SOD1 could potentially become a screening biomarker in a population with risk factors for glaucoma. Population-based studies are required to prove this, however, the detection of biomarkers like SOD1 revealing aspects of the POAG process could be improving the knowledge for the clinicians to understand and monitor a patient's response to treatments in the coming years.

Financial & competing interests disclosure

Tecnoquimicas S.A. financially supported this study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

- Glaucoma is a multifactorial disease of retinal ganglion cells and the leading cause of irreversible blindness worldwide.
- The aim of this study was to develop a noninvasive blood-based method to investigate the expression level of several oxidative stress biomarkers reported by proteomic level in aqueous humor of patients with primary open-angle glaucoma (POAG).
- The mRNA expression of eight oxidative stress genes from 15 patients diagnosed with POAG and 11 control subjects was analyzed using an RT^2 Custom Profiler PCR Array.
- Differential expression genes associated with oxidative stress in patients diagnosed with POAG versus control subjects showed significant differences for glutathione peroxidase 1, superoxide dismutase 1 (SOD1) and SOD2.
- The expression of SOD1 was lower in the POAG group than the control group.
- SOD1 is an enzyme that plays an essential role in the antioxidant defense for humans.
- Low expression levels of SOD1 in peripheral blood samples could be proposed as an important noninvasive biomarker for POAG diagnosis.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1 Saccà SC, Gandolfi S, Bagnis A *et al.* From DNA damage to functional changes of the trabecular meshwork in aging and glaucoma. *Ageing Res. Rev.* 29, 26–41 (2016).

• **Oxidative stress as pathogenetic mechanism for glaucoma is proposed.**

2 Casson RJ, Chidlow G, Wood JP, Crowston JG, Goldberg I. Definition of glaucoma: clinical and experimental concepts. *Clin. Exp. Ophthalmol.* 40(4), 341–349 (2012).

3 Fechtner RD, Khouri AS. Evolving global risk assessment of ocular hypertension to glaucoma. *Curr. Opin. Ophthalmol.* 18(2), 104–109 (2007).

4 Pasquale LR, Kang JH, Manson JE, Willett WC, Rosner BA, Hankinson SE. Prospective study of type 2 diabetes

mellitus and risk of primary open-angle glaucoma in women. *Ophthalmology* 113(7), 1081–1086 (2006).

5 Kosoko-Lasaki O, Gong G, Haynatzki G, Wilson MR. Race, ethnicity and prevalence of primary open-angle glaucoma. *J. Natl Med. Assoc.* 98(10), 1626–1629 (2006).

6 Izzotti A, Saccà SC, Longobardi M, Cartiglia C. Sensitivity of ocular anterior chamber tissues to oxidative damage and its relevance to the pathogenesis of glaucoma. *Invest. Ophthalmol. Vis. Sci.* 50(11), 5251–5258 (2009).

• **The trabecular meshwork shows the highest sensitivity levels of oxidative damage.**

7 Babar TF, Khan MF, Zaman M, Khan MD. Normal tension glaucoma. *Pak. J. Ophthalmol.* 22(2), 60–67 (2006).

8 Bagnis A, Izzotti A, Centofanti M, Saccà SC. Aqueous humor oxidative stress proteomic levels in primary open-angle glaucoma. *Exp. Eye Res.* 103, 55–62 (2012).

•• **Data support the evidence that a progressive accumulation of oxidative stress in the anterior chamber of the eye occurs during primary open-angle glaucoma.**

9 Therond P. Oxidative stress and damages to biomolecules (lipids, proteins, DNA). *Ann. Pharm. Franç.* 64(6), 383–389 (2006).

10 Saccà SC, Centofanti M, Izzotti A. New proteins as vascular biomarkers in primary open-angle glaucomatous aqueous humor. *Inv. Ophthalmol. Vis. Sci.* 53(7), 4242–4253 (2012).

•• **Found levels of 13 proteins significantly increased in the aqueous humor of glaucomatous patients compared with expression levels in healthy controls.**

11 Matés JM, Pérez-Gómez C, Nuñez de Castro I. Antioxidant enzymes and human diseases. *Clin. Bioch.* 32(8), 595–603 (1999).

12 Nucci C, Tartaglione R, Rombolà L, Morrone LA, Fazzi E, Bagetta G. Neurochemical evidence to implicate elevated glutamate in the mechanisms of high intraocular pressure (IOP)-induced retinal ganglion cell death in rat. *Neurotoxicology* 26, 935–941 (2005).

13 Quigley H. Neuronal death in glaucoma. *Prog. Ret. Eye Res.* 18(1), 35–39 (1998).

CASE REPORT
DOI: 10.5603/OJ.2021.0028

Ultra biomicroscopy findings in goniotomy-assisted transluminal trabeculotomy — a case report

Catalina Ferreira[1–4], Carlos Eduardo Rivera[1–4], Juan Carlos Aristizabal[1, 2], Ankur Seth[1, 3, 5], Edgar Muñoz

[1]Collective Innovations Colombia, Cali, Colombia
[2]Pontificia Universidad Javeriana, Cali, Colombia
[3]GSR Medical Center, Cali, Colombia
[4]GSR International, United States
[5]University of Tennessee Health Science Center, United States

ABSTRACT

BACKGROUND: Goniotomy-assisted transluminal trabeculotomy (GATT) is a minimally invasive technique that avoids conjunctival incision and is guided by light through the Schlemm's canal using a microcatheter with an illuminated tip. This technique decreases intraocular pressure (IOP) by improving flow through the Schlemm's canal. We present two cases of glaucoma patients who underwent GATT surgery for IOP control.

CASES PRESENTATION: The first case is a 19-year patient with juvenile glaucoma that underwent GATT because of uncontrolled IOP with a successful outcome. The second case is a 64-year female patient with primary open-angle glaucoma who underwent GATT surgery because of uncontrolled IOP who presented a cyclodialysis secondary to the procedure, with an adequate IOP after surgery. Ultra biomicroscopy (UBM) was used to assess the anatomical changes associated with surgery.

CONCLUSIONS: Goniotomy-assisted transluminal trabeculotomy is a safe technique but not free of risks and potential complications. Ultra biomicroscopy is a diagnostic aid that allows us to provide valuable information to evaluate the pre-surgical, post-surgical anatomy and possible complications to follow-up and guide the management in required cases.

KEY WORDS: glaucoma; intraocular pressure; goniotomy-assisted transluminal trabeculotomy

Ophthalmol J 2021; Vol. 6, 178–183

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide. It is estimated that 3.54% of the population in the world has this disease [1]. Although effective in many cases, medical treatment represents a challenge, mainly due to poor adherence, drug toxicity, and, in developing countries, the costs and access to medications are common barriers.

An alternative to conventional trabeculectomy or drainage devices for glaucoma that represents serious risks and complications for patients is minimally invasive glaucoma surgery. It is a safer option,

CORRESPONDING AUTHOR:
Carlos Rivera, Holguines Trade Center, Cra 10 11-60, office 236, tel: (2) 3165225961, (572) 5546567; e-mail: carlosriverahoyos@gmail.com, crivera@grupogsr.co

which helps decrease intraocular pressure (IOP) and reduces dependence on medications [1].

Goniotomy-assisted transluminal trabeculotomy (GATT), described by Grover et al. in 2014 [2], reduces IOP, increasing the flow of aqueous humor through the Schlemm's canal and collector channels. It is carried out with an illuminated microcatheter or a prolene 5-0 that helps identify and cannulate the Schlemm's canal in 360 degrees. Once the catheter is in position, it is pulled, causing a rupture of the trabecular meshwork. This technique uses an *ab interno* approach, is sutureless, and utilizes a conjunctival sparing technique for possible future interventions. It can be done alone or in combination with cataract surgery.

Although the treatment is 360 degrees of the angle, it is not possible in some cases. It can be limited between 180 to 300 degrees, with successful results leading to reduced IOP at 12 months follow-up [3].

Initially, GATT was indicated for primary congenital glaucoma, but recently, it has been used successfully for mild to moderate glaucoma in adults with open-angle glaucoma and juvenile glaucoma [2, 4, 5].

The most frequent complication during the first week is hyphema that resolves spontaneously [4]. Other potential complications are flattening of the anterior chamber, choroidal folds due to hypotonia, choroidal effusion, and vitreous hemorrhage [4, 6].

In the postoperative period, after resorption of the hyphema, a posterior leaflet of the trabeculae appears, called the trabecular shelf, which sometimes adheres to the peripheral iris and is seen protruding on it. This is indicative of a good surgical result [2, 4].

GATT surgery in developing countries may be limited due to high associated costs. Long-term follow-up is necessary to verify if there is a closure of drainage because of scarring of the Schlemm's canal.

In this study, we present outcomes in two postoperative clinical cases of GATT with ultra-biomicroscopic findings.

CASE 1

A 19-years-old man presented to the clinic with a 3-year diagnosis of juvenile glaucoma. The patient had been treated with brimonidine, dorzolamide, and timolol. The visual acuity (VA) of the right eye (RE) was 20/25 and in the left eye (LE) was hand movement. In the RE, he had an IOP of 13 mm Hg, open angles, and a cup/disc ratio of 0.95 excavation with superior and inferior rim thinning.

In the LE, he had an afferent pupillary defect, IOP of 34 mm Hg, open angles, and a cup/disc ratio of 100%.

It was decided to perform a GATT surgery in the LE in order to control the IOP.

In the postoperative period (POP), he presented with a hyphema that was reabsorbed in less than a week, with no sequelae. Intraocular pressure has stabilized at 12 mm Hg without medication after a year of follow-up.

In Figure 1, the ultrasound biomicroscopy shows the trabecular shelf after GATT surgery.

Patient data is not identifiable.

CASE 2

A 64-year-old female presented to the clinic with a diagnosis of primary open-angle glaucoma. The patient had received maximum medical treatment with brimonidine, dorzolamide, timolol, and latanoprost.

The corrected VA in the RE was finger counting and in the LE was 20/25.

In the RE, she had a dense cataract, the IOP was 26 mm Hg, open angle, and cup/disc ratio of 0.8 with a double notch.

In the LE, the IOP was 14 mm Hg and a cup/disc ratio of 0.6 with a slight inferior rim thinning.

Because she presented a cataract with a poorly controlled IOP despite a maximum medical treatment, it was decided to perform a combined (GATT) surgery and cataract extraction by phacoemulsification.

During the catheter insertion in the trabecular meshwork, an obstruction was felt after it passed the first quadrant and the illumination tip was not visible, so it was decided to stop the procedure and remove the catheter.

On the 4th day after surgery, she presented an IOP of 5 mm Hg and a 100% hyphema that prevented properly assessing the anterior and posterior segment.

A RE ultrasound was performed (Fig. 2–5): a hyphema was occupying almost all of the anterior chamber, the intraocular lens in the capsular bag, a plane ciliochoroidal detachment, a nasal cyclodialysis, and a cystic space in the temporal ciliary body, which was associated with a false route of the microcatheter.

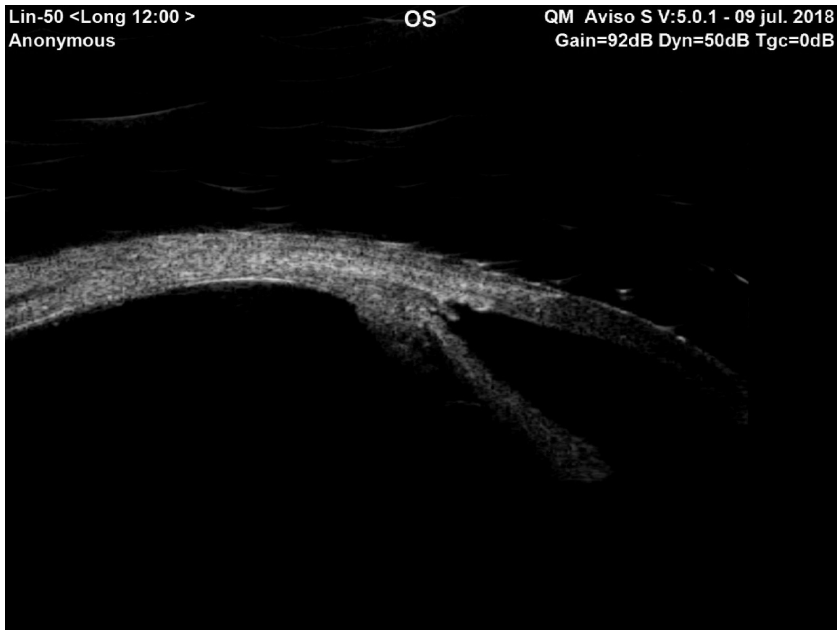


FIGURE 1. Ultra biomicroscopy (UBM): longitudinal section of the anterior chamber angle in a patient after a goniotomy-assisted transluminal trabeculotomy (GATT). There is an open Schlemm's canal and trabecular shelf

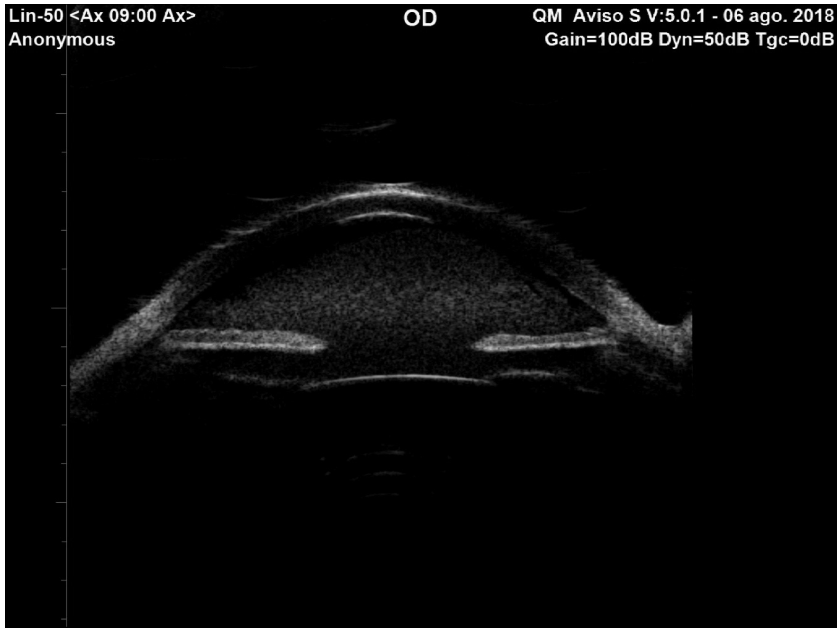


FIGURE 2. Ultra biomicroscopy (UBM): axial section. Intraocular lens in adequate position and a hyphema that occupies a large part of the anterior chamber

Management was started with cyclopentolate 1 %, three times a day, and at day 14th POP, total reabsorption of the hyphema was found, with an IOP in 10 mm Hg without medication. In the LE, the IOP was 19 mm Hg with maximum medical treatment.

The corrected VA in the RE was 20/30 and in the LE was 20/25. The patient had a follow-up of 2 years where the IOP remains at 10 mm Hg. Apparently, the limited cyclodialysis helped control the IOP.

Patients' data are not identifiable.

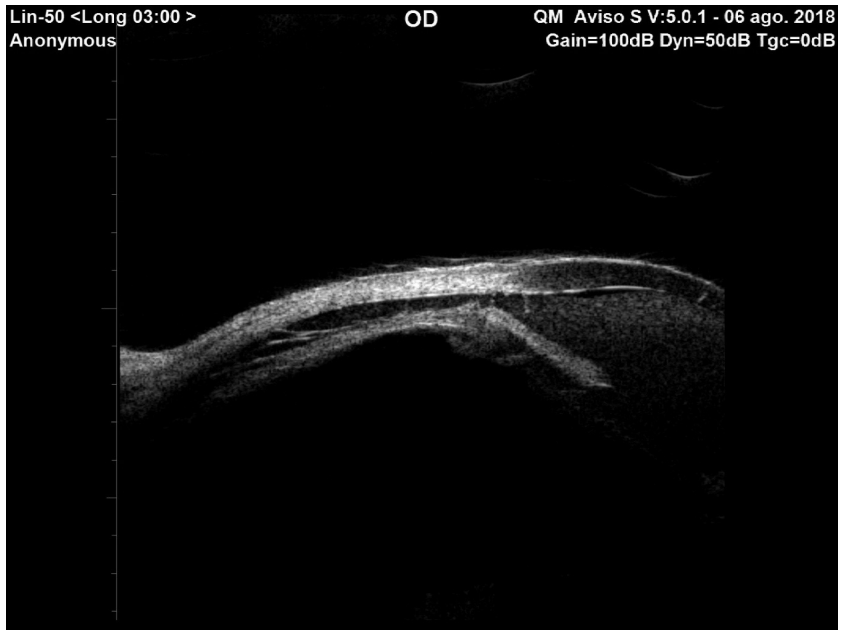


FIGURE 3. Ultra biomicroscopy (UBM): longitudinal section showing an iridodialysis, a ciliary body detachment, and a supraciliary effusion

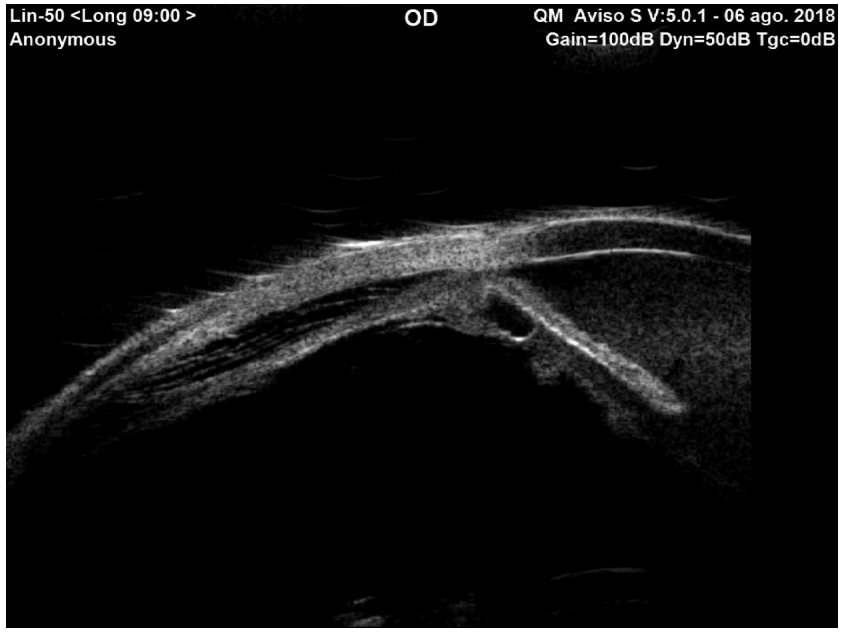


FIGURE 4. Ultra biomicroscopy (UBM): longitudinal section. Hyphema and a cystic space in the ciliary body associated with a cyclodialysis and a uveal effusion. It is likely that a misdirected catheter produces this cyst

DISCUSSION

Goniotomy-assisted transluminal trabeculotomy is a minimally invasive glaucoma surgery with an internal approach that improves the aqueous outflow through the Schlemm's canal and is based on the fact that the juxtacanalicular system is the point of the greatest resistance to flow in most cases of open-angle glaucoma [1]. It does not require a conjunctival or scleral incision and is safe and effective. Goniotomy-assisted transluminal trabeculotomy has a success rate between 68% and 90% in cases of open-angle glaucoma in children and adults [4].

Despite the advantage represented by the illumination of the catheter and that the success

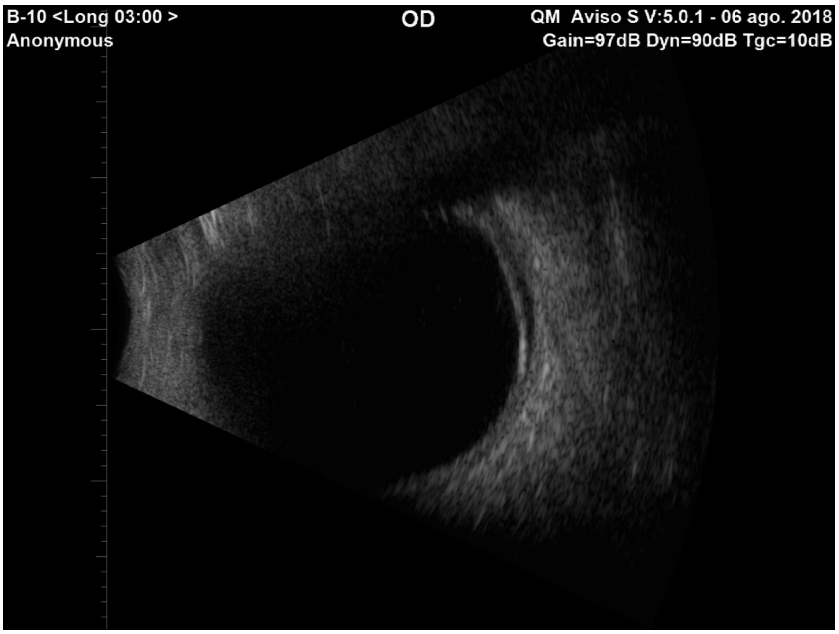


FIGURE 5. B-mode ultrasound with a 10 MHz probe in which a choroidal flat detachment is shown. Space in the ciliary body is associated with a cyclodialysis and a uveal effusion. A misdirected catheter likely produces this cyst

rate is high, the possibility of complications, such as misdirection of the catheter, can occur and have serious consequences depending on the direction taken [2].

Fortunately, thanks to the illuminated tip, it is noteworthy that it is easy to notice misdirection, in which case it can be retracted and repositioned. A posterior direction of the light should alert to a possible unnoticed passage to the sub choroid or subretinal space [7, 8].

Ultra biomicroscopy (UBM) can be used as a diagnostic tool to evaluate the pre- and post-operative anatomy. It allows visualizing complications with refractive media opacity to search for causes and provide adequate management and follow-up to patients.

UBM should be used as an elective technique in patients with suspected post-surgical or post-traumatic cyclodialysis or iridodialysis. It allows evaluation of the lesions, delimits lateral and antero-posterior extensions describing detailed choroidal compromise. The morphology of the angle and ciliary body is clearly observed, ruling out associated pathology [9].

Cyclo- and iridodyalisis can be underdiagnosed conditions or go unnoticed, being treated empirically or having spontaneous regression, mainly in cases of opaque media [9].

CONCLUSION

Goniotomy-assisted transluminal trabeculotomy surgery has a relatively long learning curve, which requires at least 5 to 10 procedures and is not free of risks and complications. The surgeon who wants to learn should handle the anatomy of the anterior chamber angle, angle of surgery and be sufficiently trained to operate with gonioprism [4]. Absolute contraindications for the procedure must be taken into account, which are the use of anticoagulants that cannot be suspended, unstable IOP, angular closure, severe endothelial compromise, or poor visualization of the trabecular meshwork [4]. Ultra biomicroscopy is a diagnostic aid that allows us to provide valuable information to evaluate the pre-surgical, post-surgical anatomy and possible complications to follow up and give guidance on the management in required cases.

REFERENCES

1. Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. Clin Ophthalmol. 2016; 10: 189–206, doi: 10.2147/OPTH.S80490, indexed in Pubmed: 26869753.
2. Grover D, Godfrey D, Smith O, et al. Gonioscopy-Assisted Transluminal Trabeculotomy, Ab Interno Trabeculotomy. Ophthalmology. 2014; 121(4): 855–861, doi: 10.1016/j.ophtha.2013.11.001, indexed in Pubmed: 24412282.
3. Shi Y, Wang H, Yin J, et al. Microcatheter-assisted trabeculotomy versus rigid probe trabeculotomy in childhood glaucoma. Br J Ophthalmol. 2016; 100(9): 1257–1262, doi: 10.1136/bjophthalmol-2015-307880, indexed in Pubmed: 26674778.

4. Grover DS, Smith O, Fellman RL, et al. Gonioscopy assisted transluminal trabeculotomy: an ab interno circumferential trabeculotomy for the treatment of primary congenital glaucoma and juvenile open angle glaucoma. Br J Ophthalmol. 2015; 99(8): 1092–1096, doi: 10.1136/bjophthalmol-2014-306269, indexed in Pubmed: 25677669.
5. Lim ME, Dao JB, Freedman SF. 360-Degree Trabeculotomy for Medically Refractory Glaucoma Following Cataract Surgery and Juvenile Open-Angle Glaucoma. Am J Ophthalmol. 2017; 175: 1–7, doi: 10.1016/j.ajo.2016.11.011, indexed in Pubmed: 27916715.
6. Shakrawal J, Bali S, Sidhu T, et al. Randomized Trial on Illuminated-Microcatheter Circumferential Trabeculotomy Versus Conventional Trabeculotomy in Congenital Glaucoma. Am J Ophthalmol. 2017; 180: 158–164, doi: 10.1016/j.ajo.2017.06.004, indexed in Pubmed: 28624326.
7. Sarkisian SR. An illuminated microcatheter for 360-degree trabeculotomy [corrected] in congenital glaucoma: a retrospective case series. J AAPOS. 2010; 14(5): 412–416, doi: 10.1016/j.jaapos.2010.07.010, indexed in Pubmed: 21035067.
8. Verner-Cole EA, Ortiz S, Bell NP, et al. Subretinal suture misdirection during 360 degrees suture trabeculotomy. Am J Ophthalmol. 2006; 141(2): 391–392, doi: 10.1016/j.ajo.2005.08.038, indexed in Pubmed: 16458706.
9. Koga-Nakamura, W. Ultrabiomicroscopía y ciclodiálisis. Rev Mex Oftalmol. 2007; 81(6): 326–333.

CASE REPORT
DOI: 10.5603/OJ.2021.0033

Retinal detachment with a giant bleeding cyst, simulating a uveal melanoma — a case report

Catalina Ferreira[1–4], Carlos Eduardo Rivera[1–4], Eduard Muñoz[1], Ankur Seth[1, 3, 6], Juan Carlos Aristizaba[2]

[1]Collective Innovations, Cali, Colombia
[2]Pontificia Universidad Javeriana, Cali, Colombia
[3]GSR Medical Center, Cali, Colombia
[4]GSR International, United States
[5]UT Health San Antonio, San Antonio, United States
[6]University of Tennessee Health Science Center, San Antonio, United States

ABSTRACT

BACKGROUND: Pseudo-melanomas are a group of pathologies that can mimic melanoma. A retinal hemorrhagic macrocyst is a rare condition that can mimic choroidal melanoma. Diagnosing it accurately is important because of the difference in prognosis and treatment. Ocular ultrasound can be used to help differentiate between these similar conditions.

CASE PRESENTATION: We present a patient with a choroidal pseudo-melanoma diagnosed accurately and on time with the aid of an ocular ultrasound.

KEY WORDS: uveal melanoma; pseudomelanoma; ocular ultrasound

Ophthalmol J 2021; Vol. 6, 199–205

INTRODUCTION

Choroidal melanoma is the most frequently diagnosed intraocular malignant tumor in Caucasian adults. It rarely occurs in Latinos, although there are no published epidemiological studies in Latin America.

In the collaborative study of Ocular Melanoma [1] with eight years of follow-up of 6078 patients recruited with sizeable choroidal melanoma (with more than 17.2 mm in baseline diameter and 9.5 mm in height), 1003 patients were found to be eligible, and 97% of those were non-Hispanic whites, with an average age of 60 years, with no preference for sex [1, 2].

Uveal melanoma represents less than 5% of all malignant melanomas [1] and leads to metastasis and death in 31% of the cases at five years [3].

Shields et al. [2] reported a study of 12,000 cases referred to the oncology service of the Wills Eye Hospital between 1978 and 2003, with suspected melanoma 14% of these cases were classified as and found to be pseudo-melanomas.

Hemorrhagic macrocyst of the retina is a rare disease that is occasionally associated with bleeding

CORRESPONDING AUTHOR:
Carlos Rivera, Holguines Trade Center, Cra 10 11-60, office 236, tel: (2) 3165225961, (572) 5546567; e-mail: carlosriverahoyos@gmail.com, crivera@grupogsr.co

inside the cyst and is frequently misdiagnosed as choroidal melanoma.

Here we describe a case report of a patient with choroidal pseudomelanoma.

CASE PRESENTATION

A 74-year-old male patient presented with a one-year history of decreased vision in the right eye. He had a report of an ultrasound from a year ago with a diagnosis of retinal detachment. On the examination of the right eye, the vision was hand motion and presented with a month of the evolution of an appearance of a large, apparently subretinal, retropupillary mass (Fig. 1). An ultrasound had been performed at another institution where they reported an intraocular mass compatible with choroidal melanoma (Fig. 2).

The clinical diagnosis was of an intraocular tumor, probably a choroidal melanoma. The patient did not present with pain, complete vision loss, or other associated symptoms.

The ultrasound found a vitreous hemorrhage associated with a subtotal retinal detachment (Fig. 3). Evidence of a giant cyst, a lower temporal hemorrhage, and a level of hyphema inside (Fig. 4 and 5). On the 7 o'clock meridian, there was a small choroidal thickening in the posterior pole, with calcification points, high reflectivity, and an irregular structure, which was diagnosed as neovascularization (Fig. 6).

In the periphery of the lesion, a double membrane image was observed secondary to a division of the layers of the retina (Fig. 7).

Ultrasonic biomicroscopy revealed a flat retinal detachment and the periphery of the cyst with vitreous hemorrhage inside. Membranes with traction were also found between the periphery of the cyst and the ciliary body (Fig. 8).

The ultrasound-aided diagnosis was made of an old retinal detachment, associated with a giant hemorrhagic cyst with a level of hyphema inside and probable neovascularization.

In a 12-month ultrasound follow-up, the visual acuity was unchanged. A vitreous hemorrhage and an old retinal detachment were observed without the presence of the cyst (Fig. 9).

DISCUSSION

In 1964, 19% of the enucleations due to uveal melanoma that were sent to the Institute of Pathology of the Armed Forces corresponded to a misdiagnosis. In 1984 it decreased to 1.4%, in 1990 it was 0.4% and in 1998 it was reported to be only 0.3% [4].

The improvement in accuracy is due to increased use of ophthalmoscopy, better recognition of lesions that simulate melanomas, and the development of the ocular ultrasound [4].

Ocular ultrasound has helped support the diagnosis of melanoma even with unclear media, providing reliable measurements of the base and height of the tumor, evaluating the extra scleral extension, guiding for the correct location of the brachytherapy plate, and monitoring the conservative treatment of these patients.

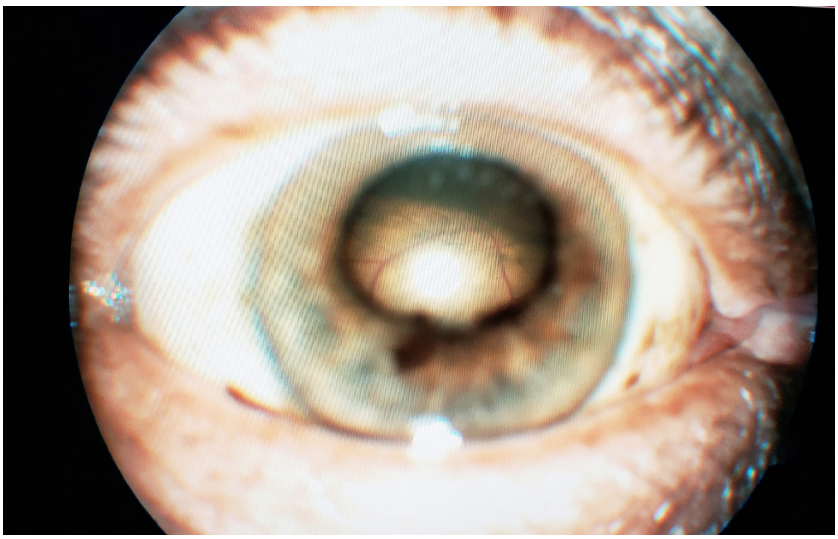


FIGURE 1. Bullous retinal detachment suggestive of a subretinal mass

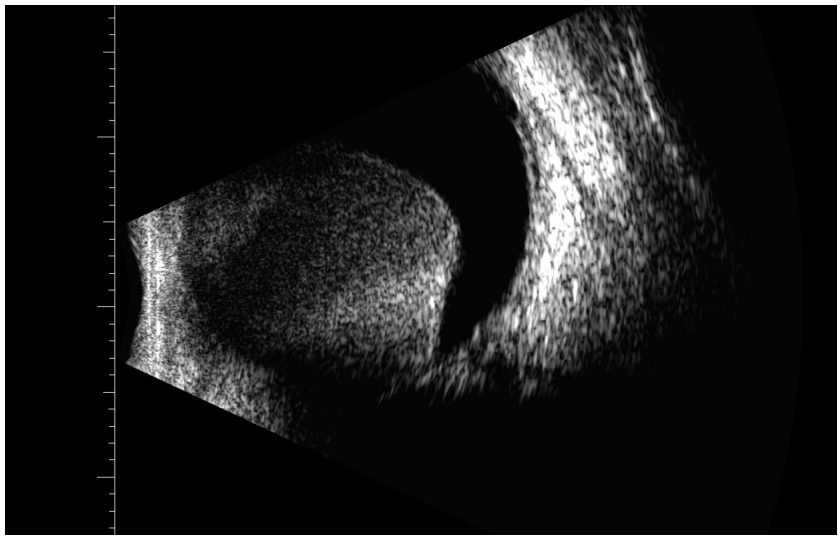


FIGURE 2. Nasal, longitudinal section with image suggestive of temporal mass

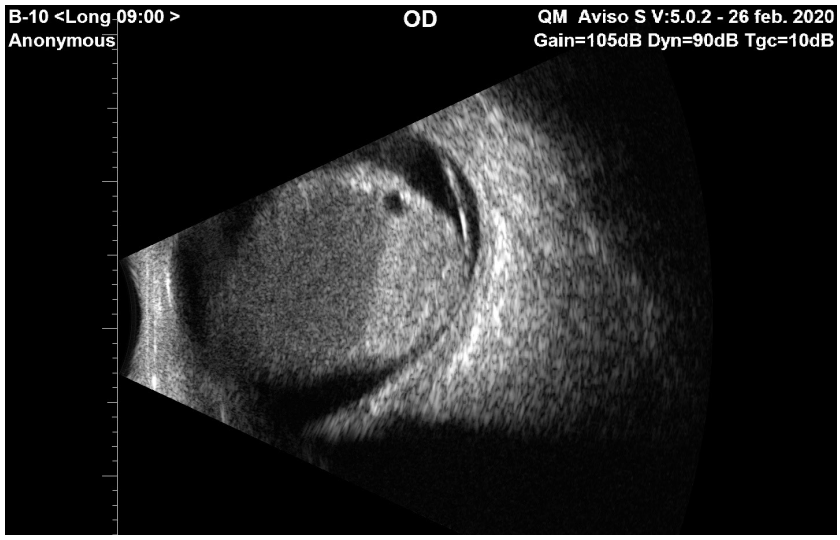


FIGURE 3. Flat retinal detachment image with a giant cyst. Note the cyst wall of irregular density, with a small cyst inside

In 2005, Shields et al. studied 1,739 patients classified as pseudo-melanoma and found 54 different pathologies. The most frequent diagnosis was choroidal nevus, which corresponded to 49% of cases, followed by a peripheral exudative hemorrhagic chorioretinopathy with 8% of cases, followed by congenital hypertrophy of the RPE at 6% [2]. Some choroidal neoplasm pathologies can be misinterpreted, such as hemangiomas, leiomyomas, and choroidal metastases. There are non-neoplastic pathologies that can simulate choroidal melanoma. In less than 1% of cases, there have been ultrasonographic images of patients with hyper mature cataracts simulating melanoma. This occurs because the lens, seen in the extreme periphery, is shown as a dome shape mass image suggestive of melanoma and can be differentiated by performing an immersion ultrasound [2, 5].

Hemorrhagic retinal or choroidal detachments may occasionally manifest as a subchoroidal or pigmented subretinal mass and represent up to 5% of patients classified as pseudo-melanomas [2, 6]. In these cases, it is essential to understand the cause of the bleeding. Highly reflective vascularized dome lesions can also be found in pathologies such as age-related macular degeneration, macroaneurysms, polypoidal choroidopathy, and trauma, among others [2, 6].

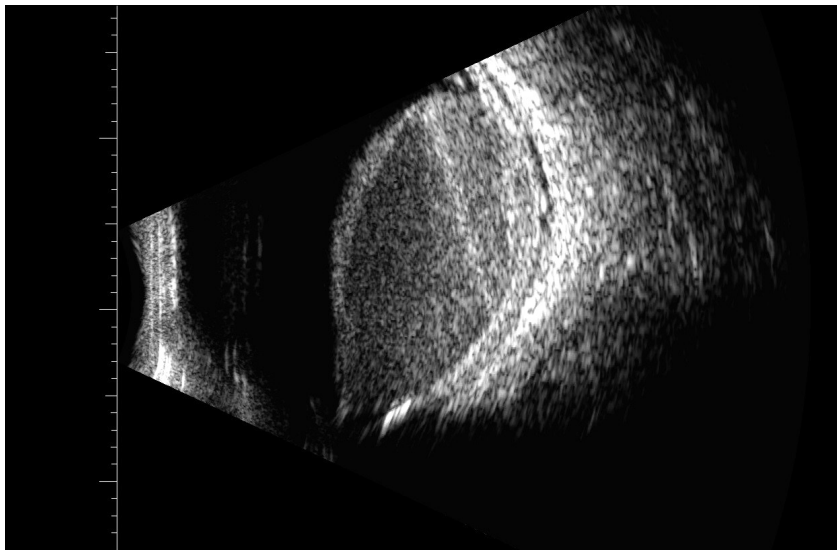


FIGURE 4. Cross-sectional image in the temporal and inferior quadrant. Imagen of a dome lesion is observed, with high-density content and a liquid level inside, compatible with hemorrhage and a level of hyphema

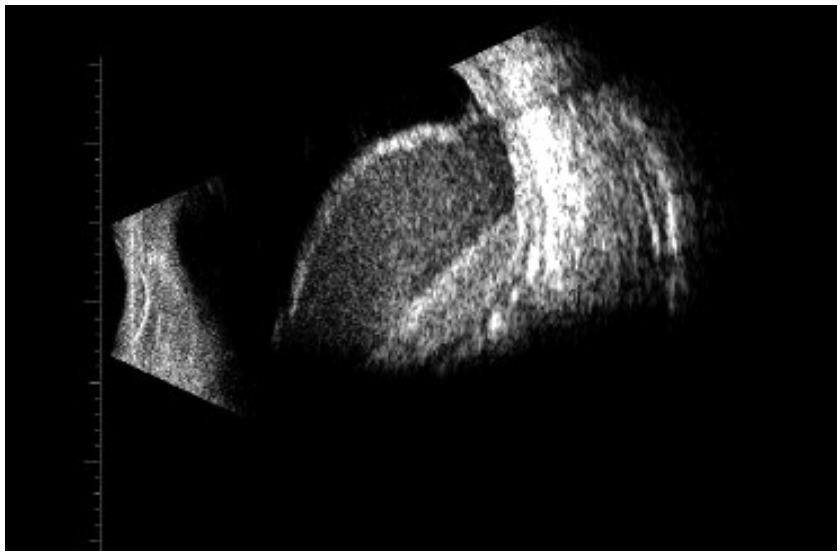


FIGURE 5. Hemorrhagic cyst. Compare figures 4 and 5 and note the movement of the hyphema with the eye movement

Although the clinical and ultrasound appearance of melanoma of comparable size to a subretinal or subchoroidal hemorrhage can be confusing, a subretinal hemorrhage tends to decrease in size on follow-up. However, it may persist for weeks to months.

Retinal macrocysts are a rare pathology that occurs in 3% of retinal detachments, usually more than three months old [7], and in some cases, they present with internal bleeding. There are few reports of cases confused with melanoma that have occasionally led to enucleation [7–9]. It is a pathology, usually asymptomatic, unilateral, with one or multiple cysts that are generally associated with chronic retinal detachment. A particular association has been seen with traumatic detachment and retinal dialysis [11], although our patient did not have a history of trauma.

The presence of blood in the cyst could be due to a rupture of the vessels that cover the cyst, the rupture of the vessels over the tear [11], or peripheral neovascularization [7, 10].

Echographically, melanoma looks like a solid mass with sound attenuation, an acoustic shadow,

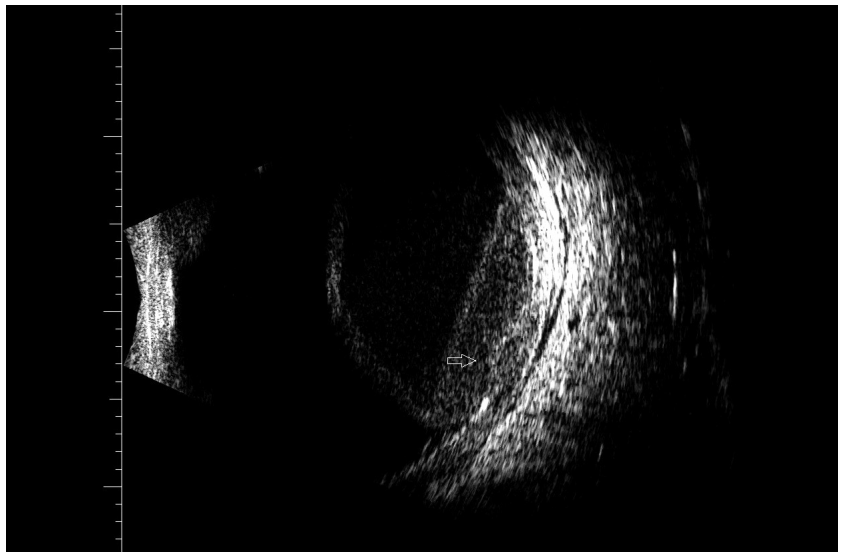


FIGURE 6. A cross-section of the posterior pole is observed. The cystic lesion and irregular choroidal thickening of high density in the ocular wall are compatible with a neovascular membrane. Note the calcium spots that create echoic shadowing

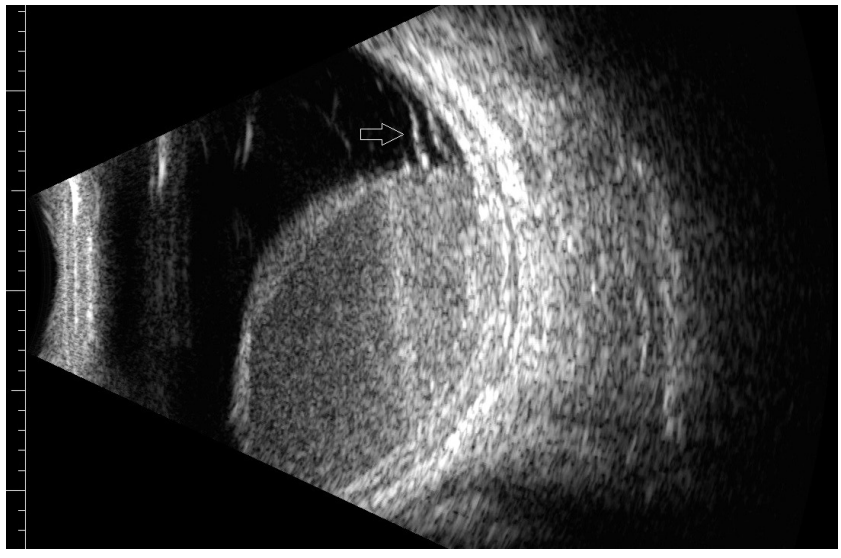


FIGURE 7. Retinal split in the periphery

and choroidal excavation. It can be in a dome or a mushroom shape [1, 11]. Although the mushroom shape is highly suggestive of melanoma, it is known that it is not pathognomonic since there are several recent reports of mushroom-shaped choroidal metastases [1]. The internal vascularity is appreciable and can be associated with a hemorrhagic or non-hemorrhagic retinal detachment and vitreous hemorrhage. Mode A classically presents as a medium to low reflectivity (60–70%) and a regular internal structure [1]. On rare occasions, the presence of cysts inside or calcium on the surface of the tumor has been reported [13].

Ultrasonic biomicroscopy has been described as an accurate diagnostic means to determine the tumor's anterior margins and help with treatment planning [13].

Unlike melanoma, a retinal detachment on ultrasound imaging is seen as a very high-density membrane that inserts into the ora serrata and optic nerve. As signs of age, there may be folds secondary to retinal vitreous proliferation, calcium, and cysts.

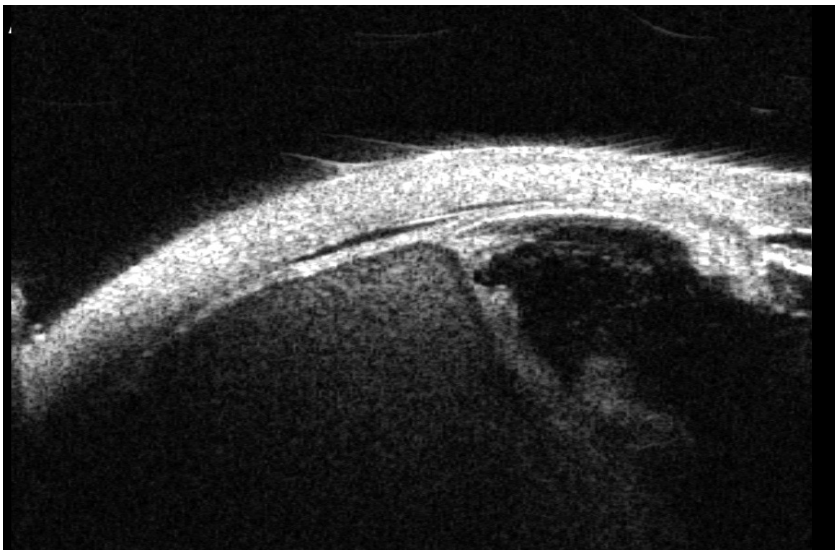


FIGURE 8. Ultrasound biomicroscopy with evidence of a flat retinal detachment. The peripheral end of the cyst is observed with evidence of bleeding inside. Membranes with traction are observed between the periphery of the cyst and the ciliary body

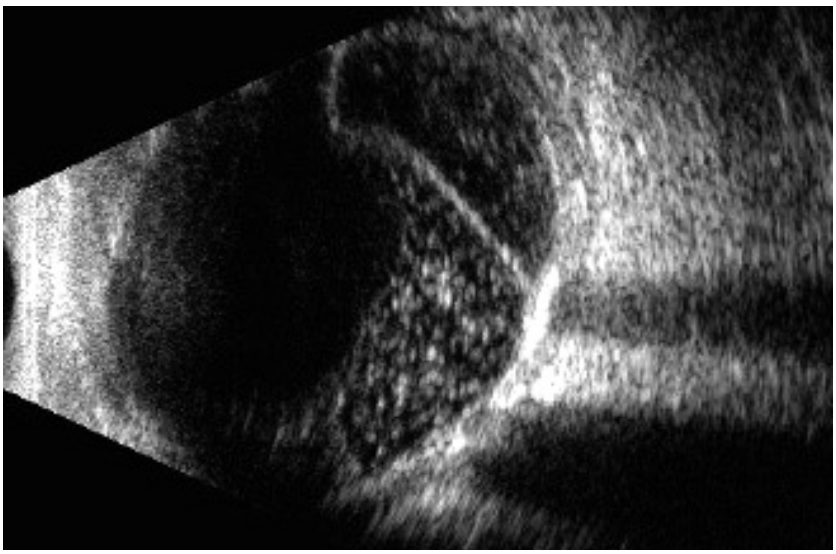


FIGURE 9. Control ultrasound at one year. Temporal inferior longitudinal section showing sub-vitreous hemorrhage, retinal detachment, and sub-retinal cholesterol. Ocular wall with calcium inside

The cysts, echographically, are observed as round lesions, dependent on the retina with very high reflectivity walls and in the cyst's periphery. In some patients, the division of the layers of the retina can be observed. [7] Occasionally, bleeding can be visualized in the interior of the cysts. This blood, like subretinal bleeding, does not coagulate but decants, producing a level of hyphema seen in our patient. It is noteworthy that the level of hyphema can be seen moving as the position of the patient's eye changes.

CONCLUSIONS

It is important to remember that the ideal management of uveal tumors must begin with a correct diagnosis. It is essential to properly differentiate between melanoma and pseudomelanoma because the treatment and prognosis of these pathologies are drastically different. Fortunately, thanks to the expertise of clinicians and the development of diagnostic technology, it is less likely to misdiagnose these patients [3].

Ocular ultrasound is a non-invasive and highly accurate method for differentiating choroidal melanoma from pseudomelanoma.

REFERENCES

1. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma I: characteristics of patients enrolled and not enrolled. COMS report no. 9. Am J Ophthalmol. 1998; 125(6): 767–778, doi: 10.1016/s0002-9394(98)00038-5, indexed in Pubmed: 9645715.
2. Shields JA, Mashayekhi A, Ra S, et al. Pseudomelanomas of the posterior uveal tract: the 2006 Taylor R. Smith Lecture. Retina. 2005; 25(6): 767–771, doi: 10.1097/00006982-200509000-00013, indexed in Pubmed: 16141866.
3. Kujala E, Mäkitie T, Kivelä T. Very long-term prognosis of patients with malignant uveal melanoma. Invest Ophthalmol Vis Sci. 2003; 44(11): 4651–4659, doi: 10.1167/iovs.03-0538, indexed in Pubmed: 14578381.
4. Boldt HC, Byrne SF, Gilson MM, et al. Collaborative Ocular Melanoma Study Group. The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma I: characteristics of patients enrolled and not enrolled. COMS report no. 9. Am J Ophthalmol. 1998; 125(6): 767–778, doi: 10.1016/s0002-9394(98)00038-5, indexed in Pubmed: 9645715.
5. Shields CL, Pellegrini M, Kligman BE, et al. Ciliary body and choroidal pseudomelanoma from ultrasonographic imaging of hypermature cataract in 20 cases. Ophthalmology. 2013; 120(12): 2546–2551, doi: 10.1016/j.ophtha.2013.05.024, indexed in Pubmed: 23916484.
6. Shields CL, Salazar PF, Mashayekhi A, et al. Peripheral exudative hemorrhagic chorioretinopathy simulating choroidal melanoma in 173 eyes. Ophthalmology. 2009; 116(3): 529–535, doi: 10.1016/j.ophtha.2008.10.015, indexed in Pubmed: 19157563.
7. Mansour AM, Jaroudi MO. Hemorrhagic retinal macrocysts, simulating choroidal melanoma: a case report. Clin Ophthalmol. 2013; 7: 973–976, doi: 10.2147/OPTH.S45711, indexed in Pubmed: 23761961.
8. Zimmerman LE, Spencer WH. The pathologic anatomy of retinoschisis with a report of two cases diagnosed clinically as malignant melanoma. Arch Ophthalmol. 1960; 63: 10–19, doi: 10.1001/archopht.1960.00950020012002, indexed in Pubmed: 13847542.
9. Ruiz RS. Hemorrhagic macrocyst of the retina. Mistaken for malignant melanoma of the choroid. Arch Ophthalmol. 1970; 83(5): 588–590, doi: 10.1001/archopht.1970.00990030588011, indexed in Pubmed: 5442149.
10. Verdaguer P, Nadal J. Intraretinal cyst secondary to longstanding retinal detachment. Eur J Ophthalmol. 2012; 22(3): 506–508, doi: 10.5301/ejo.5000034, indexed in Pubmed: 21928257.
11. Shields CL, Pellegrini M, Kligman BE, et al. Ciliary body and choroidal pseudomelanoma from ultrasonographic imaging of hypermature cataract in 20 cases. Ophthalmology. 2013; 120(12): 2546–2551, doi: 10.1016/j.ophtha.2013.05.024, indexed in Pubmed: 23916484.
12. Read R, Green R, Rao N. Metastatic adenocarcinoma with rupture through the bruch membrane simulating a choroidal melanoma. Am J Ophthalmol. 2001; 132(6): 943–945, doi: 10.1016/s0002-9394(01)01147-3, indexed in Pubmed: 11730672.
13. Maberly D, Pavlin C, McGowan H, et al. Ultrasound Biomicroscopic Imaging of the Anterior Aspect of Peripheral Choroidal Melanomas. American Journal of Ophthalmology. 1997; 123(4): 506–514, doi: 10.1016/s0002-9394(14)70176-x, indexed in Pubmed: 9124247.

CASE REPORT
DOI: 10.5603/OJ.2021.0043

Retinal nerve fiber layer defects in the presence of a physiological cup to disc ratio — a case series

Carlos Eduardo Rivera[1–4], Juan Carlos Aristizabal[1, 2], Edgar Muñoz[1, 5], Ankur Seth[1, 3, 6]

[1]Collective Innovations Colombia, Cali, Colombia
[2]Pontificia Universidad Javeriana, Cali, Colombia
[3]GSR Medical Center, Cali, Colombia
[4]GSR International, United States
[5]UT Health San Antonio, San Antonio, United States
[6]University of Tennessee Health Science Center, United States

ABSTRACT

Retinal nerve fiber layer (RNFL) defects are one of the earliest signs of glaucoma. Typically, these RNFL defects are associated with an increased cup/disc ratio and a thinning of the neuroretinal rim. When the cup/disc ratio is within normal limits, the observer can misdiagnose subtle RNFL defects and lead to an essential delay in diagnosis, which has negative visual consequences in these patients. We present a case series report addressing RNFL defects with a physiological cup/disc ratio.

KEY WORDS: glaucoma; retinal nerve fiber defects; cup/disc ratio

Ophthalmol J 2021; Vol. 6, 258–264

INTRODUCTION

Glaucoma is considered an optic neuropathy with a thinning of the peripapillary retinal nerve fiber layer and optic disc cupping secondary to retinal ganglion cell loss. One of the earliest signs of glaucoma are retinal nerve fiber layer (RNFL) defects [1]. A physiological or normal cup to disc ratio (C/D) is considered any C/D lower than 0.7, and it has a significant variability among the population [1, 3].

Generally, structural changes in the neuroretinal rim and RNFL precede visual field (VF) defects in the early stages of glaucoma. Therefore, detecting structural changes in the neuroretinal rim and RNFL is important for early glaucoma detection [2]. RNFL thinning is highly specific to glaucomatous optic neuropathy [3, 4].

We present a case series report addressing RNFL defects with a physiological cup/disc ratio.

CLINICAL CASES

This case series report was selected from an ongoing glaucoma prevalence study of 4,838 patients in Cali, Colombia. We selected patients with RNFL defects by red-free photographs in the presence of a regular cup/disc ratio. It is noteworthy that only 7 of 4838 patients met this criterion, emphasizing that this type of presentation is unusual. The mor-

CORRESPONDING AUTHOR:
Carlos Rivera, Holguines Trade Center, Cra 10 11-60, office 236, tel: (2) 3165225961, (572) 5546567; e-mail: carlosriverahoyos@gmail.com, crivera@grupogsr.co

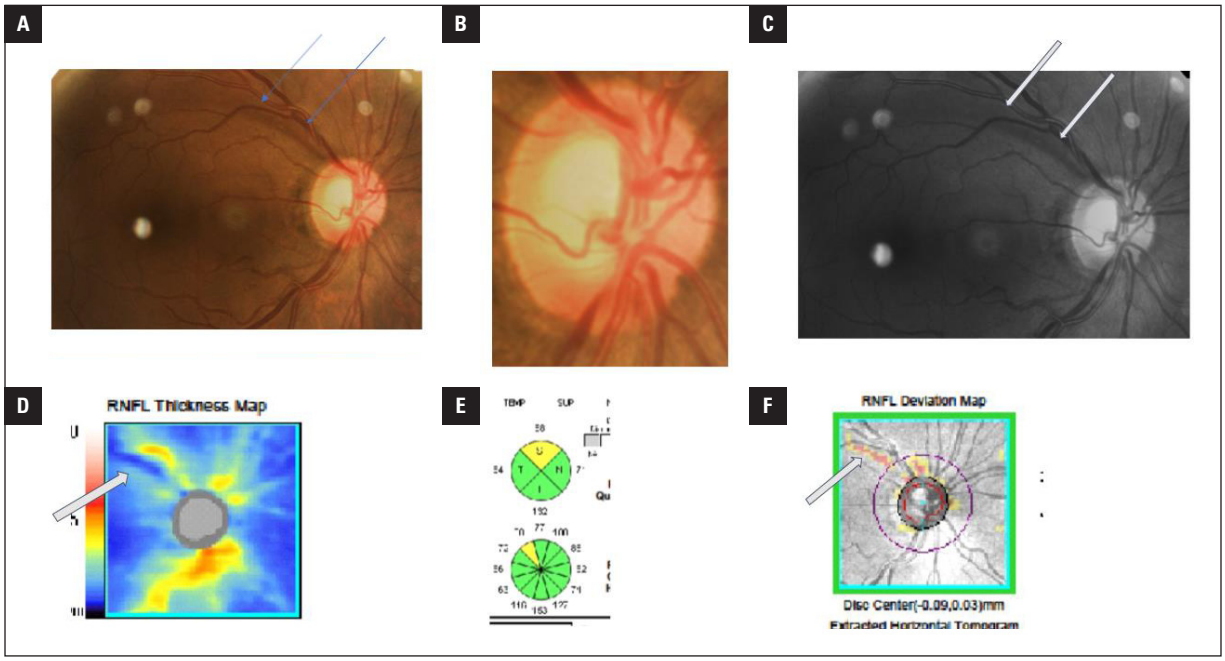


FIGURE 1. A. Right eye (RE) color fundus optic nerve image showing superior retinal nerve fiber layer (RNFL) defect (blue arrow); **B.** First plane optic nerve showing physiologic cup/disc ratio; **C.** RE red-free optic nerve image showing superior RNFL defect (white arrow); **D.** RNFL thickness map showing superior RNFL defect (white arrow); **E.** RNFL clock hour meridians showing superior pole thinning. RNFL deviation map showing in red RNFL defect (white arrow)

phometric parameters of the optic disc and RNFL thickness were measured using ZEISS CIRRUS ™ HD-OCT Model 4000 optical coherence tomography (Carl Zeiss Inc., Dublin, CA, USA).

Case 1

56-year-old female patient with an 8-year diagnosis of open-angle glaucoma in treatment with latanoprost: VA was 20/25 in both eyes; both eyes presented a normal anterior segment evaluation, IOP was 16 mm Hg and 15 mm Hg, respectively. Fundus examination showed a cup/disc (C/D) ratio of 0.5 in the right eye (RE) and C/D ratio of 0.5 in the left eye (LE) (Fig. 1).

Case 2

58-year-old male patient with a 7-year diagnosis of open-angle glaucoma in treatment with timolol/dorzolamide combination: VA was 20/25 in both eyes; anterior segment examination was normal in both eyes, IOP was 12 mm Hg and 13 mm Hg, respectively; fundus examination showed a C/D ratio of 0.4 in both eyes (Fig. 2).

Case 3

63-year-old female patient with a 9-year diagnosis of open-angle glaucoma in treatment with latanoprost and timolol/dorzolamide combination: VA was 20/25 in both eyes; anterior segment evaluation revealed mild nuclear sclerosis; IOP was 14 mm Hg in RE and 13 mm Hg in LE; fundus examination showed a C/D ratio of 0.3 in the RE and 0.4 in the LE (Fig. 3).

Case 4

59-year-old female patient with a 5-year diagnosis of open-angle glaucoma in treatment with latanoprost: VA was 20/25 in both eyes; the slit-lamp examination was normal in both eyes; IOP was 16 mm Hg in RE and 18 mm Hg in LE; fundus examination showed a cup/disc ratio of 0.5 in both eyes (Fig. 4).

Case 5

67-year-old female patient with a 12-year diagnosis of open-angle glaucoma in treatment with timolol/dorzolamide combination: VA was 20/25 in both eyes; both eyes presented intraocular lens; IOP was 17 mm Hg and 18 mm Hg, respectively; fundus examination showed a C/D ratio of 0.4 in RE and 0.4 in LE (Fig. 5).

Case 6

71-year-old male patient: VA was 20/25 in both eyes; anterior segment evaluation revealed intraocu-

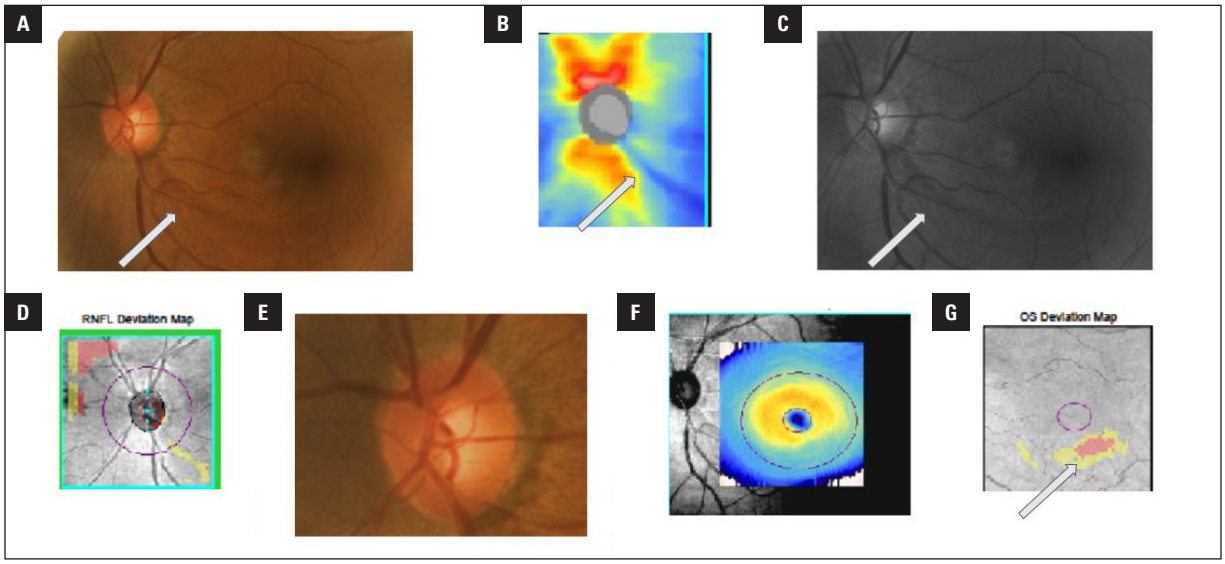


FIGURE 2. **A.** Left eye (LE) color fundus optic nerve image showing inferior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** RNFL thickness map showing inferior RNFL defect (white arrow); **C.** LE red-free optic nerve image showing inferior RNFL defect (white arrow); **D.** RNFL deviation map showing mild inferior RNFL defect (white arrow); **E.** First plane physiological cup/disc ratio; **F.** Ganglion cell complex (GCC) thickness without raphe sign; **G.** GCC deviation map showing a mild compromise

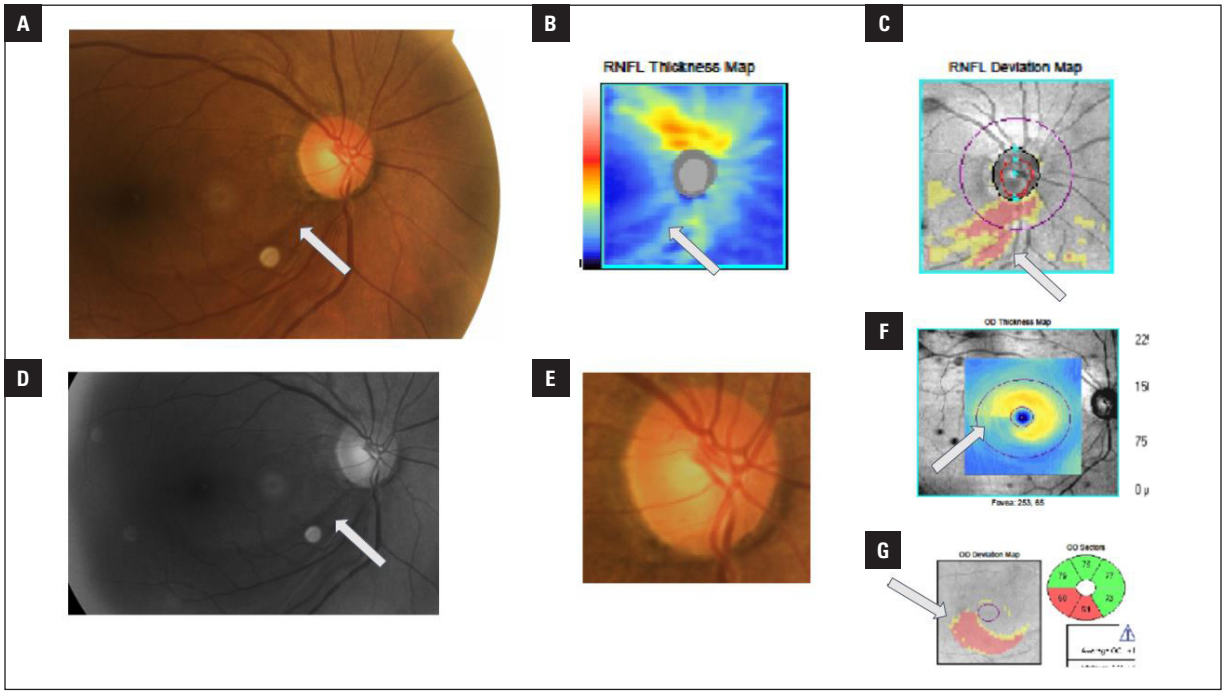


FIGURE 3. **A.** Right eye (RE) optic nerve color image showing inferior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** RNFL thickness map showing inferior RNFL defect (white arrow); **C.** RNFL deviation map showing inferior RNFL defect (white arrow); **D.** RE red-free image showing inferior RNFL defect (white arrow); **E.** First plane, RE physiologic cup/disc ratio; **F.** Ganglion cell complex (GCC) thickness map showing positive raphe sign (respects horizontal midline) (white arrow); **G.** GCC deviation map and sectors showing inferior sectors thinning (white arrow)

lar lens in both eyes; IOP was 14 mm Hg in RE and 14 mm Hg in LE; fundus examination showed a C/D ratio of 0.5 in both eyes (Fig. 6).

Case 7

49-year-old African descendant male patient with a 2-year history of primary open-angle glaucoma

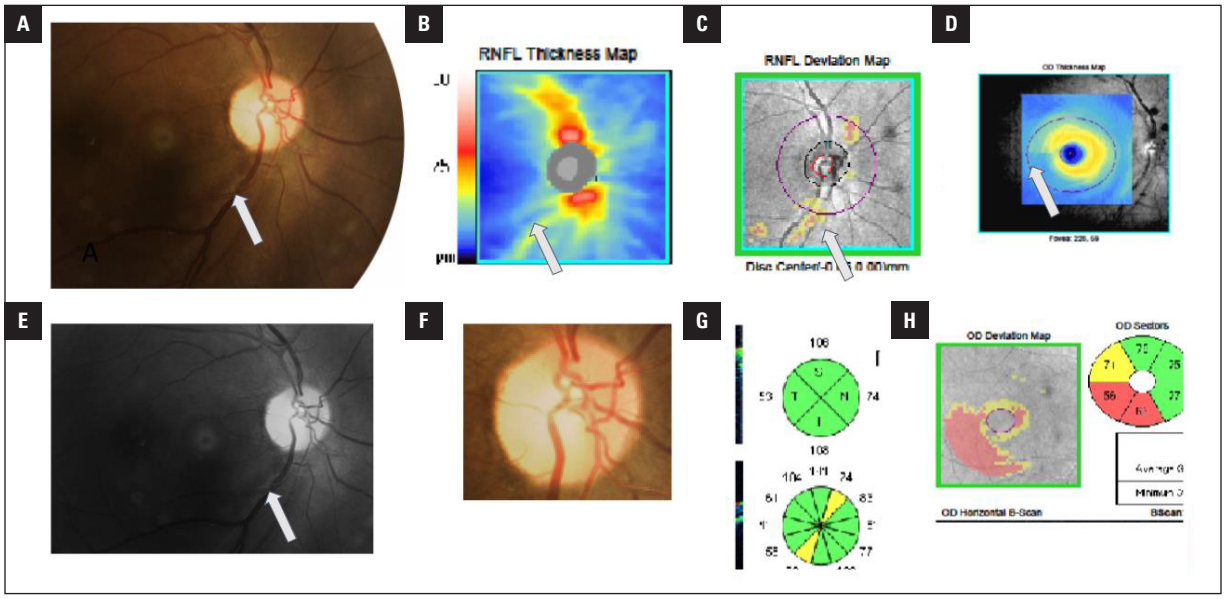


FIGURE 4. **A.** Right eye (RE) red color image showing inferior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** RNFL thickness map showing inferior RNFL defect (white line); **C.** RNFL deviation map showing inferior thinning (white arrow); **D.** Ganglion cell complex (GCC) thickness map showing positive temporal raphe sign (respects the midline) (white arrow); **E.** RE red-free optic nerve image showing inferior RNFL defect (white arrow); **F.** First plane, right optic nerve with a physiological cup/disc ratio; **G.** RNFL meridians showing inferior thinning (white arrow); **H.** GCC deviation map and meridians showing inferior thinning (white arrow)

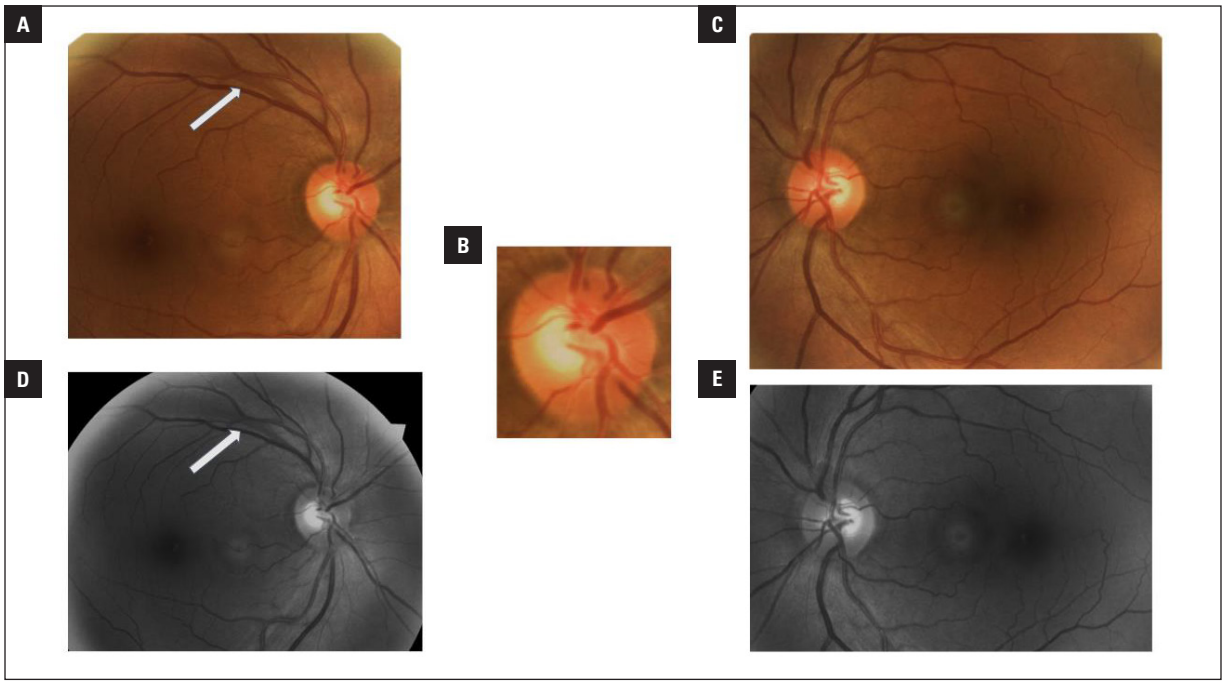


FIGURE 5. **A.** Right eye (RE) color fundus image showing superior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** First plane, right optic nerve showing a physiologic cup/disc ratio; **C.** Left eye (LE) normal color fundus image; **D.** RE red-free image showing superior RNFL defect (white arrow); **E.** LE normal red-free image

in treatment with latanoprost and timolol/dorzolamide combination: VA was 20/20 in both eyes; the slit-lamp examination was unremarkable in both eyes; IOP was 12 mm Hg in RE and 14 mm Hg in LE; fundus examination showed a C/D ratio of 0.2 in both eyes (Fig. 7–9).

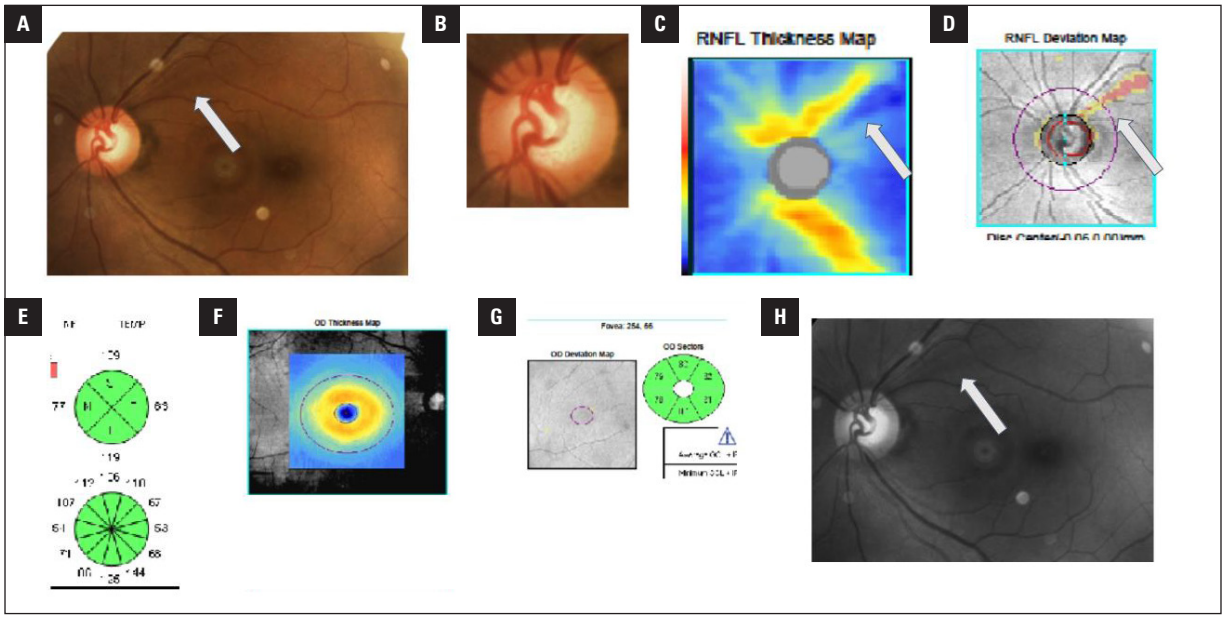


FIGURE 6. **A.** Left eye (LE) red color image showing superior retinal nerve fiber layer (RNFL) defect (white arrows); **B.** First plane, left optic nerve with a physiological cup/disc ratio; **C.** RNFL thickness map showing superior RNFL defect (white arrows); **D.** RNFL deviation map showing superior thinning (white arrow); **E.** Normal RNFL meridians; **F.** Ganglion cell complex (GCC) normal thickness map; **G.** GCC normal deviation map and meridians map; **H.** LE red-free optic nerve image showing superior RNFL defect (white arrow)

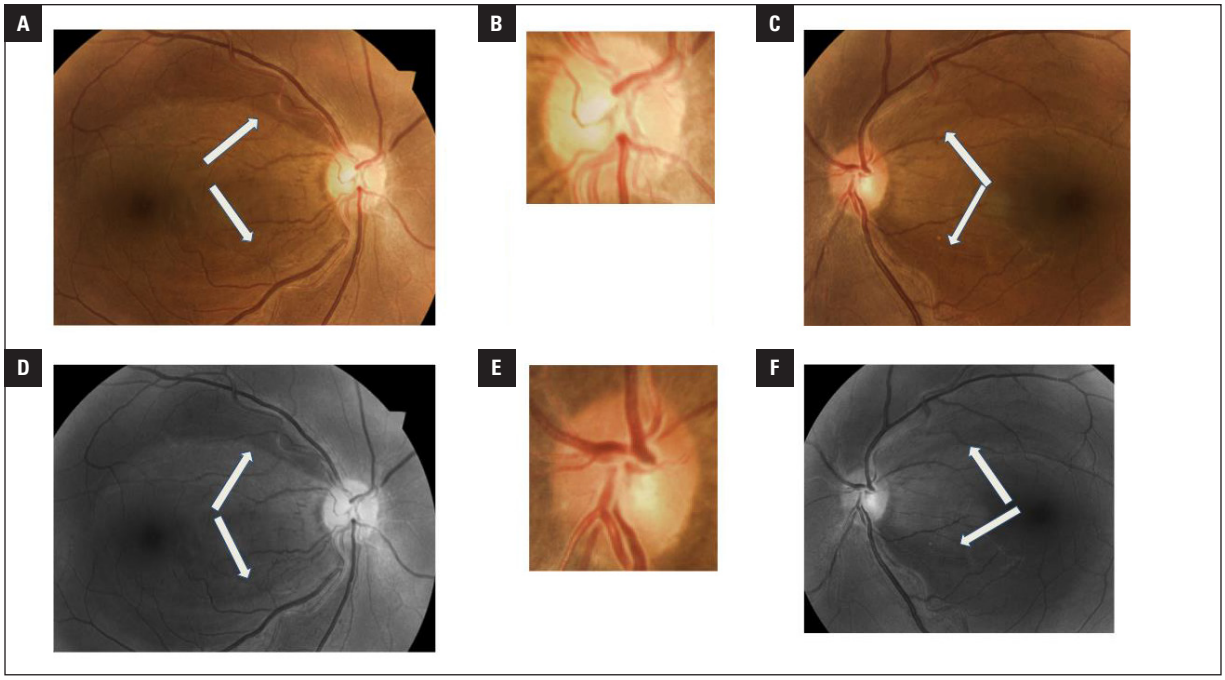


FIGURE 7. **A.** Right eye (RE) color image showing superior and inferior retinal nerve fiber layer (RNFL) defect (white arrows); **B.** RE color fundus image showing physiologic cup/disc ratio; **C.** Left eye (LE) color image showing superior and inferior RNFL (white arrows); **D.** RE red-free image showing superior RNFL defect (white arrows); **E.** LE normal color fundus image showing a physiologic cup/disc ratio; **F.** LE red-free image showing superior and inferior RNFL defect (white arrows)

DISCUSSION

Retinal nerve fiber layer defects were first described in 1913 and later in 1917 by Vogt [5]. He described the enhanced visibility of striated retinal nerve-fiber reflexes with an ophthalmoscopic illuminating system from which red (long) wavelengths of

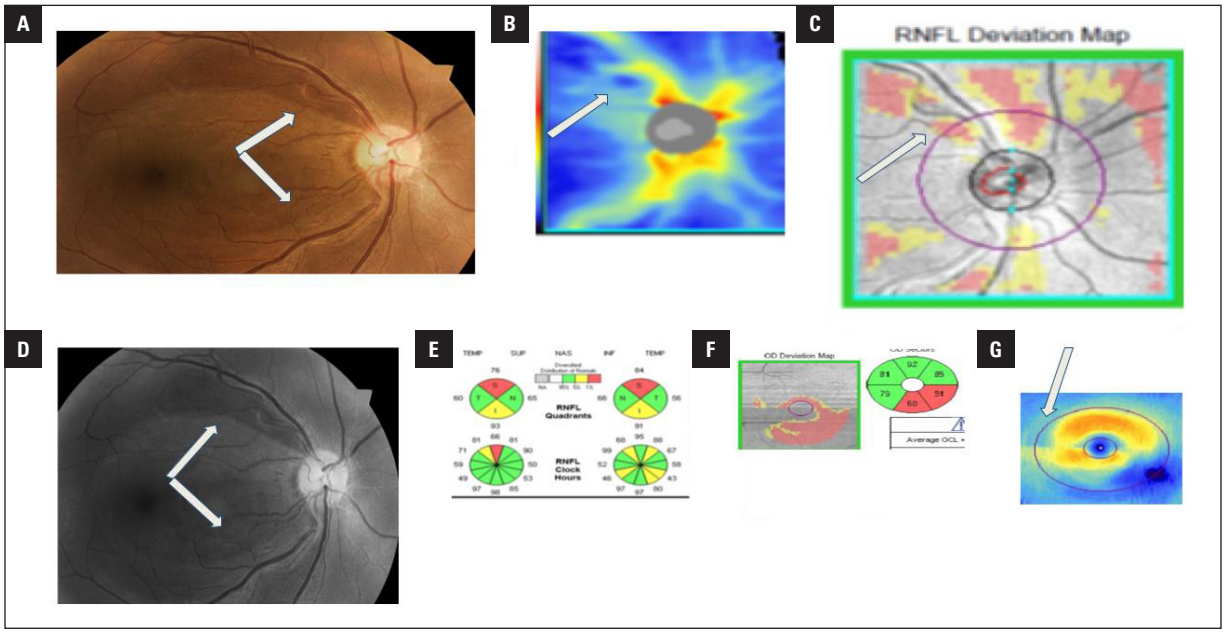


FIGURE 8. **A.** Right eye (RE) red color image showing superior and inferior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** RNFL thickness map showing superior diffuse RNFL defect (white arrow); **C.** RNFL deviation map showing superior thinning (white arrow); **D.** RE red-free optic nerve image showing superior and inferior RNFL defect (white arrow); **E.** RNFL meridians showing superior thinning; **F.** Ganglion cell complex (GCC) deviation map and meridians showing inferior thinning; **G.** GCC thickness map showing temporal raphe positive sign (white arrow)

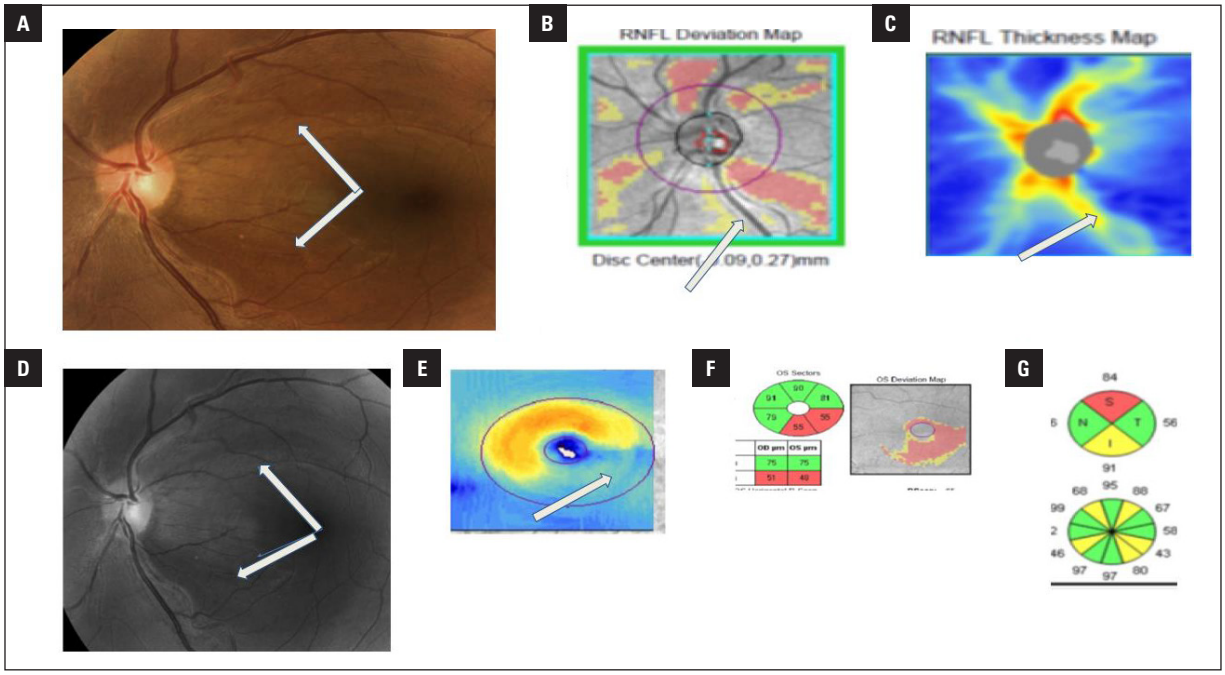


FIGURE 9. **A.** Left eye (LE) red color image showing superior and inferior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** RNFL deviation map showing superior and inferior thinning (white arrow); **C.** RNFL thickness map showing inferior thinning (white arrow); **D.** Left eye (LE) red-free optic nerve image showing superior and inferior RNFL defect (white arrow); **E.** Ganglion cell complex (GCC) thickness map showing temporal raphe positive sign (white arrow); **F.** GCC deviation map and meridians showing inferior thinning; **G.** RNFL meridians showing superior thinning

light were excluded [6]. In healthy eyes, the RNFL has a sparkly, homogeneous, striated appearance and is generally identifiable close to the superior and inferior poles of the optic disc where the RNFL is thickest [7]. The Retinal nerve fiber layer striations represent bands of retinal ganglion cells (RGC) axons separated by Muller cell processes. The highly reflective RGC axon bundles generate a bright component of the striation, and the thick non-reflective septa dividing Muller cell glial produces the dark bands between [8].

The reflectivity of RGC axon bundles is diffuse or localized. The reduction in reflectivity is proportional to a loss of RGC axons [5, 9]. Diffuse axonal loss reduces RNFL striations and increases visibility of the retinal blood vessels, which are generally embedded in the RNFL [8, 9]. Localized loss is more easily visible because it has sharply demarcated borders [7, 10]. Localized RNFL defects typically have a wedge-shaped pattern and become narrower as the RNFL bundles converge toward the disc margin [11]. Despite nonglaucomatous optic neuropathies, papilledema optic disc drusen, or ischemic retinopathies occasionally can present with localized RNFL defects, they have high specificity for glaucoma and are not found in healthy eyes.

Retinal nerve fiber layer defects are generally present with glaucoma's other optic nerve characteristics, such as superior or inferior rim thinning, enlarged C/D ratio, and B-zone of parapapillary atrophy. However, RNFL defects can also be present in a normal C/D ratio setting. When the optic nerve cup/disc ratio is typical, it is easy to miss an RNFL defect because the observer may assume that the extra disc features are also regular.

It is essential to always evaluate in the slit-lamp, with good mydriasis, the optic nerve, and retina with a green light to detect subtle RNFL defects. High-quality optic nerve color and red-free photographs can help us detect early RNFL defects and avoid misdiagnosis of glaucoma or other optic nerve abnormalities. Optical coherence tomography (OCT) has an excellent diagnostic capability in detecting early phases of glaucoma. Hwang et al. compared the ability of thickness, clock-hour, deviation maps obtained with OCT (Cirrus HD-OCT), and concluded that the RNFL thickness map showed the best performance in detecting photographic RNFL defects. Retinal nerve fiber layer defects can be detected efficiently using the RNFL thickness map [12].

CONCLUSIONS

Retinal nerve fiber layer defects are one of the earliest signs of glaucoma. These defects are generally present with superior or inferior rim thinning, but they can also be present in eyes with a normal C/D ratio. Optical coherence tomography plays an essential role in the early detection of glaucoma in these patients, especially the RNFL, GCC thickness, and deviation map. Early detection of RNFL defects can dramatically change the natural history of a patient with glaucoma.

REFERENCES

1. Kwon YH, et al. Primary Open-Angle Glaucoma. N Engl J Med. 2009; 360(11): 1113–1124, doi: 10.1056/NEJMra0804630, indexed in Pubmed: 19279343.
2. Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. Prog Retin Eye Res. 2007; 26(6): 688–710, doi: 10.1016/j.preteyeres.2007.08.001, indexed in Pubmed: 17889587.
3. Inzelberg R, Ramirez JA, Nisipeanu P, et al. Retinal nerve fiber layer thinning in Parkinson disease. Vision Res. 2004; 44(24): 2793–2797, doi: 10.1016/j.visres.2004.06.009, indexed in Pubmed: 15342223.
4. Paquet C, Boissonnot M, Roger F, et al. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci Lett. 2007; 420(2): 97–99, doi: 10.1016/j.neulet.2007.02.090, indexed in Pubmed: 17543991.
5. Hoyt WF, Schlicke B, Eckelhoff RJ. Fundoscopic appearance of a nerve-fibre-bundle defect. Br J Ophthalmol. 1972; 56(8): 577–583, doi: 10.1136/bjo.56.8.577, indexed in Pubmed: 5079403.
6. Quigley HA. Examination of the retinal nerve fiber layer in the recognition of early glaucoma damage. Trans Am Ophthalmol Soc. 1986; 84: 920–966, indexed in Pubmed: 3109098.
7. Radius RL, Anderson DR. The histology of retinal nerve fiber layer bundles and bundle defects. Arch Ophthalmol. 1979; 97(5): 948–950, doi: 10.1001/archopht.1979.01020010506027, indexed in Pubmed: 109068.
8. Airaksinen P, Drance S, Douglas G, et al. Diffuse and Localized Nerve Fiber Loss in Glaucoma. Am J Ophthalmol. 1984; 98(5): 566–571, doi: 10.1016/0002-9394(84)90242-3, indexed in Pubmed: 6496612.
9. Hoyt WF, Schlicke B, Eckelhoff RJ. Fundoscopic appearance of a nerve-fibre-bundle defect. Br J Ophthalmol. 1972; 56(8): 577–583, doi: 10.1136/bjo.56.8.577, indexed in Pubmed: 5079403.
10. Tuulonen A, Lehtola J, Airaksinen P. Nerve Fiber Layer Defects with Normal Visual Fields. Ophthalmology. 1993; 100(5): 587–598, doi: 10.1016/s0161-6420(93)31598-8, indexed in Pubmed: 8493001.
11. Jonas JB, Schiro D. Localized retinal nerve fiber layer defects in nonglaucomatous optic nerve atrophy. Graefes Arch Clin Exp Ophthalmol. 1994; 232(12): 759–760, doi: 10.1007/BF00184280, indexed in Pubmed: 7890191.
12. Hwang YH, Kim YY, Kim HKi, et al. Ability of cirrus high-definition spectral-domain optical coherence tomography clock-hour, deviation, and thickness maps in detecting photographic retinal nerve fiber layer abnormalities. Ophthalmology. 2013; 120(7): 1380–1387, doi: 10.1016/j.ophtha.2012.12.048, indexed in Pubmed: 23541761.
13. Foster PJ, Buhrmann R, Quigley HA, et al. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002; 86(2): 238–242, doi: 10.1136/bjo.86.2.238, indexed in Pubmed: 11815354.

ORIGINAL PAPER
DOI: 10.5603/OJ.2022.0006

Utility of the ganglion cell complex thickness map in glaucoma: the presence of raphe sign

Carlos Eduardo Rivera[1–4], Maria Catalina Ferreira[1–4], Juan Carlos Aristizabal[1, 2], Edgar Muñoz[1, 5], Ankur Seth[1, 3, 6]

[1]Collective Innovations Colombia, Cali, Colombia
[2]Pontificia Universidad Javeriana, Cali, Colombia
[3]GSR Medical Center, Cali, Colombia
[4]GSR International, United States
[5]UT Health San Antonio, san antonio, United States
[6]University of Tennessee Health Science Center, United States

ABSTRACT

Macular ganglion cell complex (GCC) thickness map is a functional ancillary test to detect early structural changes in glaucomatous optic neuropathy (GON). The temporal raphe sign is present in almost all patients with narrow retinal nerve fiber layer (RNFL) defect, especially when there is a small angular distance between the fovea and the RNFL defect. A case series of patients with GCC thickness map and a positive temporal raphe sign is presented.

KEY WORDS: glaucoma; retinal nerve fiber defects; cup/disc ratio; optical coherence tomography

Ophthalmol J 2022; Vol. 7, 35–41

INTRODUCTION

Glaucoma is the leading cause of visual impairment worldwide, affecting more than 70 million people [1]. This neuropathy is characterized by optic disc cupping and thinning of the peripapillary retinal nerve fiber layer and as a result, axonal and secondary retinal ganglion cell loss. One of the earliest signs of glaucoma are retinal nerve fiber layer (RNFL) defects [2]. A detailed clinical history and clinical examination help confirm the presence of glaucomatous optic neuropathy (GON). Visual field defects are highly correlated with macular GCC analysis, which is centered over the fovea.

Typically, there is a progressive retinal ganglion cell (RGC) axonal thinning in glaucoma. There is a body of evidence that having glaucomatous damage implicates macular involvement, even in the early stages of glaucoma [6, 7].

The GCC thickness map uses sector-based color code classification to detect early structural changes. A useful finding for the detection of a glaucomatous change is a step-like configuration of the ganglion cell-inner plexiform layer (GCIPL) in the horizontal raphe due to the difference in thicknesses between the inferior and superior hemispheres. This step-like configuration is called the temporal raphe sign. Usually, this sign has a good concordance with a localized RNFL defect. A case series of patients with GCC thickness map and a positive temporal raphe sign are presented.

CORRESPONDING AUTHOR:
Carlos Rivera, Holguines Trade Center, Cra 10 11-60, office 236, tel: (2) 3165225961, (572) 5546567;
e-mail: carlosriverahoyos@gmail.com, crivera@grupogsr.co

CASES PRESENTATION

The patients with a diagnosis of glaucoma were examined in GSR Medical Center, Collective Innovations Colombia, in Cali, Cauca Valley, Colombia. The morphometric parameters of the optic disc, GCC, and RNFL thickness were measured using ZEISS CIRRUS™ HD-OCT Model 5000 optical coherence tomography (Carl Zeiss Inc., Dublin, CA, USA).

Case 1

A female patient with an 8-year history of primary open-angle glaucoma (POAG), treated with latanoprost 0.005% (1 drop at night). Visual acuity in the right eye (RE) was 20/40, in the left eye (LE) — 20/40. Slit-lamp examination revealed mild cataracts in both eyes; intraocular pressure (IOP) was 14 mm Hg in RE and 13 mm Hg in LE. Fundus examination showed: RE — cup/disc (C/D) ratio 0.6 with inferior rim thinning, LE — C/D ratio 0.7 (Fig. 1).

Case 2

A female patient with a diagnosis of POAG, **actually [currently?]** treated with dorzolamide 2%/timolol 0.5% (2 times per day). Visual acuity in RE was 20/25 and in LE — 20/25. Anterior segment exam was normal in both eyes, IOP in RE was 11, and in LE was 13. Fundus examination showed in RE a C/D ratio of 0.7 with inferior rim thinning, and in LE a C/D ratio was 0.6 (Fig. 2).

Case 3

African descendant male patient diagnosed with POAG, treated with travoprost 0.004% (1 drop at night). Visual acuity in both eyes was 20/20. Anterior segment evaluation was normal, IOP was 17 mm Hg in RE and 18 mm Hg in LE. Posterior pole examination showed a C/D ratio in RE 0.2 and in LE — 0.2 (Fig. 3).

Case 4

A female patient with a history of POAG, treated with latanoprost 0.005% (1 drop at night). Visual acuity in both eyes was 20/25. Anterior segment exam revealed a centered intraocular lens, IOP was 12 mm Hg in RE and 11 mm Hg in LE. Fundus examination showed a C/D ratio in RE 0.7 with inferior rim thinning and in LE a C/D ratio was 0.8 (Fig. 4).

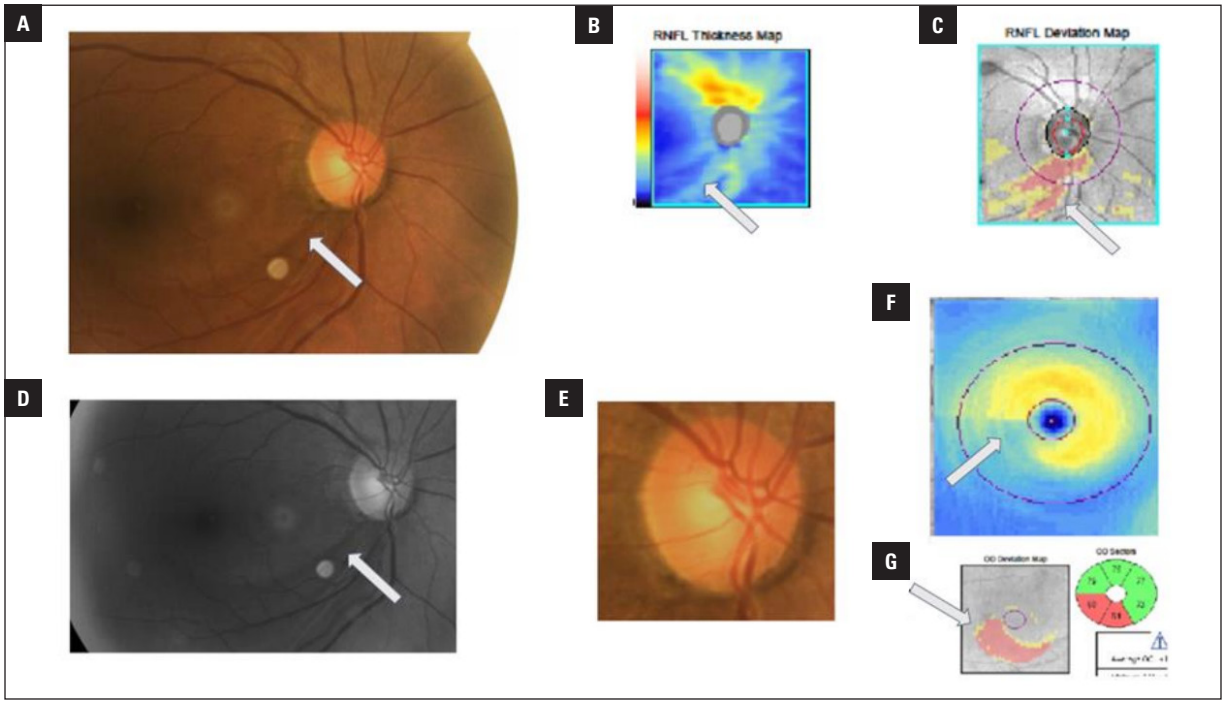


FIGURE 1. **A.** Right eye (RE) optic nerve color image showing inferior retinal nerve fiber layer (RNFL) defect (white arrow); **B.** RNFL defect thickness map indicating inferior RNFL defect (white arrow); **C.** RNFL defect deviation map showing inferior RNFL defect; **D.** RE red-free image showing inferior RNFL defect (white arrow); **E.** First plane, RE normal C/D ratio; **F.** Ganglion cell complex (GCC) thickness map indicating temporal positive raphe sign (respects horizontal midline); **G.** GCC deviation map and sectors showing thinning of the inferior sectors

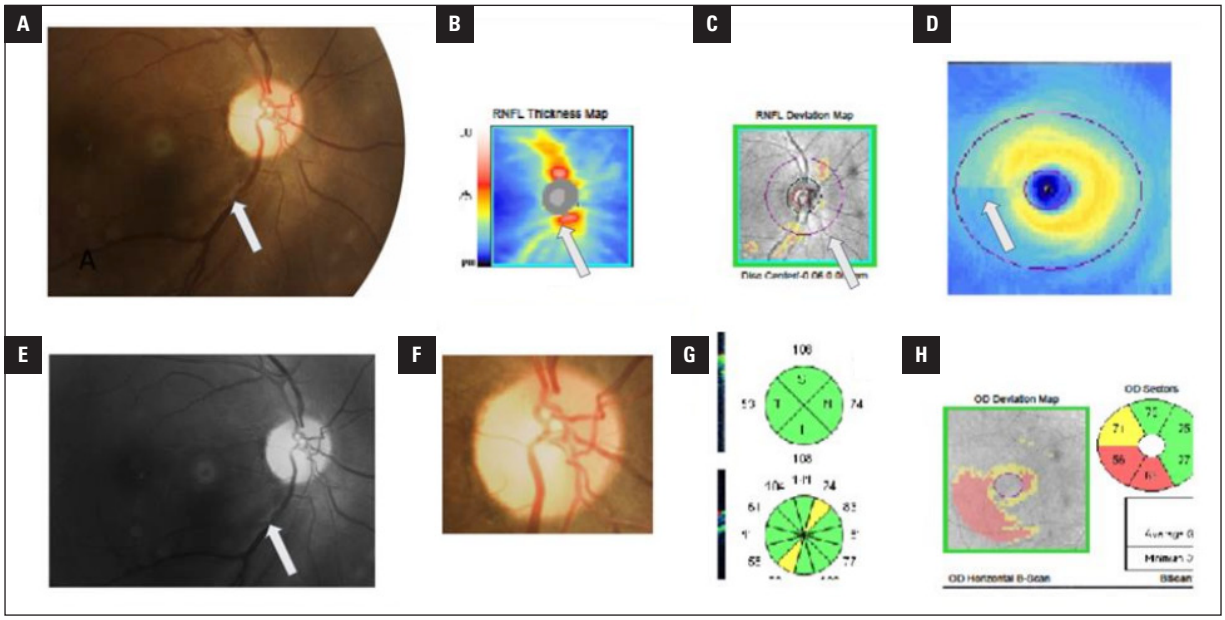


FIGURE 2. **A.** Right eye (RE) red color image showing inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** RNFL thickness map showing inferior RNFL defect (white line); **C.** RNFL deviation map showing inferior thinning; **D.** Ganglion cell complex (GCC) thickness map indicating positive temporal raphe sign; **E.** Right eye red free optic nerve image showing inferior RNFL defect; **F.** First plane right optic nerve with a normal C/D ratio; **G.** RNFL meridians indicating inferior thinning; **H.** GCC deviation map and meridians showing inferior thinning

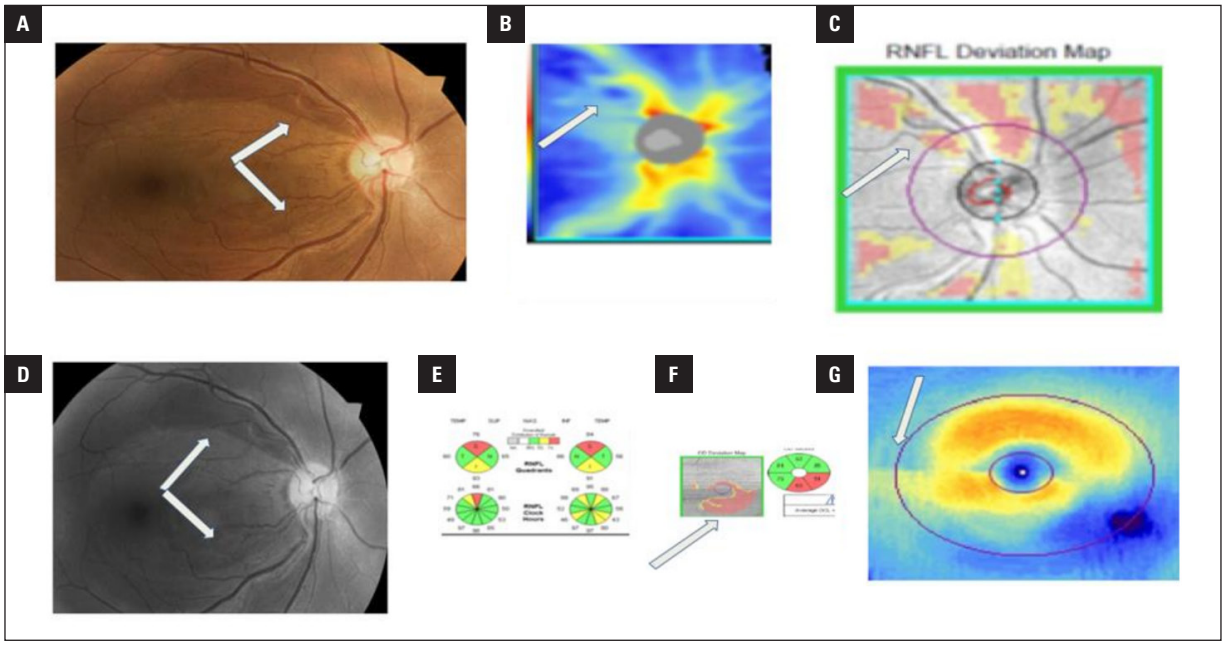


FIGURE 3. **A.** Right eye (RE) red color image indicating a superior and inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** RNFL thickness map showing superior diffuse RNFL defect (white line); **C.** RNFL deviation map showing superior thinning; **D.** RE red-free optic nerve image showing superior and inferior RNFL defect; **E.** RNFL meridians showing superior thinning; **F.** Ganglion cell complex (GCC) deviation map and meridians indicating inferior thinning; **G.** GCC thickness map indicating temporal raphe positive sign

Case 5

A female patient with a history of POAG, treated with latanoprost 0.005% (1 drop at night). Visual acuity in RE was 20/30 and in LE — 20/30. Anterior segment exam revealed mild nuclear sclerosis, IOP was 10 mm Hg in RE and 11 mm Hg in LE.

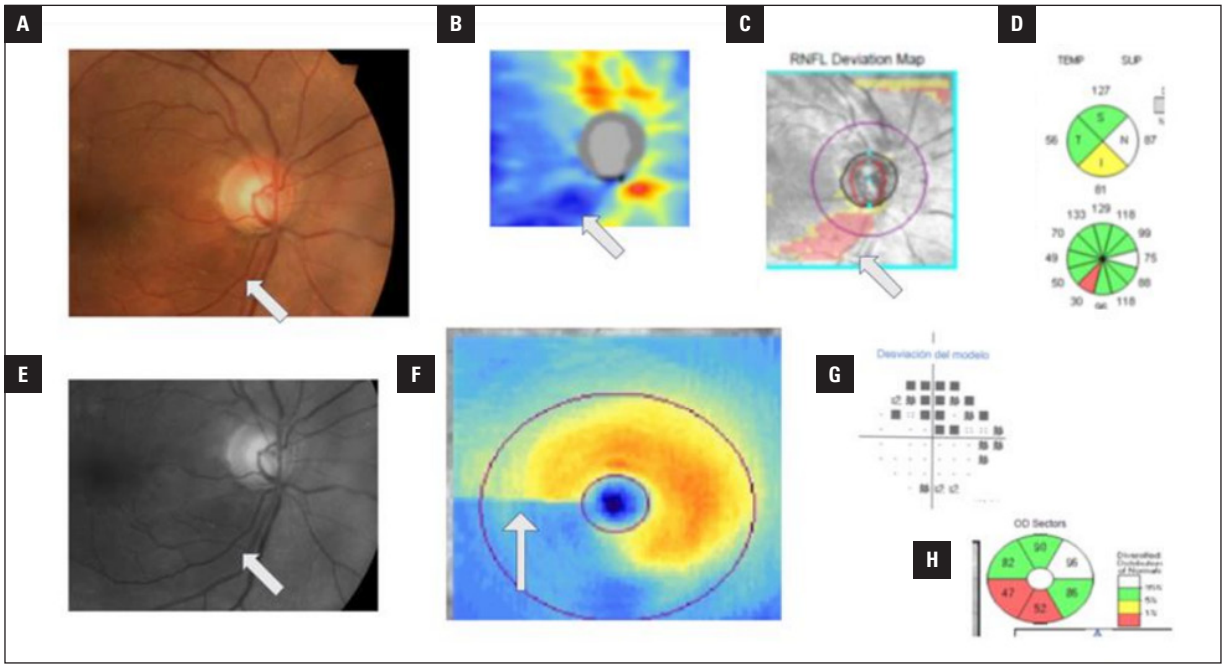


FIGURE 4. **A.** Right eye (RE) red color image showing inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** RNFL thickness map showing inferior RNFL defect (white line); **C.** RNFL deviation map showing inferior thinning; **D.** RNFL meridians showing inferior thinning; **E.** RE red-free optic nerve image indicating inferior RNFL defect; **F.** Ganglion cell complex (GCC) thickness map showing temporal raphe positive sign; **G.** Visual field showing superior arcuate defect; **H.** GCC sectors meridians showing inferior thinning

Fundus examination showed a cup/disc ratio in RE 0.8 with inferior and superior rim thinning, and in the LE a cup/disc ratio was 0.6 (Fig. 5).

Case 6

A male patient with a history of POAG, treated with dorzolamide 2%/timolol 0.5% (2 times per day) and latanoprost 0.005% (1 drop at night). Visual acuity in both eyes was 20/25. Slit-lamp examination was normal, IOP was 13 mm Hg in RE and 12 mm Hg_in LE. Fundus examination showed a C/D ratio in RE 0.8 with an inferior notch and in LE a cup/disc ratio was 0.8 with an inferior notch (Fig. 6).

Case 7

A patient with a history of POAG, treated with dorzolamide 2%/timolol 0.5% (2 times per day). Visual acuity was 20/25 in both eyes. Slit-lamp examination was normal, IOP was 12 mm Hg in RE and 11 mm Hg in LE. Fundus examination showed a C/D ratio in RE 0.5 and in LE 0.8 with inferior rim thinning (Fig. 7).

Case 8

A female patient with a history of POAG, treated with latanoprost 0.005% (1 drop at night). Visual acuity was 20/25 in both eyes. Anterior segment exam was normal, IOP was 12 mm Hg in RE and 11 mm Hg in LE. Fundus examination showed a C/D ratio in the RE 0.6 with inferior rim thinning and in LE a C/D ratio was 0.6 with inferior rim thinning (Fig. 8).

DISCUSSION

Optical coherence tomography (OCT) is a non-invasive optical technique that allows in vivo cross-sectional imaging of the optic nerve head (ONH) and the retina [3]. Cross-sectional images (B-scans) are created through longitudinal scans that can be analyzed quantitatively to measure the thickness of the retinal macular layers [4].

Hwang et al. [5] included 131 patients in a cross-sectional study with early glaucoma (mean deviation > 6.0 dB) and 132 matched healthy patients. Macular GCA images were obtained using Cirrus high-definition optical coherence tomography (HD-OCT). Red-free fundus photographs were used to analyze the location, angular distance, and width of the circumpapillary retinal nerve fiber layer (RNFL). Among the 131 patients with glaucoma, 115 (87.8%), 105 (80.2%), and 104 (79.4%) showed structural abnormalities in the GCA, devia-

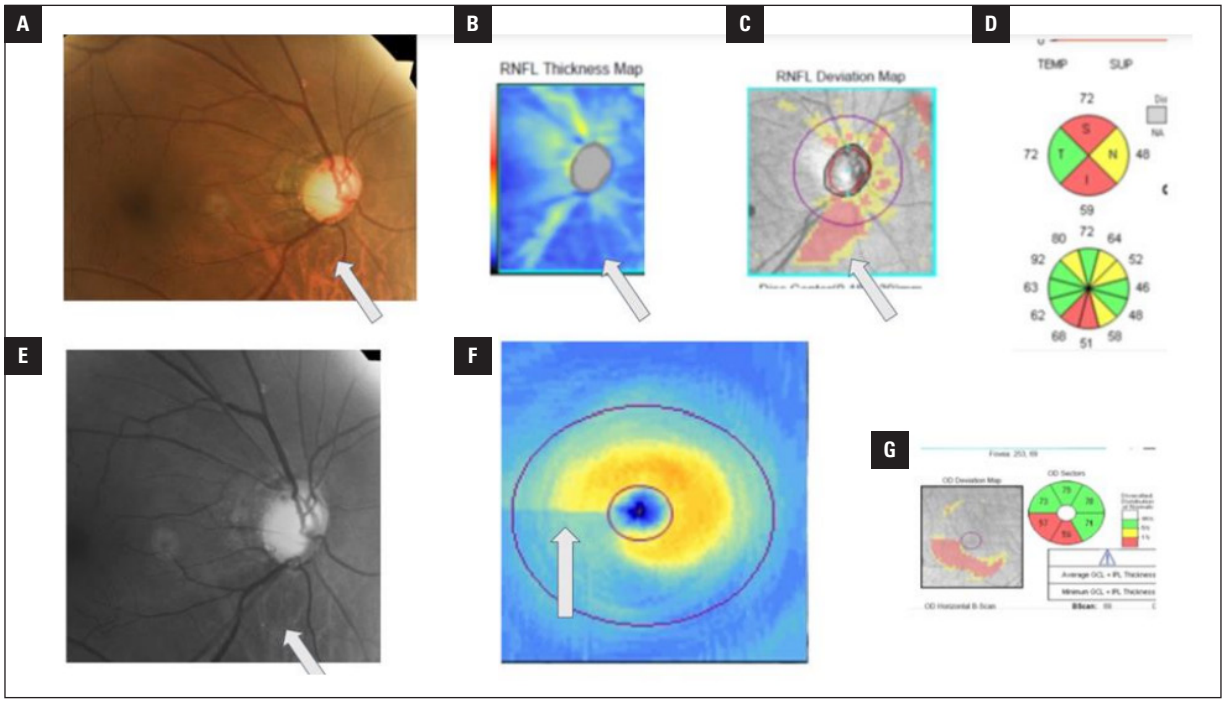


FIGURE 5. **A.** Right eye (RE) red color image showing inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** RNFL thickness map indicating inferior RNFL defect (white line); **C.** RNFL deviation map showing inferior thinning; **D.** RNFL meridians showing inferior thinning; **E.** RE red-free optic nerve image indicating inferior RNFL defect; **F.** Ganglion cell complex (GCC) thickness map showing temporal raphe positive sign; **G.** Visual field showing superior arcuate defect; **H.** GCC thickness and sector meridians showing inferior thinning

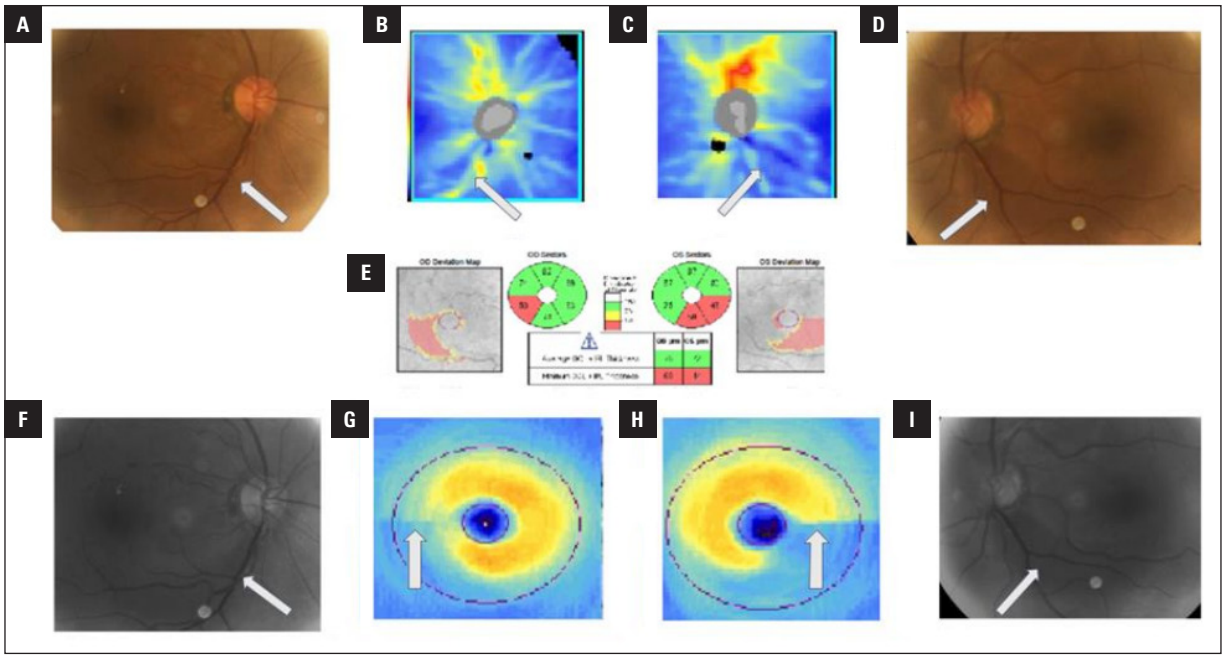


FIGURE 6. **A.** Right eye (RE) red color image indicating inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** RNFL meridian map indicating inferior thinning; **C.** Left eye (LE) red color image indicating inferior RNFL defect (white line); **D.** Ganglion cell complex (GCC) deviation and meridians indicating inferior thinning; **E.** RE red-free optic nerve image indicating inferior RNFL defect; **F.** Right GCC thickness map indicating temporal raphe positive sign; **G.** Right GCC thickness map indicating temporal raphe positive sign; **H.** RE red-free optic nerve image showing inferior RNFL defect

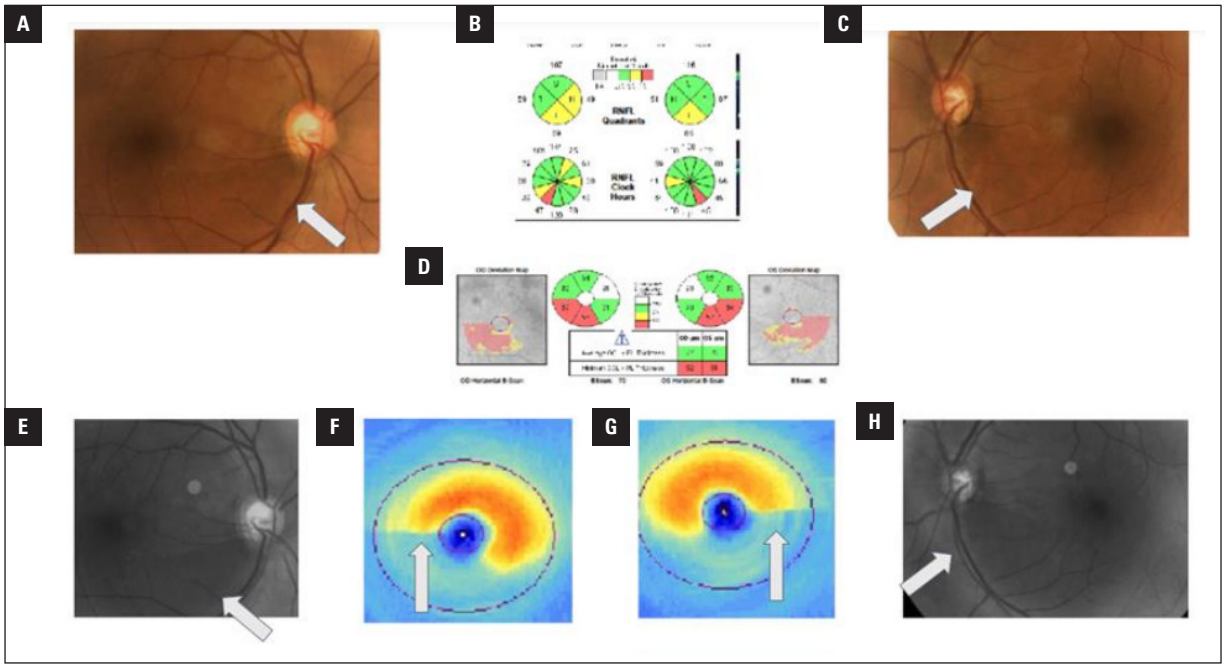


FIGURE 7. **A.** Right eye (RE) red color image indicating inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** RE RNFL thickness map indicating inferior thinning; **C.** Left eye (LE) RNFL thickness map indicating inferior thinning; **D.** LE red color image indicating inferior RNFL defect (white line); **E.** Ganglion cell complex (GCC) deviation and meridians indicating inferior thinning; **F.** RE red-free optic nerve image showing inferior RNFL defect; **G.** Right GCC thickness map indicating temporal raphe positive sign; **H.** Left GCC thickness map indicating temporal raphe positive sign; **I.** LE red-free optic nerve image indicating inferior RNFL defect

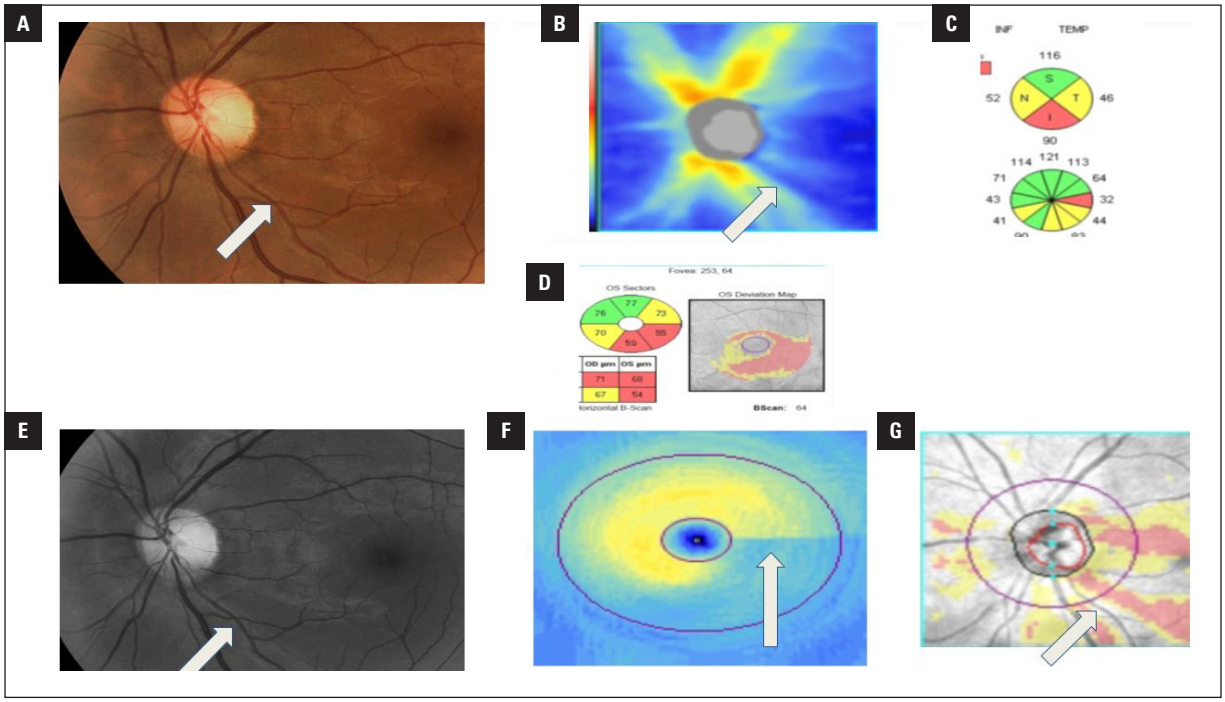


FIGURE 8. **A.** Left eye (LE) red color image indicating inferior retinal nerve fiber layer (RNFL) defect (white line); **B.** LE RNFL thickness map indicating inferior thinning; **C.** LE RNFL meridian map showing inferior thinning. LE red color image indicating inferior RNFL defect (white line); **D.** Ganglion cell complex (GCC) deviation and meridians indicating inferior thinning; **E.** LE red-free optic nerve image indicating inferior RNFL defect; **F.** Left GCC thickness map showing temporal raphe positive sign; **G.** LE RNFL deviation map showing inferior thinning

tion, sector, and thickness maps, respectively. Glaucomatous eyes with the greater angular distance between the fovea and the RNFL defect and narrower width of the RNFL defect had normal findings in the GCA maps.

Temporal RNFL enters into the superotemporal and inferotemporal aspects of the optic disc. Glaucomatous structural damage corresponding to the anatomic distribution of the RNFL is often asymmetric across the horizontal meridian because of the superior/inferior segregation [6]. Lee et al. [7] studied a total of 175 eyes of 175 patients with macular ganglion cell inner plexiform layer (mGCIPL) thinning on Cirrus (Carl Zeiss Meditec, Dublin, CA) HD-OCT. 67 eyes with GON and 73 eyes with nonglaucomatous optic neuropathy (NGON) were enrolled. A positive temporal raphe sign was defined in mGCIPL thickness maps when there was a straight line longer than one-half of the length between the inner and outer annulus in the elliptical temporal area. The temporal raphe sign was observed in 61 of 67 GON eyes (91.0%), but in only 21 of 73 NGON eyes (28.8%) ($p < 0.001$; chi-square test).

CONCLUSIONS

In this case series, we demonstrated the excellent performance of the macular GCC thickness map in detecting changes secondary to GON. The temporal raphe sign is a frequent finding among patients with GON, especially when they present with narrow and located RNFL defect, and the angular distance between fovea and RNFL defect is small.

REFERENCES

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006; 90(3): 262–267, doi: 10.1136/bjo.2005.081224, indexed in Pubmed: 16488940.
2. Kwon YH, Alward WLM. Primary Open-Angle Glaucoma. N Engl J Med. 2009; 360(25): 2679–2680, doi: 10.1056/nejmc090757, indexed in Pubmed: 19279343 .
3. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science. 1991; 254(5035): 1178–1181, doi: 10.1126/science.1957169, indexed in Pubmed: 1957169.
4. Popescu DP, Choo-Smith LP, Flueraru C, et al. Optical coherence tomography: fundamental principles, instrumental designs and biomedical applications. Biophys Rev. 2011; 3(3): 155, doi: 10.1007/s12551-011-0054-7, indexed in Pubmed: 28510064.
5. Hwang YH, Jeong YC, Kim HKi, et al. Macular ganglion cell analysis for early detection of glaucoma. Ophthalmology. 2014; 121(8): 1508–1515, doi: 10.1016/j.ophtha.2014.02.019, indexed in Pubmed: 24702756.
6. Um TW, Sung KR, Wollstein G, et al. Asymmetry in hemifield macular thickness as an early indicator of glaucomatous change. Invest Ophthalmol Vis Sci. 2012; 53(3): 1139–1144, doi: 10.1167/iovs.11-8373, indexed in Pubmed: 22247461.
7. Lee J, Kim YK, Ha A, et al. Temporal Raphe Sign for Discrimination of Glaucoma from Optic Neuropathy in Eyes with Macular Ganglion Cell-Inner Plexiform Layer Thinning. Ophthalmology. 2019; 126(8): 1131–1139, doi: 10.1016/j.ophtha.2018.12.031, indexed in Pubmed: 30576683.

CASE REPORT
DOI: 10.5603/OJ.2021.0042

Optical coherence tomography findings in compressive optic neuropathy and pre-existing glaucoma

Carlos Eduardo Rivera[1–4], Catalina Ferreira[1–4], Juan Carlos Aristizabal[1, 2], Edgar Muñoz[1, 5], Ankur Seth[1, 3, 6]

[1]Collective Innovations Colombia, Cali, Colombia
[2]Pontificia Universidad Javeriana, Cali, Colombia
[3]GSR Medical Center, Cali, Colombia
[4]GSR International, United States
[5]UT Health San Antonio, San Antonio, United States
[6]University of Tennessee Health Science Center, United States

ABSTRACT

BACKGROUND: We present the optical coherence tomography (OCT) findings in macular ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL) in a case of a female patient with craniopharyngioma and preexisting glaucoma.

CASE PRESENTATION: 80-year-old female patient with a history of successfully suprasellar resection of craniopharyngioma performed eight years earlier and preexisting primary open-angle glaucoma treated with latanoprost indicated a one-month history of decreased vision in the left eye. The visual field showed a vertical hemifield defect in the right eye and an inferior arcuate defect in the left eye. A cerebral magnetic resonance image confirmed a new suprasellar tumor. The patient was successfully operated on one week after diagnosis. Visual acuity in her left eye improved substantially after surgery.

RESULTS: Optical coherence tomography of macular and RNFL showed thinning in the patient's right eye that corresponded with the vertical visual field defect. A "C" pattern that compromised the horizontal meridian differentiated from glaucoma that respects the horizontal meridian. The visual field showed a vertical hemifield defect in the right eye and an inferior arcuate defect in the left eye.

CONCLUSIONS: Optical coherence tomography is a non-invasive imaging procedure. It helps identify compression of the anterior visual pathways, resulting in progressive thinning of RNFL and macular ganglion cell complex (GCC). It has a good correlation with visual fields.

KEY WORDS: optical coherence tomography; glaucoma; craniopharyngioma; visual field; visual acuity

Ophthalmol J 2021; Vol. 6, 249–254

CORRESPONDING AUTHOR:
Carlos Rivera, Holguines Trade Center, Cra 10 11-60, office 236, tel: (2) 3165225961, (572) 5546567; e-mail: carlosriverahoyos@gmail.com, crivera@grupogsr.co

INTRODUCTION

Chiasmal compression predominantly affects crossed nerve fibers associated with the nasal hemiretina, leaving uncrossed nerve fibers that originate in the temporal hemiretina relatively preserved [1]. Chiasmal compression is traditionally diagnosed by a characteristic temporal visual field (VF) defect along the vertical meridian.

Optical coherence tomography (OCT) is a non-invasive optical technique that allows *in vivo* cross-sectional imaging of the optic nerve head and the retina [2]. The thickness of the retinal macular layers is analyzed through cross-sectional images (B-scans) [3].

The inner retinal layers are the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL). The GCL encompasses the cell bodies of the ganglion cells of the retina. The axons of the retinal ganglion cells form the RNFL that travel out of the eye in the optic nerve, chiasm, and tract and finally synapse in the lateral geniculate body before conveying their information to the visual cortex. Compressive lesions in the optic nerve, chiasm, or tract will manifest as thinning of the RNFL and GCL [4].

Optical coherence tomography evaluations of the RNFL and GCL can be performed through peripapillary RNFL thickness and macular cube OCT images. They can help differentiate compressive optic neuropathies from glaucoma and other optic nerve neuropathies [5].

We present the OCT macular and RNFL findings in a case of a female patient with craniopharyngioma and preexisting glaucoma.

CASE REPORT

We present a case of an 80-year-old female patient with a one-month history of decreased vision in her left eye. The patient had a history of successfully suprasellar resection of craniopharyngioma eight years earlier, primary open-angle glaucoma treated with latanoprost. Visual field defect showed a vertical hemifield defect in her right eye and an inferior arcuate defect in her left eye. Cerebral magnetic resonance imaging confirmed the new appearance of the suprasellar tumor.

We diagnosed:

- in the right eye: best-corrected visual acuity (BCVA) — 20/30, mild cataract, open angles, intraocular pressure (IOP) — 14 mm Hg, cup/disc (C/D) ratio — 0.3;
- in the left eye: BCVA — 20/70, mild cataract, open angles, IOP — 14 mm Hg, C/D ratio — 0.8, superior and inferior rim thinning.

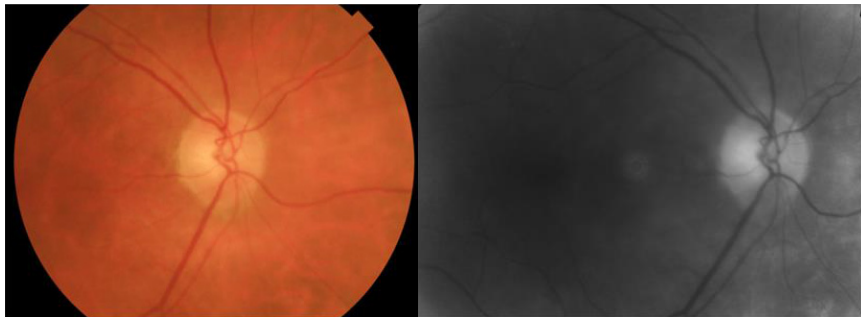


FIGURE 1. Right eye; **A.** Color optic nerve image; **B.** Red free image

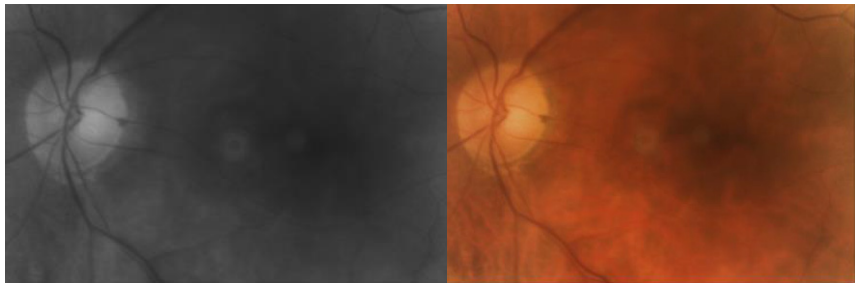


FIGURE 2. Left eye; **A.** Color optic nerve image; **B.** Red free image

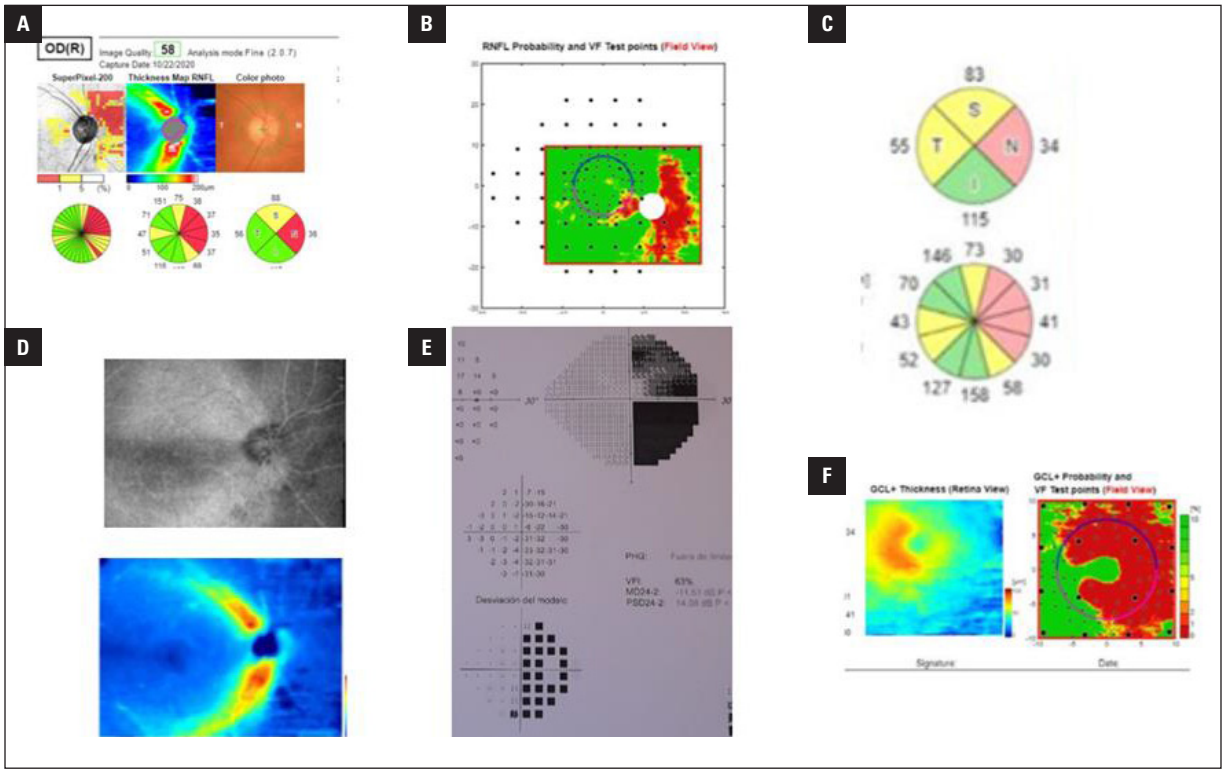


FIGURE 3. Right eye; **A.** RNFL deviation and clock hour meridian showing nasal thinning; **B.** RNFL probability and VF test points showing vertical temporal damage; **C.** RNFL clock hour meridian showing nasal thinning; **D.** Enface and thickness map showing nasal damage; **E.** Visual field showing temporal nasal defect; **F.** GCL thickness map showing "C" pattern compromising horizontal raphe. GCL — probability VF test points showing temporal damage

Optical coherence tomography findings in the right eye showed a nasal thinning in thickness, meridian, deviation, and enface map. RNFL and GCL probability maps showed a temporal defect that resembled a temporal visual field defect. All these findings were in the presence of a physiologic C/D ratio.

These findings were typical of a compressive optic neuropathy.

Optical coherence tomography findings in the left eye showed superotemporal thinning in thickness, meridian, deviation, and enface map.

RNFL and GCL probability maps showed an inferior arcuate defect resembling the inferior arcuate defect present in the visual field. All these findings were correlated with a C/D ratio of 0.8 with superior and inferior thinning. These findings were more compatible with glaucomatous optic neuropathy than compressive optic neuropathy.

The patient was successfully operated on one week after diagnosis. Visual acuity in her left eye improved substantially.

This case has a unique presentation where the right eye shows a physiological C/D ratio in the presence of a vertical hemifield defect with a perfect OCT correlation, typical of compressive optic neuropathy. On the other hand, the left eye showed a typical superior thinning with a corresponding inferior arcuate visual field defect and a very good OCT correlation, typical of glaucomatous neuropathy.

Visual acuity of the patient's left eye recovered to 20/30, the same level before surgery.

DISCUSSION

Compressive optic neuropathies typically present themselves

with slow, progressive, painless vision loss. Clinically it can help to differentiate them from other optic neuropathies [4]. The lesions most seen are meningiomas, craniopharyngioma, internal carotid or ophthalmic artery aneurysms and pituitary adenomas [6]. Reduced visual acuity, altered color vision, abnormal visual fields, pallor of the optic nerve are the clinical features of compressive optic neuropathies [7].

OCT findings include a "band atrophy" due to a more significant thinning of the horizontal sectors

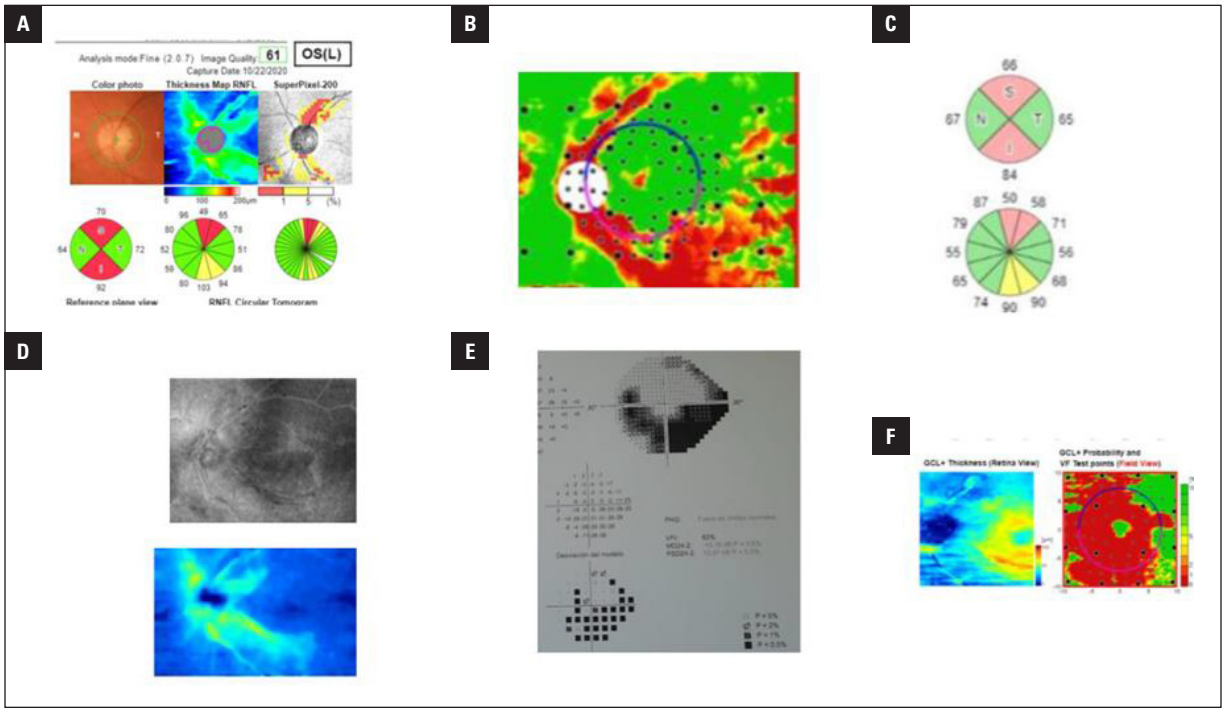


FIGURE 4. Left eye. **A.** RNFL deviation and clock hour meridian showing superotemporal thinning; **B.** RNFL probability and VF test points showing inferior arcuate damage; **C.** RNFL clock hour meridian showing superotemporal thinning; **D.** Enface and thickness map showing superotemporal thinning; **E.** Visual field showing the inferior arcuate defect and nasal step; **F.** GCL thickness map showing an unspecified pattern. GCL — probability VF test points showing an unspecified pattern

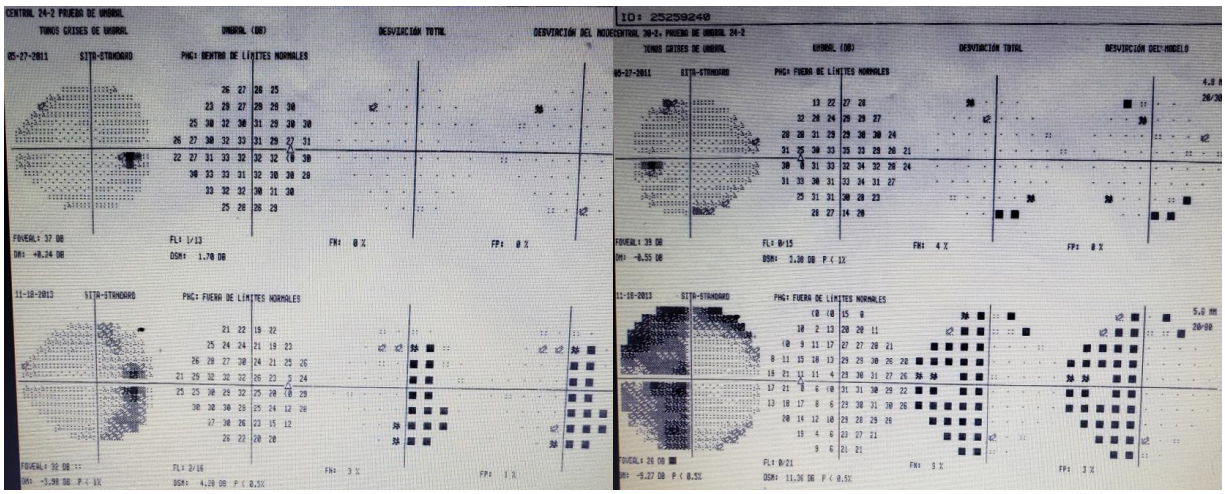


FIGURE 5. The visual field findings in 2013 when the craniopharyngioma was diagnosed for the first time. At this time, the defects were completely different from the actual presentation in the left eye. In 2013, the right eye showed a similar nasal hemifield involvement. The left eye showed a temporal hemifield defect as opposed to the actual presentation, where it showed an inferior arcuate defect. 2011 visual fields showed no visual field compromise in both eyes, as opposed to 2013 visual fields hemifield compromise mentioned previousl

of the RNFL compared with the vertical portion of the optic disc [8]. On the other hand, the pattern in glaucoma affects the vertical portion (superior and inferior quadrants) of the optic disc [9]. Patients with bitemporal hemianopsia have demonstrated reduced RNFL thickness measured by OCT compared with healthy controls [10].

The fovea, which is the center of the visual field, is measured with field macular GCC analysis, and it can easily be correlated with the visual field defect.

Patients with bitemporal visual field loss from chiasmal compression have shown a better correlation with macular GCC than RNFL measurements [11]. Patients with chiasmal compression have a greater degree of thinning in the nasal macula than healthy controls. Due to the disruption of the crossing fibers originating in the nasal retina, these findings explain this pattern [12, 13]

In patients with compressive lesions of the anterior visual pathways, there is a correlation between preoperative macular GCC thickness and postoperative visual outcome. In a study of twenty-three patients with chiasmal compression imaged with the cirrus high-definition optical coherence tomography macular cube, RNFL scan protocols, and automated (30-2 Humphrey) visual fields, authors concluded that patients with better postoperative 30-2 Humphrey visual fields had greater preoperative macular GCC thickness [14]. Pre- and postoperative RNFL and macular GCC to assess the postoperative follow-up are the guidelines for patients with pituitary adenomas recommended by The Congress of Neurological Surgeons [15].

After surgery, in patients with RNFL and macular GCC, the thinning may persist or even worsen despite having normal visual fields [16]. Several patients may appear to have a "paradoxical" worsening of the OCT measurements coincident with the improvement of the visual function because it takes at least six weeks for retrograde degeneration to be complete. After removal of the conduction block followed by secondary remyelination and restoration of axoplasmic flow, visual recovery occurs in stages months to years after surgery [17, 18]. Future presentations of recurring compression may manifest first as progressive thinning of the macular GCC and RNFL.

The discovery of incidental mass lesions in close proximity to the visual pathways is not uncommon because of the frequent use of neuroimaging in clinical practice. In a study of forty patients undergoing surgical resection of para-chiasmal lesions, patients were prospectively assessed before surgery with a complete neuro-ophthalmic examination, including standard automated visual field (VF) testing and OCT measurements of RNFL thickness. It was found that 15% of patients had thin RNFLs in the presence of normal visual field testing. Patients with compressive optic neuropathies can present damage to the anterior visual pathways before visual field loss occurs [19].

In a study of 23 patients (46 eyes) with pituitary adenomas, 12 eyes had normal visual fields, and 34 eyes had visual field defects. Authors concluded that the preperimetric group had normal RNFL thickness but significantly reduced OCT macular GCC thickness compared with healthy controls. They emphasize the utility of OCT of the macular GCC in the evaluation of these patients because nasal thinning of the macular GCC was found to be a better predictor than RNFL parameters in detecting chiasmal compression [20].

CONCLUSIONS

Optical coherence tomography is a routine non-invasive imaging device in ophthalmology. It is in evaluating patients with compressive lesions of the anterior visual pathways. The RNFL and macular GCC thickness can help differentiate compressive optic neuropathies from other neuropathies, including glaucoma.

In this case, in particular, OCT findings showed a high correlation with visual field defect and contributed to a correct diagnosis.

REFERENCES

1. Hoyt WF, Luis O. The primate chiasm. Details of visual fiber organization studied by silver impregnation techniques. Arch Ophthalmol. 1963; 70: 69–85, doi: 10.1001/archopht.1963.00960050071013, indexed in Pubmed: 13955217.
2. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. Science. 1991; 254(5035): 1178–1181, doi: 10.1126/science.1957169, indexed in Pubmed: 1957169.
3. Popescu DP, Choo-Smith LP, Flueraru C, et al. Optical coherence tomography: fundamental principles, instrumental designs and biomedical applications. Biophys Rev. 2011; 3(3): 155, doi: 10.1007/s12551-011-0054-7, indexed in Pubmed: 28510064.
4. Micieli JA, Newman NJ, Biousse V. The role of optical coherence tomography in the evaluation of compressive optic neuropathies. Curr Opin Neurol. 2019; 32(1): 115–123, doi: 10.1097/WCO.0000000000000636, indexed in Pubmed: 30418197.
5. Bussel II, Wollstein G, Schuman JS. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. Br J Ophthalmol. 2014; 98(Suppl 2): ii15–ii19, doi: 10.1136/bjophthalmol-2013-304326, indexed in Pubmed: 24357497.
6. Al-Dahmani K, Mohammad S, Imran F, et al. Sellar Masses: An Epidemiological Study. Can J Neurol Sci. 2016; 43(2): 291–297, doi: 10.1017/cjn.2015.301, indexed in Pubmed: 26522017.
7. Biousse V, Newman N. Diagnosis and clinical features of common optic neuropathies. Lancet Neurol. 2016; 15(13): 1355–1367, doi: 10.1016/s1474-4422(16)30237-x, indexed in Pubmed: 27839652.
8. Unsöld R, Hoyt WF. Band atrophy of the optic nerve. The histology of temporal hemianopsia. Arch Ophthalmol. 1980; 98(9): 1637–1638, doi: 10.1001/archopht.1980.01020040489020, indexed in Pubmed: 7425927.
9. Mwanza JC, Oakley JD, Budenz DL, et al. Cirrus Optical Coherence Tomography Normative Database Study Group. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. Ophthalmology. 2011; 118(2): 241–248.e1, doi: 10.1016/j.ophtha.2010.06.036, indexed in Pubmed: 20920824.
10. Sun M, Zhang Z, Ma C, et al. Quantitative analysis of retinal layers on three-dimensional spectral-domain optical coherence tomography for

pituitary adenoma. PLoS One. 2017; 12(6): e0179532, doi: 10.1371/journal.pone.0179532, indexed in Pubmed: 28628662.
11. Akashi A, Kanamori A, Ueda K, et al. The detection of macular analysis by SD-OCT for optic chiasmal compression neuropathy and nasotemporal overlap. Invest Ophthalmol Vis Sci. 2014; 55(7): 4667–4672, doi: 10.1167/iovs.14-14766, indexed in Pubmed: 25015351.
12. Zehnder S, Wildberger H, Hanson JVM, et al. Retinal Ganglion Cell Topography in Patients With Visual Pathway Pathology. J Neuroophthalmol. 2018; 38(2): 172–178, doi: 10.1097/WNO.0000000000000589, indexed in Pubmed: 29210928.
13. Monteiro MLR, Hokazono K, Fernandes DB, et al. Evaluation of inner retinal layers in eyes with temporal hemianopic visual loss from chiasmal compression using optical coherence tomography. Invest Ophthalmol Vis Sci. 2014; 55(5): 3328–3336, doi: 10.1167/iovs.14-14118, indexed in Pubmed: 24764062.
14. Tieger MG, Hedges TR, Ho J, et al. Ganglion Cell Complex Loss in Chiasmal Compression by Brain Tumors. J Neuroophthalmol. 2017; 37(1): 7–12, doi: 10.1097/WNO.0000000000000424, indexed in Pubmed: 28192385.
15. Newman S, Turbin R, Bodach M, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Pretreatment Ophthalmology Evaluation in Patients With Suspected Nonfunctioning Pituitary Adenomas. Neurosurgery. 2016; 79(4): E530–E532, doi: 10.1227/neu.0000000000001388, indexed in Pubmed: 27635960.
16. Danesh-Meyer HV, Wong A, Papchenko T, et al. Optical coherence tomography predicts visual outcome for pituitary tumors. J Clin Neurosci. 2015; 22(7): 1098–1104, doi: 10.1016/j.jocn.2015.02.001, indexed in Pubmed: 25891894.
17. Moon CH, Hwang SC, Ohn YH, et al. The time course of visual field recovery and changes of retinal ganglion cells after optic chiasmal decompression. Invest Ophthalmol Vis Sci. 2011; 52(11): 7966–7973, doi: 10.1167/iovs.11-7450, indexed in Pubmed: 21896856.
18. Cottee L, Daniel C, Loh W, et al. Remyelination and recovery of conduction in cat optic nerve after demyelination by pressure. Exp Neurol. 2003; 184(2): 865–877, doi: 10.1016/s0014-4886(03)00310-8, indexed in Pubmed: 14769379.
19. Danesh-Meyer HV, Papchenko T, Savino PJ, et al. In vivo retinal nerve fiber layer thickness measured by optical coherence tomography predicts visual recovery after surgery for parachiasmal tumors. Invest Ophthalmol Vis Sci. 2008; 49(5): 1879–1885, doi: 10.1167/iovs.07-1127, indexed in Pubmed: 18263812.
20. Yum HRi, Park SH, Park HYL, et al. Macular Ganglion Cell Analysis Determined by Cirrus HD Optical Coherence Tomography for Early Detecting Chiasmal Compression. PLoS One. 2016; 11(4): e0153064, doi: 10.1371/journal.pone.0153064, indexed in Pubmed: 27049647.

Scientific Research Publishing

Open Journal of Ophthalmology, 2020, 10, 99-114
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Prevalence of Primary Open Angle Glaucoma among Patients with Diagnosis of Systemic Hypertension and Diabetes Mellitus: The Colombian Glaucoma Study

Carlos E. Rivera[1*], Erika Cantor[2], Andres Castillo[3], Alexander Martinez[4], Lyle Newball[5], Juan C. Rueda[6], Alejandro Valencia[7], Sandra Belalcazar[8], Tulio Cabal[9], Oscar Albis-Donado[10], Fabian Mendez[11]

[1]Fundación Oftalmológica del Valle, Cali, Colombia
[2]Institute of Statistics, Universidad de Valparaiso, Valparaiso, Chile
[3]Department of Biology, Faculty of Natural & Exact Sciences, Universidad del Valle, Cali, Colombia
[4]Ophthalmology Residency Program, Universidad del Valle, Centro Médico Imbanaco, Cali, Colombia
[5]Clínica Lynd Newball, San Andrés Islas, Colombia
[6]FOSCAL Internacional, Bucaramanga, Colombia
[7]Glaucoma Unit Medellin Colombia
[8]Fundación Oftalmológica Nacional, Bogotá, Colombia
[9]Clínica Visión Cabal, Buga, Colombia
[10]Visual Sense, Private Practice, Mexico City, Mexico
[11]School of Public Health, GESP Group, Universidad del Valle, Cali, Colombia
Email: *carlosriverahoyos@gmail.com

How to cite this paper: Rivera, C.E., Cantor, E., Castillo, A., Martinez, A., Newball, L., Rueda, J.C., Valencia, A., Belalcazar, S., Cabal, T., Albis-Donado, O. and Mendez, F. (2020) Prevalence of Primary Open Angle Glaucoma among Patients with Diagnosis of Systemic Hypertension and Diabetes Mellitus: The Colombian Glaucoma Study. *Open Journal of Ophthalmology*, **10**, 99-114.
https://doi.org/10.4236/ojoph.2020.102012

Received: March 12, 2020
Accepted: April 26, 2020
Published: April 29, 2020

Abstract

Objective: To establish the prevalence and risk factors of Primary Open Angle Glaucoma (POAG) among patients with Systemic Hypertension (SH) and Diabetes Mellitus (DM) in six cities of Colombia. **Methods:** A cross-sectional study among hypertensive and diabetic patients was conducted in Colombia. This study included 2067 subjects older than 50 years of age diagnosed with SH and/or DM. Participants underwent a complete ophthalmic examination including intraocular pressure (IOP) measurement by Goldmann tonometry and blood pressure measurement. The glaucoma diagnosis was confirmed by structural and functional evidence. Interviews and standardized questionnaires were used to evaluate participants' lifestyle and other health conditions. **Results:** Among participants with DM/SH, 142 cases of POAG were confirmed for a prevalence of 5.6% [95% CI: 4.6 - 6.6], while 9.1% were glaucoma suspects [95% CI: 7.8% - 10.4%]. The majority of confirmed cases (77.5%) were undiagnosed. The prevalence of POAG was significantly higher with male gender, greater age, and diastolic blood pressure > 90 mmHg as risk factors.

Conclusion: We found a high prevalence of POAG in patients with adequate SH and DM care in a novel Latino population. We also found great unawareness of the disease in this population. Our results have potentially enormous public health implications for Colombia and other Latino populations.

Keywords

Open Angle-Glaucoma, Glaucoma, Systemic Hypertension, Diabetes Mellitus

1. Introduction

World-wide, the prevalence of glaucomatous optic neuropathy is estimated to be around 60 million cases, which implies there could be close to 8.4 million cases of blindness from glaucoma. The burden of glaucoma is expected to increase significantly, to an estimated 80 million people with glaucomatous optic neuropathy and 11.2 million blind by 2020 [1].

Many epidemiologic studies have been conducted in African-derived populations and non-Hispanic whites in the US and worldwide on the prevalence of glaucoma [2]-[11]. However, there have been relatively few studies in the Latino population [10] [12], especially in Colombia, South America, so the prevalence of glaucoma and its association with systemic hypertension (SH) and diabetes mellitus (DM) is currently unknown in this setting.

Diabetes Mellitus (DM) has been previously associated with glaucoma prevalence, specifically with Primary Open Angle Glaucoma (POAG), but results vary widely and some are even contradictory: some find a direct relationship between DM and POAG [12] [13] [14] [15] [16]; others report a relationship between glucose levels and intraocular pressure (IOP) but do not show a relationship between DM and POAG [17]; and finally, there are some studies that find no relationship [18] [19]. The proposed causal relationship is that the known microvascular changes from DM may facilitate or induce glaucoma damage independently or by the coexistence with elevated IOP and other comorbidities.

Blood pressure (BP) and IOP have a direct proportional relationship, where, the higher the BP, the greater the IOP [20]. In contrast, an association between patients with treated SH who present nocturnal hypotension and glaucoma progression has also been reported. Still, there is no convincing explanation for the exact mechanism by which SH and glaucoma are related [21].

The aim of the study is to establish the prevalence of glaucoma in patients over 50 years of age and diagnosis of SH and/or DM in 6 cities of Colombia, and report on related risk factors.

2. Materials and Methods

2.1. Study Design

This is a cross-sectional study of hypertensive and diabetic patients of six cities in Colombia (Bogotá, Buga, Bucaramanga, Cali, Medellin, and San Andres),

conducted from September 2014 to January 2019. At enrollment, individuals were ≥50 years of age and were treated with antihypertensive and/or anti-diabetic medications for at least 1 year. The diagnosis of DM and SH were verified according to the guidelines for each disease [22] [23]. Patients with severe associated comorbidities (renal failure, congestive heart failure, sleep apnea, autoimmune diseases with biological therapy), previous intraocular surgery (trauma , retinal detachment, complicated cataract surgery, macular degeneration or maculopathy) or congenital ocular pathology (e.g., coloboma) were excluded. All participants were selected from SH and DM control programs. The Universidad del Valle Review Board approved this study (Approval Code 030-014), all participants signed an informed consent form. This research was conducted according to the tenants of the Declaration of Helsinki.

2.2. Procedures

Interviews and questionnaires were used to evaluate factors related to participants' lifestyle, and other health conditions, including socioeconomic status, associated comorbidities, education and nutrition. Family history of glaucoma and knowledge of the disease were also recorded. Physical activity was measured using the International Physical Activity Questionnaire (IPAQ). In addition, a physical examination was performed that included measurement of height, weight, abdominal circumference, heart rate and systolic (SBP) and diastolic blood pressure (DBP).

Blood pressure (BP) was measured in sitting position after 5 minutes of rest, using a sphygmomanometer (Welch Allyn, New York, U.S.). The cut-off values of BP were defined according to the guidelines for the management of Arterial hypertension of the European Society of Hypertension (ESH) [23]. High BP was defined as SBP > 140 mm Hg or DBP > 90 mm Hg. Low BP was defined as SBP < 110 mm Hg and DBP < 60 mm Hg. Mean arterial BP (MABP) was calculated as (1/3)SBP + (2/3)DBP. The Ocular Perfusion Pressure (OPP) was defined as 2/3 MABP-IOP. The highest IOP value between the two eyes was used to calculate OPP.

2.3. Ophthalmic Evaluation

Each participant underwent a complete ophthalmologic examination, including visual acuity, refraction, slit-lamp examination, intraocular pressure and pachymetry measurements. The IOP measurement was obtained from the average of three values by Goldmann tonometry. Gonioscopy was performed in a dark room using a 4-mirror goniolens (Ocular Instruments Inc., Bellevue, WA) in primary position, with a slit beam less than 2 mm in height, followed by a dilated funduscopic examination with a 78 diopter (D) lens for evaluating the optic disc, (Ocular Instruments Inc., Bellevue, WA). Central corneal thickness (CCT) was calculated based on the average of three consecutive measurements using a PachPen handheld pachymeter (Accutome, Inc., Pennsylvania, USA).

In suspected cases of glaucoma, the diagnosis was confirmed using visual field (VF) test with the 24-2 Swedish Interactive Threshold Algorithm (Humphrey, Carl Zeiss Meditec, Inc) and optic nerve photos with a DRS camera (digital retinography system, Centervue, Fremont, CA, USA). Glaucomatous eyes had to have at least 2 consecutive, reliable, and repeatable standard automated perimetry examinations with either a pattern standard deviation (PSD) outside the 95% normal limits or a glaucoma hemifield test result outside normal limits. Reliable visual fields had rates of false-positives, fixation losses and false-negative errors of 20% or less to be included. Trained glaucoma specialists performed the examinations using standardized protocols.

2.4. Diagnosis of Glaucoma

Suspected and confirmed cases of glaucoma were defined according to the criteria specified by Foster *et al.* [24] confirmed glaucoma was defined as structural and functional evidence of glaucomatous damage in at least one eye that met the following criteria: 1) horizontal or vertical cup-disc ratio 0.7 (97.5th percentile), focal glaucomatous disc change (disc hemorrhage, notch of the neuroretinal rim, marked sloping of rim tissue, narrowest remaining rim of 0.1 disc diameter or less), cup/disc asymmetry 0.2 (97.5th percentile), associated with a glaucomatous VF defect; 2) horizontal or vertical cup-disc ratio 0.8 (99.5th percentile), focal glaucomatous disc change, asymmetry 0.3 (99.5th percentile) with absence of functional evidence of glaucomatous damage (if the subject could not satisfactorily complete the VF examination). Cases that did not meet all criteria were classified as suspected glaucoma. In addition, VF defects that were not explained by any other disease, like asymmetry across the horizontal midline, visual defects located in the mid-periphery or clustered in neighboring test points, were defined as compatible with the disease.

2.5. Sample Size and Statistical Analysis

Sample size calculation was based on expected prevalence of POAG of 8%, a 95% confidence interval level and a precision of 2%; based on these parameters the estimated sample size was of 1632 patients (hypertensive and/or diabetic), who were all recruited from SH and DM control programs.

The glaucoma prevalence was calculated as the ratio between the number of individuals with suspected or confirmed glaucoma and the number of individuals included in the study. Continuous variables were summarized with mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical variables were described with proportions.

The patients were divided into three groups according to the status of diagnosis of POAG: confirmed cases, suspected cases and those without glaucoma. Participants with angle-closed or secondary glaucoma were excluded for this analysis. The comparison between categories of continuous variables was performed using ANOVA or the Kruskal-Wallis tests. Binary and categorical characteristics were compared using a chi-square or Fisher's exact tests. A multinomial logistic

regression model was applied to determine factors associated with POAG. Model selection was performed using a backward selection methodology; variables with p values < 0.20 in bivariate analysis were included. Odds Ratios (OR) were estimated with 95% confidence interval and goodness-of-fit was evaluated using a likelihood ratio test and the smallest model deviance. A level of significance of 0.05 was used. All analyses were carried out using Stata13® (STATA Corp, College Station, TX, USA).

3. Results

A total of 2085 subjects completed the interview and ophthalmologic examination, of which 18 were excluded because they met one or more exclusion criteria. The average age of the 2067 participants was 65.6 ± 8.8 years, 64.1% (1324) were female, 11.0% (228) had only DM, 59.6% (1231) had only SH and 29.4% (608) had both diseases. Of 2067 SH and/or DM patients, 142 were identified with confirmed glaucoma and 226 subjects with suspected glaucoma (**Figure 1**). From 1902 participants who completed the question about the family history of glaucoma, 20.9% (398) answered affirmatively. Of 142 participants who were identified as confirmed glaucoma in the present study, 22.5% (32) had been previously diagnosed.

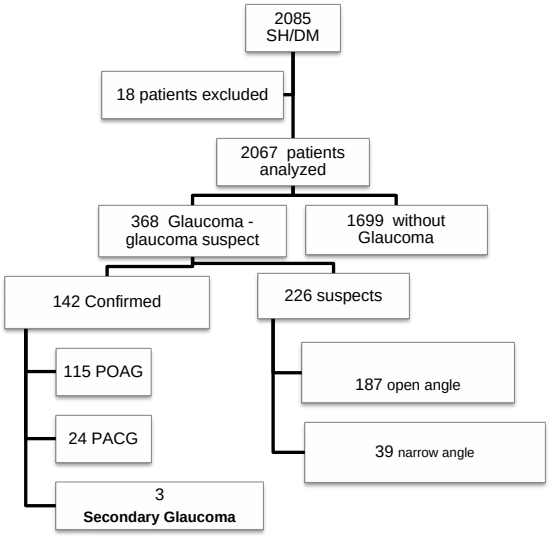
3.1. Prevalence of Glaucoma

Prevalence of confirmed POAG was 5.6% [95% CI: 4.6 - 6.0], with a higher prevalence observed among those with SH only. In addition, the proportion of suspected cases was higher among participants with DM only (**Table 1**). The prevalence of POAG according to age and sex is described in **Table 2**. Confirmed POAG was more frequent in men at all ages. A higher prevalence of suspected POAG was found in cases under 59 years and older than 80 years. The prevalence of confirmed POAG was higher in diabetic or hypertensive patients with time since diagnosis of more than 5 years, while suspected POAG was more frequent in patients with an evolution of the disease less than 5 years (**Figure 2**).

3.2. Characteristics of Patients with or without POAG

The sociodemographic and clinical characteristics of 2085 cases with and without POAG are described in **Table 3**. Confirmed cases of POAG were more frequent among men and above 70 years of age. The proportion of self-identified individuals as African-descendant was more frequent in cases with suspected POAG. As compared with cases without glaucoma, suspected and confirmed POAG cases reported high physical activity more frequently. No statistically significant differences were found between groups regarding marital status, level of education, alcohol consumption, smoking status, weight, height, body mass index (BMI) and abdominal circumference. The percentage of cases with a family history of glaucoma was significantly higher (29.2%) in confirmed cases of POAG (**Table 3** and **Table 4**).

Significant differences were found in DBP, with a higher proportion of confirmed POAG cases with pressure < 60 mm Hg or >90 mm Hg. Self-reported autoimmune disease was more frequent in confirmed POAG. A higher proportion of cases with thyroid disease was found among patients without glaucoma, in comparison with suspected and confirmed POAG ($p < 0.05$) (Table 3 and Table 4).



POAG: Primary open angle glaucoma; PACG Primary Angle Closed Glaucoma; SH: Systemic Hypertension; DM: diabetes Mellitus.

Figure 1. Flowchart of the study participants.

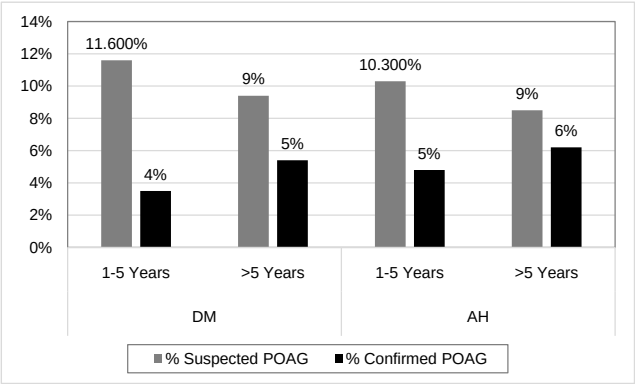


Figure 2. Prevalence of POAG according to time since diagnosis of DM or SH.

Table 1. Prevalence of POAG.

Glaucoma	Total % [95% CI]	DM % [95% CI]	SH % [95% CI]	DM/AP % [95% CI]
Confirmed	5.6 [4.6 - 6.6]	4.8 [2.4 - 8.5]	6.2 [4.9 - 7.7]	4.4 [2.9 - 6.4]
Suspect	9.1 [7.8 - 10.4]	11.4 [7.6 - 16.3]	8.6 [7.1 - 10.3]	10.5 [8.2 - 13.2]
Total	14.6 [13.1 - 16.2]	16.3 [11.7 - 21.5]	14.9 [12.9 - 16.9]	13.5 [10.9 - 16.5]

POAG: Primary open angle glaucoma; SH: Systemic Hypertension; DM: diabetes; CI: Confidence interval.

Table 2. Prevalence of POAG according to sex and age.

Age	Confirmed POAG			Suspected POAG		
	Women % [95% CI]	Men % [95% CI]	Total % [95% CI]	Women % [95% CI]	Men % [95% CI]	Total % [95% CI]
50 - 59	2.7 [1.5 - 4.9]	6.8 [3.9 - 11.6]	4.0 [2.7 - 5.9]	9.5 [7.0 - 12.8]	11.9 [7.9 - 17.6]	10.2 [8.0 - 13.0]
60 - 69	3.5 [2.2 - 5.6]	6.0 [3.8 - 9.4]	4.5 [3.2 - 6.1]	9.3 [7.0 - 12.1]	8.4 [5.7 - 12.1]	8.9 [7.1 - 11.1]
70 - 79	6.8 [4.5 - 10.1]	11.3 [7.7 - 16.1]	8.6 [6.5 - 11.3]	7.4 [5.0 - 10.8]	8.1 [5.2 - 12.5]	7.7 [5.7 - 10.2]
>80	5.6 [2.3 - 12.8]	8.9 [3.3 - 21.6]	6.7 [3.5 - 12.4]	10.1 [5.3 - 18.4]	11.1 [4.6 - 24.2]	10.4 [6.3 - 16.9]

POAG: Primary open angle glaucoma; CI: Confidence interval.

Table 3. Sociodemographic, clinical and ocular characteristics of cases with and without POAG.

Variable	Confirmed (n = 115)	Suspect (n = 187)	No Glaucoma (n = 1699)	p value	Total (n = 2001)
Age n (%)					
50 - 59	23 (20.0)	59 (31.5)	480 (28.3)	0.018	562 (28.1)
60 - 69	36 (31.3)	72 (38.5)	664 (39.1)		772 (38.5)
70 - 79	47 (40.9)	42 (22.5)	445 (26.2)		42 (22.5)
>80	9 (7.8)	14 (7.5)	108 (6.4)		14 (7.5)
Sex n (%)					
Female	56 (48.7)	118 (63.1)	1105 (65.0)	0.002	1279 (63.9)
Male	59 (51.3)	69 (36.9)	594 (34.9)		722 (36.1)
Race n (%)					
Non White-White (mestizo)	95 (82.6)	133 (71.1)	1345 (79.2)	0.018	1573 (78.6)
Black	5 (4.3)	16 (8.6)	81 (4.8)		102 (5.1)
White	10 (8.7)	28 (14.9)	233 (13.7)		271 (13.5)
Other	5 (4.3)	10 (5.3)	40 (2.3)		55 (2.7)
Marital Status n (%)					
Other	45 (39.1)	68 (36.6)	734 (43.2)	0.167	847 (42.4)
Married/Free Union	70 (60.9)	118 (63.4)	964 (56.8)		1152 (57.6)
Educational Level n (%)					
High school or less	90 (78.9)	142 (76.8)	1257 (75.2)	0.621	1489 (75.6)
Other	24 (21.0)	43 (23.2)	414 (24.8)		481 (24.4)
Physical Activity n (%)					
Low or inactive	69 (60.0)	108 (57.7)	1123 (66.1)	0.006	1300 (64.9)
Moderate	33 (28.7)	57 (30.5)	474 (27.9)		564 (28.2)
high	13 (11.3)	22 (11.8)	102 (6.0)		137 (6.8)
Smoker n (%)					
Non smoker	63 (55.3)	114 (61.0)	1029 (60.7)	0.819	1206
Ex-smoker	46 (40.3)	66 (35.3)	593 (35.0)		
Smoker	5 (4.4)	7 (3.7)	72 (4.2)		
Alcohol n (%)					
Never	81 (71.1)	127 (69.0)	1251 (74.2)	0.270	1459 (73.5)
With some frecuency	33 (28.9)	57 (31.0)	436 (25.8)		526 (26.5)
Processed meat n (%)					
High Consumption	15 (13.3)	36 (19.3)	177 (10.5)	0.001	228 (11.5)
Low Consumption	98 (86.7)	150 (80.6)	1508 (89.5)		1756 (88.5)
Red meat n (%)					
High Consumption	65 (56.5)	112 (59.9)	1024 (60.3)	0.720	1201 (60.1)
Low Consumption	50 (43.5)	75 (40.1)	673 (39.7)		798 (39.9)
Salt n (%)					
Low Consumption	106 (93.8)	179 (95.7)	1634 (96.9)	0.142	1919 (96.6)
High Consumption	7 (6.2)	8 (4.3)	52 (3.1)		67 (3.4)

Continued

Fruits n (%)					
High Consumption	93 (80.9)	161 (86.1)	1457 (86.0)	0.309	1711 (85.7)
Low Consumption	22 (19.1)	26 (13.9)	237 (14.0)		285 (14.3)
Family History n (%)					
Yes	31 (29.2)	33 (19.3)	314 (20.0)	0.069	378 (20.5)
Systemic Diagnosis n (%)					
DM	11 (9.6)	26 (13.9)	180 (10.6)		217 (10.8)
SH	77 (66.9)	106 (56.7)	1013 (59.7)	0.329	1196 (59.8)
DM/SH	27 (23.5)	55 (29.4)	505 (29.7)		587 (29.3)
Weight Kg					
Median (RIQ)	70.0 (61.7 - 80.0)	71.0 (63.0 - 80.0)	70.0 (62.0 - 80.0)	0.865	70.0 (62.0 - 80.0)
Height cms					
Median (RIQ)	162.0 (155.0 - 170.0)	160.0 (155.0 - 167.0)	160.0 (154.0 - 167.0)	0.194	160.0 (155.0 - 167.0)
BMI					
Median (RIQ)	26.9 (23.9 - 30.2)	26.9 (24.6 - 30.7)	27.2 (24.5 - 30.7)	0.479	27.1 (24.5 - 30.7)
Abdominal Circumference					
Median (RIQ)	97.0 (90.0 - 104.0)	96.0 (88.0 - 102.0)	96.0 (89.0 - 104.0)	0.628	96.0 (89.0 - 104.0)
DBP					
<60	18 (15.6)	28 (15.3)	163 (9.7)		209 (10.6)
61 - 70	32 (27.8)	50 (27.3)	449 (26.7)		531 (26.8)
71 - 80	37 (32.2)	63 (34.4)	714 (42.5)	0.003	814 (41.1)
81 - 90	15 (13.0)	36 (19.7)	260 (15.5)		311 (15.7)
>90	13 (11.3)	6 (3.3)	94 (5.6)		113 (5.7)
SBP					
<110	24 (20.9)	50 (27.3)	321 (19.1)		395 (19.9)
111 - 120	31 (26.9)	47 (25.7)	539 (32.1)	0.093	617 (31.2)
121 - 140	44 (38.3)	66 (36.1)	656 (39.1)		766 (38.7)
>140	16 (13.9)	20 (10.9)	164 (9.7)		200 (10.1)
Comorbidities n (%)					
Dyslipidemia	50 (43.4)	83 (44.4)	757 (44.9)	0.949	890 (44.8)
Migraine	10 (8.8)	16 (8.6)	186 (11.0)	0.530	212 (10.6)
Autoimmune dis	23 (21.1)	17 (9.7)	191 (11.8)	0.015	231 (12.2)
Coronary Disease	17 (14.9)	37 (19.9)	283 (16.7)	0.472	337 (16.9)
Cáncer	8 (7.0)	6 (3.2)	78 (4.6)	0.304	92 (4.6)
Thyroid disease	16 (14.0)	25 (13.4)	392 (23.1)	0.001	(1.7)
IOP					
Median (IQR)	15 (12 - 20)	15 (13 - 17)	14 (12 - 16)	0.001	14 (12 - 16)
CCT					
<500	23 (20.2)	28 (15.1)	209 (12.9)		260 (13.6)
>500	91 (79.8)	157 (84.9)	1406 (87.1)	0.076	1654 (86.4)
Median (IQR)	530.0 (505.0 - 551.2)	529.0 (509.0 - 552.5)	534.0 (513.0 - 558.0)		533.0 (512.0 - 557.0)
OPP n (%)					
<40	28 (24.6)	41 (22.4)	221 (13.2)		290 (14.7)
41 - 50	51 (44.7)	82 (44.8)	818 (48.8)		951 (48.2)
51 - 60	26 (22.8)	55 (30.0)	541 (32.3)	0.000	622 (31.5)
>60	9 (7.9)	5 (2.7)	96 (5.7)		110 (5.6)
Median (IQR)	46.5 (40.0 - 51.4)	46.2 (40.8 - 51.9)	47.8 (43.2 - 52.2)		47.5 (42.8 - 52.2)

IOP: Intraocular Pressure; CCT: IQR: Interquartile Range; OPP: Ocular perfusion pressure: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 4. Multivariate analysis of the risk factors associated with POAG.

Variables	% Confirmed POAG	Confirmed POAG OR [95% IC]	% Suspected POAG	Suspected POAG OR [95% IC]
Age				
50 - 59	4.09%	1	10.50%	1
60 - 69	4.66%	1.06 [0.57 - 1.96]	9.33%	1.02 [0.67 - 1.55]
70 - 79	8.80%	2.55 [1.38 - 4.71]**	7.87%	0.99 [0.60 - 1.62]
>80	6.87%	1.88 [0.72 - 4.86]	10.69%	1.34 [0.63 - 2.87]
Sex				
Female	4.38%	1	9.23%	1
Male	8.17%	1.99 [1.22 - 3.25]**	9.56%	0.95 [0.65 - 1.41]
Race				
Non White-White(mestizo)	6.04%	1	8.46%	1
Black	4.90%	0.74 [0.27 - 2.05]	15.69%	1.84 [0.97 - 3.48]*
White	3.69%	0.57 [0.25 - 1.30]	10.33%	1.27 [0.77 - 2.08]
Other	9.09%	0.86 [0.24 - 3.06]	18.18%	1.69 [0.72 - 3.94]
Marital Status				
Other	5.31%	1	8.03%	1
Married/Free Union	6.08%	1.20 [0.73 - 1.98]	10.24%	1.51 [1.02 - 2.23]*
Family History n (%)				
No	5.11%	1	9.41%	1
Yes	8.20%	1.62 [0.98 - 2.67]*	8.73%	0.97 [0.63 - 1.51]
Physical Activity n (%)				
Low or inactive	5.31%	1	8.31%	1
Moderate	5.85%	1.03 [0.62 - 1.71]	10.11%	1.44 [0.98 - 2.11]*
high	9.49%	1.97 [0.93 - 4.15]*	16.06%	2.35 [1.33 - 4.16]**
Processed meat n (%)				
Low Consumption	5.58%	1	8.54%	1
High Consumption	6.58%	1.22 [0.61 - 2.41]	15.79%	1.89 [1.18 - 3.03]**
DBP mm Hg				
<60	8.61%	1.91 [0.78 - 4.67]	13.40%	1.12 [0.55 - 2.30]
61 - 70	6.03%	1.57 [0.85 - 2.93]	9.42%	1.25 [0.77 - 2.05]
71 - 80	4.55%	1	7.74%	1
81 - 90	4.82%	1.69 [0.77 - 3.70]	11.58%	1.96 [1.10 - 3.48]**
>90	11.50%	5.84 [1.66 - 20.52]**	5.31%	0.60 [0.13 - 2.86]
Autoimmune disease				
No	5.16%	1	9.48%	1
Yes	9.96%	2.20 [1.24 - 3.92]**	7.36%	0.82 [0.45 - 1.48]
Thyroid disease				
No	6.28%	1	10.32%	1
Yes	3.70%	0.47 [0.25 - 0.88]**	5.77%	0.65 [0.40 - 1.05]*
IOP				
<21 mm Hg	4.81%	1	9.20%	1
≥21 mm Hg	34.43%	7.18 [3.09 - 16.69]***	17.75%	1.55 [0.59 - 4.04]
CCT				
<500	8.85%	1.94 [1.09 - 3.43]**	10.77%	1.10 [0.67 - 1.81]
>500	5.50%	1	9.49%	1
OPP				
<40	9.66%	1.08 [0.50 - 2.31]	14.14%	2.23 [1.27 - 3.91]**
41 - 50	5.36%	1	8.62%	1
51 - 60	4.18%	0.62 [0.29 - 1.27]	8.84%	0.72 [0.41 - 1.24]
>60	8.18%	0.41 [0.09 - 1.73]	4.55%	0.38 [0.08 - 1.86]

*p < 0.10; **p < 0.05; ***p < 0.001; IOP: Intraocular Pressure; CCT: IQR: Interquartile Range; OPP: Ocular perfusion pressure: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

The proportion of IOP ≥ 21 mmHg was 1.8% among the patients without glaucoma, 4.8% in the group with suspected POAG and 18.2% in the one with confirmed POAG. Figure 3 shows the distribution of IOP according to POAG diagnosis. CCT < 500 were more frequent in cases with confirmed POAG. Figure 3 shows the distribution of IOP according to diagnosis. The number of cases with low values of OPP (<40 mm Hg) was higher in cases with suspected or confirmed POAG compared to the non-glaucoma group (Table 3 and Table 4).

3.3. Risk Factors Associated with POAG

In the multivariate analysis, the risk factors related to glaucoma suspects were high physical activity, high consumption of processed meat, high DBP values and low OPP values. While, older age, male sex, diagnosis of autoimmune disease, IOP > 21 mm Hg and CCT < 500 were associated with the diagnosis of confirmed POAG (Table 4).

4. Discussion

This study, to our knowledge, is the first program-based study to report the prevalence and clinical characteristics of glaucoma in subjects over 50 years of age in Colombia. Our study was performed in six cities of the country including patients older than 50 years with SH and/or DM. The decision to select this age criteria, in addition to adjusting to the central hypothesis of the investigation, was based on efficiency criteria in the design. Specifically, the decision was made by observing that in previous studies the prevalence of glaucoma below 50 years is very low, namely: Barbados, 1.4% [4], LALES, 1.32% [10], Project VER, 0.5% [25], Baltimore 0.18% [3]; as well as the prevalence of SH and DM in people younger than 50 years in Colombia [26] [27].

As expected, the prevalence of POAG in our study was 5.6%, which is higher than those reported in most studies [1]-[8] [10] [25]. This finding is due to the fact that our population corresponded to diabetic and/or hypertensive patients, unlike other previous population-based studies where the only inclusion criteria was age (over 40 years), independently of any systemic disease. It is noteworthy that the prevalence of glaucoma in our Latino DM/SH population almost equals the observed 7% prevalence among the African-descendant population in the Barbados study [4]. Also, is important to notice that the prevalence of POAG could be similar between Latinos and African-descendant patients. Future studies in a wider and more representative latino population will help us better discern the similarities and differences with African-descendant populations.

The prevalence of POAG in our study among individuals 70 - 79 years old was 8.6% [6.5 - 11.3], while in those with 50 to 59 years old was 4.0% [2.7 - 5.9]. Our study, reflect an age-related increase in prevalence of POAG, similar observations have been reported previously in other prevalence studies [10] [25].

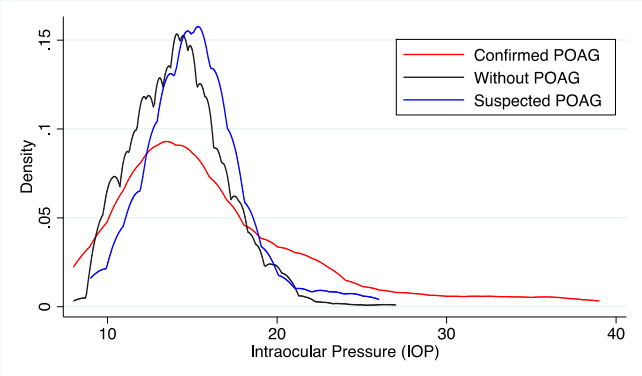


Figure 3. Intraocular pressure distribution curve according to diagnosis.

Our results are worrisome regarding the poor knowledge of the diagnosis in this group of patients with SH and DM (more than 75% were unaware), since the late diagnosis of glaucoma can lead to severe visual impairment. A similar situation was described in the LALES study, over 75% (n = 220) of the 291 persons with POAG had no history of glaucoma or treatment for glaucoma. Similarly, over 75% (n = 165) of those diagnosed with ocular hypertension were previously undiagnosed [10]. Other similar rates where described in Northern Italy (78%) [20] and are higher than those found in other population-based studies in Melbourne (50%) [7], Blue Mountains (51%) [6], Baltimore (58% in blacks and 50% in non-Hispanic whites) [3], Rotterdam (53%) [5], Barbados (51%) [4], and Arizona (62%) [25].

Costa *et al.* performed a comparative study among 183 patients interviewed at the Wills Eye Hospital (Philadelphia, USA) and 100 patients from the Glaucoma Service at the University of Campinas (Campinas, Brazil). Linear regression analysis showed a positive relationship between level of education and knowledge about glaucoma (r: 0.65, p: 0.001). This study concludes that knowledge about glaucoma significantly varies in an urban population when one is located in a high-income country (US), where one third had no knowledge of the disease, compared to a middle-income country (Brazil) in which two-thirds had no knowledge of the disease [28].

The lack of awareness of the disease should influence decision making across the health system to implement effective and permanent strategies for the early detection of the disease with the aim of facilitating that patients with risk factors have access to a timely treatment. This situation is more alarming if we take into account that patients from SH and DM programs participating in this study are supposed to be routinely evaluated by doctors and nurses to control underlying disease. This is the best scenario, since 30% - 50% of patients with DM are unaware of their disease or do not have access to such programs [27].

A trend for a higher prevalence of POAG in those with more than 5 years of being diagnosed with DM and/or SH was observed (**Figure 2**). Similar to our results, The Los Angeles Latino Study (LALES) LALES reported 5894 participants, 1157 (19.6%) had DM type 2 and 288 (4.9%) had POAG. The prevalence

of POAG 40% higher in participants with DM than in those without DM (age/gender/intraocular pressure-adjusted odds ratio, 1.4; 95% confidence interval, 1.03 - 1.8; p value 0.03). Trend analysis revealed that a longer duration of DM (stratified into 5-year increments) was associated with a higher prevalence of POAG ($p < 0.0001$) [12].

To the best of our knowledge, this is the first population based study to report this independent association between longer duration of DM and higher prevalence of POAG in a latino population outside the US. Additionally, a systematic review by Minwen *et al.* of DM as a risk factor for POAG, including thirteen studies—seven case-control studies and six population-based cohort studies—reported a pooled RR of the association between DM and POAG, based on the risk estimates of the six cohort studies, to be 1.40 (95% CI, 1.25 - 1.57) [29].

DM may affect vascular autoregulation of the retina and optic nerve causing microvascular damage. Vascular disturbances to the anterior portion of the optic nerve are postulated to be at least partially responsible for optic nerve head changes, which can result in glaucomatous optic neuropathy [30] [31] [32]. Additionally, DM also compromises glial and neuronal functions and metabolism in the retina, which can make retinal neurons, including retinal ganglion cells, more susceptible to glaucomatous damage [33]. The higher prevalence of POAG in subjects with longer duration of DM might be related to a prolonged insult to the retina and optic nerve via vascular, glial, and neuronal factors.

Similar to DM, SH diagnosed for more than 5 years was also related to higher prevalence of POAG. Additionally, elevated DBP showed a tendency to be positively related to POAG. Specifically, the prevalence of POAG was approximately four-fold among the subjects with DBP > 90 mm Hg as compared to those with a DBP between 71 and 80 mm Hg. In SH, an endothelial dysfunction is observed initially due to the alteration in endothelin, which leads to a change in the size of the arterioles, then an increase in resistance to blood flow, reduction of perfusion and finally a loss of vascular autoregulation [34].

The Los Angeles Latino Study (LALES) evidenced that patients with SBP greater than 160 mm Hg and those with MAP greater than 110 mm Hg had a higher prevalence of POAG (OR 2.0 and 1.6, respectively). In addition, patients with a DBP of less than 60 mm Hg had a higher prevalence of POAG (OR: 1.9) [21]. This bimodal relationship between arterial pressure and glaucoma evidenced in LALES was also seen in our study.

Our study included two important vascular risk factors for glaucoma. The implementation of standardized protocols for conducting the study makes the information collected from the six participating cities comparable, increasing the quality of the information. Furthermore, given that the sociodemographic and risk factors surveys were performed before the ophthalmologic evaluation, this would reduce the presence of a differential information bias between patients diagnosed with suspicious or confirmed POAG in comparison with healthy subjects.

The suspected and confirmed case definition of POAG was based on international criteria used by other population studies [24], which facilitates the com-

parison of results. Also, the diagnosis of glaucoma was based on optic disc and VF criteria, independent of IOP level with a standardized criterion.

On the other hand, a potential weakness of our research is that individuals were directly enrolled at SH and DM programs. This could imply these patients represent a modified cohort, due to changes induced in their habits and lifestyles according to recommendations made at programs designed for them. So asymptomatic and non-diagnosed SH/DM individuals could have an even higher prevalence of glaucoma. Due to the cross-sectional design of our study, it is not possible to conclusively establish causal associations. However, these findings represent a starting point for further studies that attempt to evaluate the temporal association between the factors evaluated and glaucoma in patients with SH and/or DM. Another potential weakness is the fact that it is impossible to know if patients who have already undergone cataract surgery had developed neuropathy before or after surgery, and that there may probably be cases that originally had chronic closed angles or at least narrow or intermittent closures.

5. Conclusions

In summary, the high prevalence of POAG in patients with SH and DM in a latino population and the high unawareness of the disease present public health implications in Colombia and Latin America. Future studies have to be carried out to generalize these findings to the entire population with and without risk factors.

This study should be a basis to create a public health policy where all DM and SH patients have a referral to a complete ophthalmological evaluation at least once a year.

Ethical Statements

The Universidad del Valle Review Board approved this study (Approval Code 030-014), and all participants signed informed consent. This research was conducted according to the Declaration of Helsinki.

Acknowledgements

The authors would like to thank Tecnoquimicas S.A. for their financial support for this study. The funder had no role in the design, data collection, analysis and interpretation of the data, nor on the writing of the study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Quigley, H. and Broman, T. (2006) The Number of People with Glaucoma Worldwide in 2010 and 2020. *British Journal of Ophthalmology*, **90**, 262-267. https://doi.org/10.1136/bjo.2005.081224

[2] Klein, R., Klein, B.E., Linton, K.L. and De Mets, D.L. (1991) The Beaver Dam Eye Study: Visual Acuity. *Ophthalmology*, **98**, 1310-1315. https://doi.org/10.1016/S0161-6420(91)32137-7

[3] Tielsch, J.M., Sommer, A., Witt, K., Katz, J. and Royall, R.M. (1990) Blindness and Visual Impairment in an American Urban Population. The Baltimore Eye Survey. *Archives of Ophthalmology* (*Chicago*, *Ill* 1960), **108**, 286-290. https://doi.org/10.1001/archopht.1990.01070040138048

[4] Hyman, L., Wu, S.Y., Connell, A.M., *et al.* (2001) Prevalence and Causes of Visual Impairment in The Barbados Eye Study. *Ophthalmology*, **108**, 1751-1756. https://doi.org/10.1016/S0161-6420(01)00590-5

[5] Klaver, C.C., Wolfs, R.C., Vingerling, J.R., Hofman, A. and de Jong, P.T. (1998) Age-Specific Prevalence and Causes of Blindness and Visual Impairment in an Older Population: The Rotterdam Study. *Archives of Ophthalmology* (*Chicago*, *Ill* 1960), **116**, 653-658. https://doi.org/10.1001/archopht.116.5.653

[6] Mitchell, P., Smith, W., Chey, T. and Healey, P.R. (1997) Open-Angle Glaucoma and Diabetes. The Blue Mountains Eye Study, Australia. *Ophthalmology*, **104**, 712-718. https://doi.org/10.1016/S0161-6420(97)30247-4

[7] Wensor, M.D., McCarty, C.A., Stanislavsky, Y.L., Livingston, P.M. and Taylor, H.R. (1998) The Prevalence of Glaucoma in the Melbourne Visual Impairment Project. *Ophthalmology*, **105**, 733-739. https://doi.org/10.1016/S0161-6420(98)94031-3

[8] Munoz, B., West, S.K., Rubin, G.S., *et al.* (2000) Causes of Blindness and Visual Impairment in a Population of Older Americans: The Salisbury Eye Evaluation Study. *Archives of Ophthalmology* (*Chicago*, *Ill* 1960), **118**, 819-825. https://doi.org/10.1001/archopht.118.6.819

[9] Kreft, D., Doblhammer, G., Guthoff, R.F. and Frech, S. (2019) Prevalence, Incidence, and Risk Factors of Primary Open-Angle Glaucoma: A Cohort Study Based on Longitudinal Data from a German Public Health Insurance. *BMC Public Health*, **19**, 851. https://doi.org/10.1186/s12889-019-6935-6

[10] Varma, R., Francis, B.A., *et al.* (2004) Prevalence of Open-Angle Glaucoma and Ocular Hypertension in Latinos: The Los Angeles Latino Eye Study. *Ophthalmology*, **111**, 1439-1448. https://doi.org/10.1016/j.ophtha.2004.01.025

[11] Kim, K.E., Kim, M.J., Park, K.H., *et al.* (2016) Prevalence, Awareness, and Risk Factors of Primary Open-Angle Glaucoma: Korea National Health and Nutrition Examination Survey 2008-2011. *Ophthalmology*, **123**, 532-541. https://doi.org/10.1016/j.ophtha.2015.11.004

[12] Chopra, V., Varma, R., Francis, B.A., Wu, J., Torres, M. and Azen, S.P. (2008) Type 2 Diabetes Mellitus and the Risk of Open-Angle Glaucoma. The Los Angeles Latino Eye Study. *Ophthalmology*, **115**, 227-233. https://doi.org/10.1016/j.ophtha.2007.04.049

[13] Klein, B.E., Klein, R. and Jensen, S.C. (1994) Open-Angle Glaucoma and Older-Onset Diabetes. The Beaver Dam Eye Study. *Ophthalmology*, **101**, 1173-1177. https://doi.org/10.1016/S0161-6420(94)31191-2

[14] Dielemans, I., de Jong, P.T., Stolk, R., Vingerling, J.R., Grobbee, D.E. and Hofman, A. (1996) Primary Open-Angle Glaucoma, Intraocular Pressure, and Diabetes Mellitus in the General Elderly Population. The Rotterdam Study. *Ophthalmology*, **103**, 1271-1275. https://doi.org/10.1016/S0161-6420(96)30511-3

[15] Song, B.J., Aiello, L.P. and Pasquale, L.R. (2016) Presence and Risk Factors for Glaucoma in Patients with Diabetes. *Current Diabetes Reports*, **16**, 124. https://doi.org/10.1007/s11892-016-0815-6

[16] Zhao, Y.X. and Chen, X.W. (2017) Diabetes and Risk of Glaucoma: Systematic Review and a Meta-Analysis of Prospective Cohort Studies. *International Journal of Ophthalmology*, **10**, 1430-1435.

[17] Kahn, H.A. and Milton, R.C. (1980) Alternative Definitions of Open-Angle Glaucoma. Effect on Prevalence and Associations in the Framingham Eye Study. *Archives of Ophthalmology* (*Chicago*, *Ill* 1960), **98**, 2172-2177. https://doi.org/10.1001/archopht.1980.01020041024003

[18] Bankes, J.L. (1967) Ocular Tension and Diabetes Mellitus. *British Journal of Ophthalmology*, **51**, 557-561. https://www.ncbi.nlm.nih.gov/pubmed/6035958 https://doi.org/10.1136/bjo.51.8.557

[19] Tielsch, J.M., Katz, J., Quigley, H.A., Javitt, J.C. and Sommer, A. (1995) Diabetes, Intraocular Pressure, and Primary Open-Angle Glaucoma in the Baltimore Eye Survey. *Ophthalmology*, **102**, 48-53. https://doi.org/10.1016/S0161-6420(95)31055-X

[20] Bonomi, L., Marchini, G., Marraffa, M., Bernardi, P., Morbio, R. and Varotto, A. (2000) Vascular Risk Factors for Primary Open Angle Glaucoma: The Egna-Neumarkt Study. *Ophthalmology*, **107**, 1287-1293. https://doi.org/10.1016/S0161-6420(00)00138-X

[21] Memarzadeh, F., Chung, J., Azen, S.P., Varma, R., *et al.* (2010) Blood Pressure, Perfusion Pressure, and Open-Angle Glaucoma: The Los Angeles Latino Eye Study. *Investigative Ophthalmology & Visual Science*, **51**, 2872-2877. https://doi.org/10.1167/iovs.08-2956

[22] American Diabetes Association (2010) Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, **33**, S62-S69. https://doi.org/10.2337/dc10-S062

[23] Mancia, G., Fagard, R., Narkiewicz, K., *et al.* (2013) ESH/ESC Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal*, **34**, 2159-2219. https://doi.org/10.1093/eurheartj/eht151

[24] Foster, P.J., Buhrmann, R., Quigley, H. and Johnson, G.J. (2002) The Definition and Classification of Glaucoma in Prevalence Surveys. *British Journal of Ophthalmology*, **86**, 238-243. https://doi.org/10.1136/bjo.86.2.238

[25] Quigley, H., West, S.K., Rodriguez, J., Munoz, B., Klein, R. and Snyder, R. (2001) The Prevalence of Glaucoma in a Population-Based Study of Hispanic Subjects: Proyecto VER. *Archives of Ophthalmology*, **119**, 1819-1826. https://doi.org/10.1001/archopht.119.12.1819

[26] Bautista, L.E., Vera-Cala, L.M., Villamil, L., Silva, S.M., Peña, I.M. and Luna, L.V. (2002) Factores de riesgo asociados con la prevalencia de hipertensión arterial en adultos de Bucaramanga, Colombia. *Salud Pública de México*, **44**, 399-405. https://doi.org/10.1590/S0036-36342002000500003

[27] Vargas-Uricoechea, H. and Casas-Figueroa, L.A. (2015) An Epidemiologic Analysis of Diabetes in Colombia. *Annals of Global Health*, **81**, 742-753. https://doi.org/10.1016/j.aogh.2015.11.001

[28] Costa, V.P., Spaeth, G.L., Smith, M., Uddoh, C., Cabral Vasconcellos, J.P. and Kara-José, N. (2006) Patient Education in Glaucoma: What Do Patients Know about Glaucoma? *Arquivos Brasileiros de Oftalmologia*, **69**, 923-927. https://doi.org/10.1590/S0004-27492006000600024

[29] Zhou, M., Wang, W., Huang, W. and Zhang, X. (2014) Diabetes Mellitus as a Risk Factor for Open-Angle Glaucoma: A Systematic Review and Meta-Analysis. *PLoS ONE*, **9**, e102972. https://doi.org/10.1371/journal.pone.0102972

[30] Yanagi, M., Kawasaki, R., Wang, J.J., Wong, T.Y., Crowston, J. and Kiuchi, Y. (2011) Vascular Risk Factors in Glaucoma: A Review. *Clinical and Experimental Ophthalmology*, **39**, 252-258. https://doi.org/10.1111/j.1442-9071.2010.02455.x

[31] Gerber, A.L., Harris, A., Siesky, B., *et al.* (2015) Vascular Dysfunction in Diabetes and Glaucoma. *Journal of Glaucoma*, **24**, 474-479. https://doi.org/10.1097/IJG.0000000000000137

[32] Sayin, N., Kara, N. and Pekel, G. (2015) Ocular Complications of Diabetes Mellitus. *World Journal of Diabetes*, **15**, 562-566. https://doi.org/10.4239/wjd.v6.i1.92

[33] Kanamori, A., Nakamura, M., Mukuno, H., Maeda, H. and Negi, A. (2004) Diabetes Has an Additive Effect on Neural Apoptosis in Rat Retina with Chronically Elevated Intraocular Pressure. *Current Eye Research*, **28**, 47-54. https://doi.org/10.1076/ceyr.28.1.47.23487

[34] Anderson, D.R. (1999) Introductory Comments on Blood Flow Autoregulation in the Optic Nerve Head and Vascular Risk Factors in Glaucoma. *Survey of Ophthalmology*, **43**, S5-S9. https://doi.org/10.1016/S0039-6257(99)00046-6

International Journal of Science and Technology Research Archive

ISSN: 0799-6632 (Online)

Journal homepage: https://sciresjournals.com/ijstra/

(RESEARCH ARTICLE)

Check for updates

Central corneal thickness associations with systemic factors: The Colombian glaucoma study

Carlos Eduardo Rivera [1, 2, *], Sebastian Canal [2] and Ankur Seth [2]

[1] *Ophthalmology Department, Javeriana University, Cali, Colombia.*
[2] *Ophthalmology Department, Collective Innovations Colombia, Cali; Colombia.*

International Journal of Science and Technology Research Archive, 2023, 04(01), 026–031

Publication history: Received on 21 November 2022; revised on 28 December 2022; accepted on 31 December 2022

Article DOI: https://doi.org/10.53771/ijstra.2023.4.1.0180

Abstract

Abstract Objective: To establish Central Corneal Thickness associations with systemic factors in six cities of Colombia.

Methods: A cross-sectional study was conducted in Colombia among hypertensive and diabetic patients. Two thousand sixty-seven subjects older than 50 diagnosed with SH and DM were included. Participants underwent a complete ophthalmic examination, including intraocular pressure (IOP) measurement by Goldmann tonometry, Central Corneal Thickness (CCT), and Blood pressure. The glaucoma diagnosis was confirmed by structural and functional evidence.

Results: In multiple regression analysis, a trend of thinner corneal thicknesses was observed, with increasing decades of life, 60 - 69 years (-7.14 microns (µm) p: 0.58), 70- 79 years (-2.05 µm p: 0.38), > 80 years (-7.3 p <0.056) being almost statistically significant only in patients older than 80 years. Female patients had thinner CCT (- 5.04 µm) than male patients. African- Colombian patients had thinner corneas (-9.6 µm) than mestizo patients (P= 0.002). Patients with migraine had thicker CCT (6.83 µm p <0.024) compared with no- migraine patients. Diabetic patients had thicker CCT (3.91 µm) than non-diabetic patients (P= 0.039). Finally, a 0.66 µm increase per mm hg of the systolic pressure (P=0.024) and a 0.99 µm decrease per mm hg of Systolic Perfusion Pressure (P=0.038) was observed, but no association was found between CCT and Systemic Hypertension.

Conclusion: Our study highlights the relationship between systemic factors such as age, sex, race, DM, systolic blood pressure, migraine, and systolic perfusion pressure with an ocular biomarker such as CCT.

Keywords: Open angle-glaucoma; Central Corneal Thickness; Systemic Hypertension; Diabetes Mellitus; Intraocular pressure; Migraine; Systolic pressure

1 Introduction

Corneal thickness is defined as the distance between the epithelium (anterior surface of the cornea) and the endothelium (posterior surface of the cornea); as the cornea is a prolate surface, the thickness is not the same in its central portion as in the periphery. Pachymetry can measure the thickness in microns of the central part of the cornea. This measurement varies throughout life and, in recent years, has become a critical factor in the study and diagnosis of glaucoma, taking into account that the measurement of intraocular pressure (IOP) can vary according to the central corneal thickness (CCT)[1,2].

The 2002 ocular hypertension treatment study concluded that patients with central corneal thickness measurements of less than 555 µm were three times more at risk of developing primary open-angle glaucoma (POAG) compared to a

* Corresponding author: Carlos Eduardo Rivera Hoyos. carlosriverahoyos@gmail.com

higher CCT (1). Since then, multiple studies have been conducted to investigate the relationship between central corneal thickness (CCT) and the likelihood of glaucoma and to identify whether systemic diseases such as systemic hypertension (SH) or diabetes mellitus (DM) influence corneal thickness.

Among these is a study conducted in Namil Meon, a central region of Korea, where patients over 40 years of age with a diagnosis of glaucoma were studied. A total of 1259 right eyes that met the inclusion criteria were evaluated. This study showed that as people aged, the CCT decreased at a rate of approximately 4 μm per decade of life, and the higher the IOP, the higher the CCT (2.73 μm /1 mmHg) and the longer the axial length, the greater the CCT. Concerning systemic diseases, it was found that patients with SH had thinner corneas (5.5 μm), and no association was found between CCT and diabetes[4].On the other hand, a study was carried out in Singapore that looked for associations between ocular and systemic diseases and central corneal thickness, in which it was found, as in the previous study, that CCT is thicker in young people and subjects with higher IOP; also patients with thicker corneas were found in patients with a history of diabetes. In conclusion, it was established that people with some metabolic component have a higher CCT, possibly secondary to alterations in the physiology of the corneal endothelium[5].

In Amsterdam, the Netherlands, the influence of chronic diabetes on the shape and thickness of the cornea was investigated in a study of both types I and II diabetes patients and healthy patients, in which the average CCT for each group was 578 μm for the control group, 586 μm for patients with DM I and 578 μm for patients with DM II. No statistical association was found between the two types of diabetes and central corneal thickness (P = 0.19)[6].

Ultimately of the relevant studies that have been conducted, a study in Nepal aimed to compare the CCT and IOP in patients with primary open-angle glaucoma (POAG) and healthy patients, where no significant difference was found between the CCT of glaucoma patients and those who did not have the diagnosis[7].

The relationship between Central Corneal Thickness and systemic factors in a Colombian population is currently unknown.

The Colombian Glaucoma study is a cross-sectional study among hypertensive and diabetic patients conducted in 6 cities in Colombia. It assessed the prevalence and relationships between these two vascular risk factors. [8]. The study aims to establish the relationship and distribution between central corneal thickness and glaucoma among patients diagnosed with systemic hypertension and diabetes mellitus in six cities in Colombia.

2 Material and methods

2.1 Study Design

A cross-sectional study of diabetic and hypertensive patients in six cities in Colombia was conducted from September 2014 to January 2019. At enrollment, individuals were ≥ 50 years old and treated with antihypertensive and anti-diabetic medications for at least one year. The diagnosis of DM and SH was verified according to the guidelines for each disease. [9], [10]. All participants were selected from SH and DM control programs. The Valle University Review Board approved this study (Approval Code 030-014), and all participants signed an informed consent form. This research was conducted according to the tenants of the Declaration of Helsinki.

2.2 Procedures

Interviews and questionnaires were used to evaluate factors related to participants' lifestyles and other health conditions, including socioeconomic status, associated comorbidities, education, and nutrition. In addition, a physical examination was performed that included measurement of height, weight, abdominal circumference, heart rate , systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.3 Ophthalmic evaluation

Each participant underwent a complete ophthalmologic examination, including visual acuity, refraction, slit-lamp examination, intraocular pressure, and pachymetry measurements. The IOP measurement was obtained from the average of three values by Goldmann tonometry. Gonioscopy was performed in a dark room using a 4-mirror goniolens (Ocular Instruments Inc., Bellevue, WA) in the primary position, with a slit beam less than 2 mm in height, followed by a dilated funduscopic examination with a 78 diopter (D) lens for evaluating the optic disc, (Ocular Instruments Inc., Bellevue, WA). Central corneal thickness (CCT) was calculated based on the average of three consecutive measurements using a PachPen handheld pachymeter (Accutome, iNC., Pennsylvania, USA).

In suspected cases of glaucoma, the diagnosis was confirmed using a visual field (VF) test with the 24-2 Swedish Interactive Threshold Algorithm (Humphrey, Carl Zeiss Meditec, Inc) and optic nerve photos with a DRS camera (digital retinography system, Centervue, Fremont, CA, USA). Trained glaucoma specialists performed the examinations using standardized protocols.

2.4 Diagnosis of Glaucoma

Suspected and confirmed cases of glaucoma were defined according to the criteria specified by Foster et al.[24] confirmed glaucoma was defined as structural and functional evidence of glaucomatous damage in at least one eye.

2.5 Statistical Analysis

Linear regression analysis was performed to assess the effect of predictive variables of systemic factors, using CCT as the dependent variable. Using a backward selection strategy, variables with p values <0.20 in bivariate analysis were included in the model selection process. A level of significance of 0.05 was used. All analyses were carried out using Stata13® (STATA Corp, College Station, TX, USA).

3 Results

Table 1 Multiple Regression Analysis. CCT as the dependent variable.

Central Corneal Thickness	**B - coefic**	**P. value**	**[95% Conf.**	
			inferior	**superior**
Age(years)				
60-69	-1.15	0.58	-5.23	2.93
70 -79	-2.05	0.386	-6.68	2.58
>80	-7.3	0.059	-14.89	0.28
sex				
female	-5.04	0.005	-8.57	-1.5
Ethnicity base: mestizo				
African - Colombian	-9.66	0.002	-15.66	-3.65
White	0.24	0.926	-4.86	5.34
Body Mass Index				
Overweight	-1.65	0.42	-5.66	2.36
Obesity	3.94	0.079	-0.46	8.35
Intraocular Pressure	0.52	0.299	-0.46	1,49
Family History of Glaucoma	-1.22	0.555	-5.26	2.83
Dyslipidemia	1.84	0.276	-1.47	5.15
Migraine	6.33	0.024	0.85	11.81
Ocular Perfusion Pressure	-0.08	0.725	-0.53	0.37
Systolic Perfusion Pressure	-0.99	0.038	-1.93	-0.06
Diastolic Perfusion Pressure	0			
Systemic Hypertension	-5.07	0.094	-10.99	0.86
Diabetes Mellitus	3.91	0.039	0.2	7.61
Systolic Pressure	0.66	0.024	0.09	1.23

A total of 2085 subjects completed the interview and ophthalmologic examination, of which 18 were excluded because they met one or more exclusion criteria. One thousand nine hundred seventy-four patients had Central Corneal

Thickness measurement. The average age of the 2067 participants was 65.6±8.8 years; 65.93% (1324) were female, 11.0% (227) had only DM, 59.6% (1231) had only SH, and 29.4% (608) had both diseases. Of 2067 SH and DM patients, 142 were identified with confirmed glaucoma and 226 subjects with suspected glaucoma. [8].

In multiple regression analysis, CCT as a dependent variable, a trend of thinner corneal thicknesses was observed, with increasing decades of life, 60 - 69 years (-7.14 µm p:0.58), 70- 79 years (-2.05 µm p: 0.38), > 80 years (-7.3 p <0.056) being almost statistically significant only in patients older than 80 years. Female patients had thinner CCT (- 5.04 µm p= 0.005)) than male patients. African- Colombian patients had thinner corneas (-9.6 µm) than mestizo patients (P= 0.002). Patients with migraine had thicker CCT (6.83 µm p <0.024) compared with no- migraine patients. Diabetic patients had thicker CCT (3.91 µm) than non-diabetic patients (P= 0.039). Finally, a 0.66 µm increase per mm hg of the systolic pressure (P=0.024) and a 0.99 µm decrease per mm hg of Systolic Perfusion Pressure (P=0.038) were observed. However, no association was found between CCT and Systemic Hypertension. (Table 1)

4 Discussion

It is increasingly important to know the associations between central corneal thickness (CCT) with systemic and ocular factors, allowing more accurate and timely diagnoses.

4.1 Age and CCT

In our study, a trend of thinner corneal thicknesses was observed with increasing decades of life, being almost statistically significant only in patients older than 80. (p <0.056)

Contrary to our results, in a population-based glaucoma prevalence study of residents aged > 40 years in Korea, In univariate analysis, a thicker CCT was correlated significantly with younger age (P < 0.001), CCT decreased by 4.0 µm for every decade of life (95% confidence intervals [CI] 2.4-5.5 m) [4]. These findings also correlate with the Singapore study, which also found an association of decreased CCT with older age (P < 0.001) with an average of 5.1 microns/decade [5].

4.2 Gender and CCT

Our study evidenced female patients with thinner CCT (- 5.04 microns) than male patients.

In this study item, we found multiple discrepancies between various studies because there is no agreement on whether there is an association between any specific sex. The Singapore study, a population-based cross-sectional study of 3,280 Malay subjects, found no statistical difference in CCT between the sexes (P = .16) [5].

On the other hand, the Nepalese study carried out with patients diagnosed with glaucoma and healthy patients found that in the group of patients with glaucoma, women had significantly thicker corneas than men with a difference of 10.9 µm (P = 0.003), while in the group of healthy patients there was no statistical difference [7].

Finally, concerning the results of the Korean study, it was found that males had higher average CCT (5.8 µm more, (P = 0.001)) than females [4].

4.3 Ethnicity and CCT

In our study, African- Colombian patients had thinner corneas (-9.6 µm) than mestizo patients (P= 0.002). Similar results were found in a South African Eye Study. The mean CCT readings in the African, mixed ethnicity and Caucasian participants were 514.77±31.86, 531.77±35.17, and 549.97±30.51 µm (P<0.001) [11].). Similar to what was reported, Wang et al. in a multiethnic population study where blacks had thinner CCT (537.3 µm, SD 39.9), and the thickest corneas were reported in Whites (558.5 µm, SD 40.3) [12].

4.4 Migraine and CCT

Our results showed that patients with migraine had thicker CCT (6.83 µm p <0.024) compared with no- migraine patients.

Contrary to our results, Doyle and co-authors, in a retrospective analysis, studied 108 eyes of 54 patients with Normal Tension Glaucoma (NTG) and 54 patients with primary open-angle glaucoma (POAG). Mean CCT was 512 ± 31 µm in the group of patients with NTG with vascular risk factors such as migraine (n = 13) and 533 ± 31 µm in patients with

NTG without vascular risk factors (n = 41) (p = 0.034). Central corneal thickness in NTG was significantly lower than in POAG, and corneas were thinner in NTG patients with vascular risk factors as migraine.

4.5 Diabetes Mellitus and CCT

In our study, diabetic patients, had thicker CCT (3.91 µm) than non-diabetic patients (P= 0.039). Similar results were found in The Singapore Malay Eye Study, a population-based cross-sectional study of three thousand two hundred eighty Malay adults ages 40–80. After controlling for gender and age, central corneas were significantly thicker in persons with diabetes than those without diabetes (547.2 µm vs. 539.3 µm, P<0.001) [13].

Opposed to our results, Wiemer et al.; compared diabetes (type I and II) with healthy patients, where no significant variation was found between the CCT of the three groups [6]. It also coincides with the results obtained by Hwang et al., where no significant association was found between these two variables. (P=0.892) [4].

4.6 Systemic Hypertension, Systolic blood pressure, Systolic Perfusion pressure, and CCT

The associations found are related statistically significantly to Arterial Pressure and Systolic Perfusion Pressure but not directly to Systemic Hypertension.

In multiple regression analysis, we could establish a 0.66 µm increase per mm hg of the systolic pressure (P=0.024) and a 0.99 µm decrease per mm hg of Systolic Perfusion Pressure (P=0.038), but no association was found between CCT and Systemic Hypertension.

Wong and co-authors conducted a Chinese population-based cross-sectional study similar to our results. In multiple regression models, CCT increased with greater Radial Corneal Curvature (P < .001) and Diabetes Mellitus (P <0.03), diminished with age (P < .001), but no relationship was found with Systemic Hypertension. [14] Also, Nishituzs studied a population of Japanese adults. After multivariate adjustment, characteristics associated with increased CCT were HbA1c concentrations, body mass index, impaired glucose tolerance, diabetes, and current smoking, but no association was found with Systemic Hypertension [15]. Contrary to our results, a Korean study concluded that Subjects with Systemic Hypertension had 4.1 µm thinner CCT than those without hypertension (age, sex-adjusted, P < 0.027)(6). We did not find scientific literature regarding the association of systolic pressure and systolic blood pressure with CCT, so we considered these novel findings.

This study, to our knowledge, is the first program-based study to report associations between CCT and systemic factors in a Colombian population.

A strength of our study is the recruitment of patients with two essential vascular risk factors for glaucoma. The implementation of standardized protocols for conducting the study makes the information collected from the six participating cities comparable, increasing the quality of the information. One potential weakness of our research is that people were directly enrolled in the SH and DM programs, which likely represents a modified cohort due to changes in their lifestyles and habits, probably not reflective of a real-world scenario. Due to the study's cross-sectional design, it is impossible to establish causal associations conclusively. However, these findings represent a starting point for further studies that evaluate the biological association between CCT and systemic factors.

5 Conclusion

Our study highlights the relationship between systemic factors such as age, sex, race, DM, systolic blood pressure, migraine, and systolic perfusion pressure with an ocular biomarker such as CCT.

Compliance with ethical standards

Acknowledgments

The authors would like to thank Tecnoquimicas S.A for their financial support for this study. The funder had no role in the design, data collection, analysis, and interpretation of the data or the writing of the study. We also want to thank all the participants of the Colombian Glaucoma Study: Erica Cantor E, Andres Castillo, Alexander Martinez, Lile Newball L., Juan Carlos Rueda, Alejandro Valencia, Sandra Belalcazar, Tulio Cabal, Oscar Albis - Donado, Fabian Mendez.

Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of ethical approval

The Universidad del Valle Review Board approved this study (Approval Code 030-014), and all participants signed informed consent. This research was conducted according to the Declaration of Helsinki.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] C. G. V. De Moraes, «Risk Factors for Visual Field Progression in Treated Glaucoma» Arch. Ophthalmol., vol. 129, n.o 5, p. 562, may 2010, doi: 10.1001/archophthalmol.2011.72.

[2] M. O. Gordon et al., «The Ocular Hypertension Treatment Study», ARCH OPHTHALMOL, vol. 120, p. 7, 2002.

[3] M. O. Gordon et al., «The Ocular Hypertension Treatment Study», ARCH OPHTHALMOL, vol. 120, p. 7, 2002.

[4] Y. H. Hwang, H. K. Kim, y Y. H. Sohn, «Central Corneal Thickness in a Korean Population: The Namil Study», Investig. Opthalmology Vis. Sci., vol. 53, n.o 11, p. 6851, oct. 2012, doi: 10.1167/iovs.12-10173.

[5] D. H. W. Su, T. Y. Wong, P. J. Foster, W.-T. Tay, S.-M. Saw, y T. Aung, «Central Corneal Thickness and its Associations With Ocular and Systemic Factors: The Singapore Malay Eye Study», Am. J. Ophthalmol., vol. 147, n.o 4, pp. 709-716.e1, abr. 2009, doi: 10.1016/j.ajo.2008.10.013.

[6] N. G. M. Wiemer, M. Dubbelman, P. J. Kostense, P. J. Ringens, y B. C. P. Polak, «The Influence of Chronic Diabetes Mellitus on the Thickness and the Shape of the Anterior and Posterior Surface of the Cornea», Cornea, vol. 26, n.o 10, pp. 1165-1170, dic. 2007, doi: 10.1097/ICO.0b013e31814fa82f.

[7] L. Agarwal, N. Agrawal, B. P. Badhu, y P. Lavaju, «Central corneal thickness and intraocular pressure in patients of primary open angle glaucoma and normal population in Nepalese population: A hospital based study», Nepal. J. Ophthalmol., vol. 11, n.o 1, pp. 46-54, sep. 2019, doi: 10.3126/nepjoph.v11i1.25418.

[8] C. E. Rivera et al., «Prevalence of Primary Open Angle Glaucoma among Patients with Diagnosis of Systemic Hypertension and Diabetes Mellitus: The Colombian Glaucoma Study», Open J. Ophthalmol., vol. 10, n.o 02, pp. 99-114, 2020, doi: 10.4236/ojoph.2020.102012.

[9] K. Narkiewicz y J. Redon, «2013 ESH/ESC Guidelines for the management of arterial hypertension», p. 72.

[10] American Diabetes Association, «Diagnosis and Classification of Diabetes Mellitus», Diabetes Care, vol. 33, n.o Supplement_1, pp. S62-S69, ene. 2010, doi: 10.2337/dc10-S062.

[11] S. O. Baboolal y D. P. Smit, «South African Eye Study (SAES): ethnic differences in central corneal thickness and intraocular pressure», Eye, vol. 32, n.o 4, pp. 749-756, abr. 2018, doi: 10.1038/eye.2017.291.

[12] S. Y. Wang, R. Melles, y S. C. Lin, «The Impact of Central Corneal Thickness on the Risk for Glaucoma in a Large Multiethnic Population»:, J. Glaucoma, vol. 23, n.o 9, pp. 606-612, dic. 2014, doi: 10.1097/IJG.0000000000000088.

[13] D. H. W. Su et al., «Diabetes, Hyperglycemia, and Central Corneal Thickness», Ophthalmology, vol. 115, n.o 6, pp. 964-968.e1, jun. 2008, doi: 10.1016/j.ophtha.2007.08.021.

[14] D. Wang et al., «Intraocular Pressure, Central Corneal Thickness, and Glaucoma in Chinese Adults: The Liwan Eye Study», Am. J. Ophthalmol., vol. 152, n.o 3, pp. 454-462.e1, sep. 2011, doi: 10.1016/j.ajo.2011.03.005.

[15] K. Nishitsuka et al., «Determinants and Risk Factors for Central Corneal Thickness in Japanese Persons: The Funagata Study», Ophthalmic Epidemiol., vol. 18, n.o 5, pp. 244-249, oct. 2011, doi: 10.3109/09286586.2011.594206.

International Journal of Science and Technology Research Archive

ISSN: 0799-6632 (Online)

Journal homepage: https://sciresjournals.com/ijstra/

(RESEARCH ARTICLE)

Check for updates

Central corneal thickness distribution among patients diagnosed with systemic hypertension and diabetes mellitus: The Colombian glaucoma study

Carlos Eduardo Rivera [1, 2, *], Valeria Villabona [2] and Ankur Seth [2]

[1] *Opthalmology Department, Javeriana University, Cali, Colombia,*
[2] *Opthalmology Department, Collective Innovations Colombia.*

International Journal of Science and Technology Research Archive, 2023, 04(01), 038–045

Publication history: Received on 22 November 2022; revised on 28 December 2022; accepted on 31 December 2022

Article DOI: https://doi.org/10.53771/ijstra.2023.4.1.0182

Abstract

Objective: To establish the Central Corneal Thickness (CCT) distribution among patients diagnosed with systemic hypertension (SH) and diabetes mellitus (DM) in six cities of Colombia.

Methods: A cross-sectional study was conducted in Colombia among hypertensive and diabetic patients. This study included 2,067 subjects older than 50 diagnosed with SH and DM. Participants underwent a complete ophthalmic examination, including intraocular pressure (IOP) measurement by Goldmann tonometry, Central Corneal Thickness (CCT). The glaucoma diagnosis was confirmed by structural and functional evidence.

Results: The average central corneal thickness was 538.91 microns (µm). The mean CCT of males was significantly thicker (542.43 µm) when compared with females (536.96 um) ($p < 0.001$). Glaucoma patients had thinner corneas (533.15 µm) than glaucoma suspects (535.99 µm) and non-glaucoma patients (539.15 µm) ($p<0.044$). A decrease of approximately 2-3 um was observed for each decade of life, 50 - 60 years (540.50 µm), 60 - 70 years (539.97 µm), 70 - 80 years (537.41 µm), older than 80 years (532.14 µm) almost reaching a statistically significant value($p<0.056$). Mestizo subjects had thicker corneas than white (caucasian) and African - descendants; 538.29 µm, 539.29 um, 531.05 µm, respectively ($p < 0.012$). Patients with Intraocular Pressure (IOP) lower than 15 mmHg had thinner corneas than patients with IOP between 15 - 21 mmHg and higher than 21 mmHg; 536.92 µm, 543.41 µm, 559.50 µm, respectively (p: 0000).

Conclusions: CCT is thicker in males compared to females. Glaucoma patients had thinner corneas than glaucoma suspects and non-glaucoma patients. Older patients (>80 years) had thinner corneas than younger patients. Mestizo subjects had thicker corneas than white (caucasian) and African - descendants. Patients with lower Intraocular Pressure (IOP) had thinner corneas than patients with higher IOP mmHg.

Keywords: Open angle-glaucoma; Central Corneal Thickness; Systemic Hypertension; Diabetes Mellitus; Intraocular Pressure

1 Introduction

When Goldmann and Schmidt first described the Goldman applanation tonometry, they assumed no variations in the central corneal thickness (CCT) (1). With the creation of precise and accurate pachymeters, they realized that variations in CCT are a phenomenon to consider when assessing corneal health status, corneal diseases, intraocular pressure (IOP) values, eligibility for laser refractive surgery, corneal transplants and associated procedural complications, and risk profiling for ocular diseases such as ocular hypertension and glaucoma (2,3).

* Corresponding author: Carlos Eduardo Rivera Hoyos; Email:carlosriverahoyos@gmail.com

CCT is related to demographic factors such as age and ethnicity. Foster et al. (4) and Brand et al. (5) reported a thinning of 10 um per decade and 6.3 um per decade in corneas, respectively. Concerning ethnicity, La Rosa et al. (6) reported that the average CCT in whites (approximately 556 μm) is more than the average CCT in African Americans (approximately 518-534 μm) (7–11,12,13. Foster et al. (4) reported a CCT in Mongolians of 495 and 514 μm in the right and left eye, respectively. Additionally, people from Japan (517-532 μm) (10,14,15) and India (511 μm) (16) have thinner corneas when compared with Caucasians (542-558 μm) (6,11,17), Chinese 542 μm (8), Korean 554 μm (18) and Hispanic 547 μm patients (19).

In 2002, Gordon M et al. published "The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma" (OHTS) (20) where they found increased CCT measurements in ocular hypertensive subjects and described decreased CCT as a significant risk factor for the development of Primary open-angle glaucoma (POAG) in patients with ocular hypertension (OH). Since that moment, other studies like the European Glaucoma Prevention Study (EGPS) (21, 22), Early Manifest Glaucoma Trial (23), the Barbados Eye Study (24), and the Los Angeles Latino Eye Study (LALES) (25) were conducted and found similar results.

Regarding systemic diseases, the OHTS (5) described a higher CCT in patients with diabetes mellitus type 2 (DM) when compared with patients without diabetes, similar to the Barbados study results (11), the Singapore Malay Eye Study (26), The Liwan Eye study (27) and the Funagata study (28). Conversely, the OHTS (5) did not find a difference in patients reporting systemic hypertension.

To our knowledge, there are no population-based data on CCT measurements in the population of Colombia itself. The Colombian Glaucoma Study is a population-based eye survey of six cities in Colombia (31). This survey offers the opportunity to describe the distribution of CCT in a large Colombian population-based cohort of Hypertensive and Diabetic Patients.

2 Material and methods

2.1 Study Design

A cross-sectional study of diabetic and hypertensive patients in Colombia was conducted from September 2014 to January 2019. At enrollment, individuals were ≥ 50 and treated with antihypertensive and anti-diabetic medications for at least one year. The diagnosis of DM and SH was verified according to the guidelines for each disease (32,33). All participants were selected from SH and DM control programs. The Valle University Review Board approved this study (Approval Code 030-014), and all participants signed an informed consent form. This research was conducted according to the tenants of the Declaration of Helsinki.

2.2 Procedures

Interviews and questionnaires were used to evaluate factors related to participants' lifestyles and other health conditions, including socioeconomic status, associated comorbidities, education, and nutrition. In addition, a physical examination was performed that included measurement of height, weight, abdominal circumference, heart rate and systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.3 Ophthalmic evaluation

Each participant underwent a complete ophthalmologic examination, including visual acuity, refraction, slit-lamp examination, intraocular pressure, and pachymetry measurements. The IOP measurement was obtained from the average of three values by Goldmann tonometry. Central corneal thickness (CCT) was calculated based on the average of three consecutive measurements using a PachPen handheld pachymeter (Accutome, iNC., Pennsylvania, USA).

In suspected cases of glaucoma, the diagnosis was confirmed using a visual field (VF) test with the 24-2 Swedish Interactive Threshold Algorithm (Humphrey, Carl Zeiss Meditec, Inc) and optic nerve photos with a DRS camera (digital retinography system, Centervue, Fremont, CA, USA). Reliable visual fields had rates of false-positive, fixation losses, and false-negative errors of 20% or less. Trained glaucoma specialists performed the examinations using standardized protocols.

2.4 Diagnosis of Glaucoma

Suspected and confirmed cases of glaucoma were defined according to the criteria specified by Foster et al. (34) confirmed glaucoma was defined as structural and functional evidence of glaucomatous damage in at least one eye.

2.5 Statistical Analysis

Continuous variables were summarized with mean± standard deviation (SD) or median and Interquartile range (IQR), while categorical variables were described with proportions.

The patients were divided into three groups according to the status of diagnosis of Glaucoma: confirmed cases, suspected cases, and those without glaucoma. Binary and categorical characteristics were compared using chi-square or Fisher's exact tests. Odds Ratios (OR) Were estimated with a 95% confidence interval, and goodness-of-fit was evaluated using a likelihood ratio test and the minor model deviance. A level of significance of 0.05 was used. All analyses were carried out using Stata13® (STATA Corp, College Station, TX, USA).

3 Results

A total of 2085 subjects completed the interview and ophthalmologic examination, of which 18 were excluded because they met one or more exclusion criteria. The average age of the 2067 participants was 65.6±8.8 years; 65.93% (1324) were female, 11.0% (227) had only DM, 59.6% (1231) had only SH, and 29.4% (608) had both diseases. Of 2067 patients, 142 were identified with confirmed glaucoma and 226 subjects with suspected glaucoma. (31)

Of 2067 SH and DM patients, 1974 had CCT measurements. The average central corneal thickness was 538.91 um (figure 1). 702 male and 1272 female subjects had CCT measurements. The mean CCT of males was significantly thicker (542.43 µm) when compared with females (536.96 µm) (p <0.001). Glaucoma patients had thinner corneas (533.15 µm) when compared with glaucoma suspects (535.99 µm) and non-glaucoma patients (539.15 µm) (p<0.044). (Table 1)

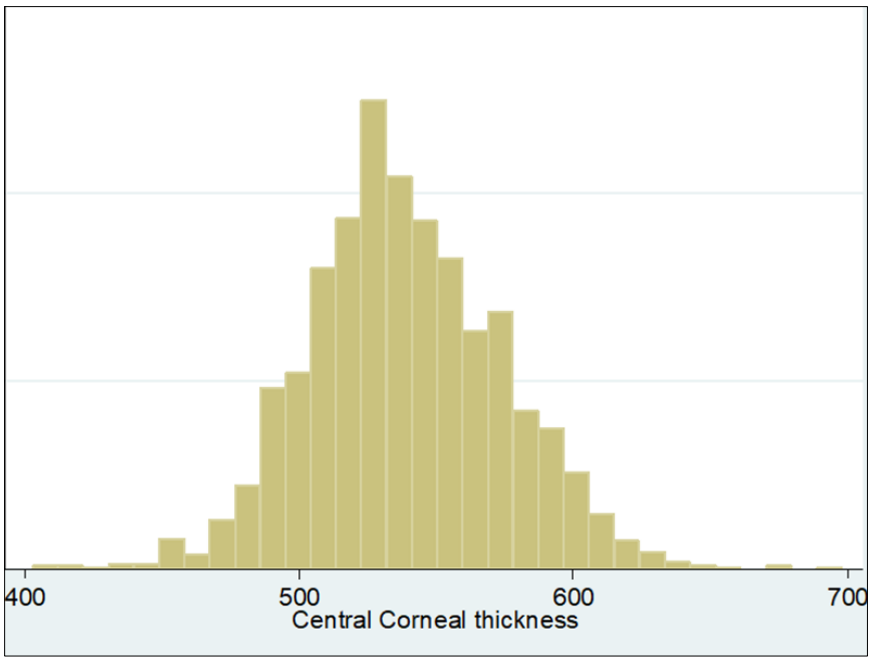


Figure 1 Distribution of Central Corneal Thickness (microns)

Concerning age, a decrease of approximately 2-3 um was observed for each decade of life, 50 - 60 years (540.50 µm), 60 - 70 years (539.97 um), 70 - 80 years (537.41 µm), older than 80 years (532.14 µm) almost reaching a statistically significant value(p<0.056). Regarding ethnicity, Mestizo subjects had thicker corneas than white (caucasian) and African - descendants; 538.29 µm, 539.29 µm, 531.05 µm, respectively, with a level of significance (p <0.012). (Table 1) Concerning IOP, patients with IOP lower than 15 mmHg had thinner corneas than patients with IOP between 15 - 21 mmHg and higher than 21 mmHg; 536.92 µm, 543.41 µm, 559.50 µm, respectively (p: 0000). Table 1 and Figure 2

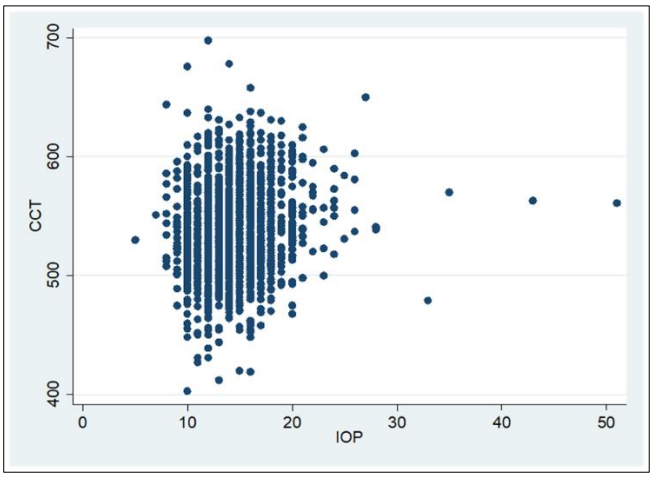


Figure 2 Relation of IOP (mmHg) and CCT (µm)

Table 1 Central Corneal Thickness distribution

	Central corneal thickness (microns)			
	n	**Mean**	**Std.Devi.**	**P. value**
Sex				
Male	702	542.4387	35.08609	
Female	1,272	536.9615	35.6054	<0.001
Primary open Angle Glaucoma				
Positive	140	533.12	36.396878	
Negative	1,612	539.812	35.488836	
Suspect	222	535,9865	34.748675	0.83
Age (years)				
50-59	543	540.5009	34.090333	
60-69	773	539.9703	36.867188	
70-79	526	537.4068	35.101782	
>80	132	532.1364	34.095683	0.056
Ethnicity				
Mestizo	1575	539.79	34.82	
African descendent	157	531.05	34.18	
White	242	538.29	40.03	0.012
Intraocular pressure				
<15 mmHg	1440	536.92	34.85	
15-21 mmHg	496	543.42	36.85	
>21 mmHg	32	559.5	33.23	0.000
Total	1,974	538.9093	35.509675	

4 Discussion

4.1 CCT and sex

Our results concluded that the mean CCT of males was thicker (542.43 μm) when compared with females (536.96 μm) (p <0.001), similar to what was found in a study with Taiwanese adults (29), the European glaucoma prevention study (2) and a multiethnic population (30), in contrast with findings in the OHTS study (5) where females had slightly thicker corneas (5 μm) than their male counterparts.

4.2 CCT and Glaucoma

In our study, Glaucoma patients had thinner corneas (533.15 μm) in comparison with glaucoma suspects (535.99 μm) and regular patients (539.15 μm) (p<0.044), similar to what was described in the Barbados study (11)) whereas CCT decreases, POAG risk increase with 40% higher likelihood of POAG per 40 μm thinner CCT (OR, 1.41). Likewise, the Los Angeles Latino Eye Study (LALES) (25) found thinner corneas in glaucomatous patients (544.6 um) in comparison with ocular hypertensive patients (561 uμm) and normal patients (546.5 μm), they conclude that low CCT < 504 μm is a significant risk factor for glaucoma. In comparison to the Tema Eye Survey in Africa (3) that described a CCT in the population of 533.9 ± 34.0 μm but in the multivariable linear regression analysis, there was a significant association with higher IOP (P < .001) but not with glaucoma.

4.3 CCT and Age

We observed a decrease of approximately 2 -3 um for each decade of life, 50 - 60 years (540.50 um), 60 - 70 years (539.97 um), 70 - 80 years (537.41 um), older than 80 years (532.14 um) almost reaching a statistically significant value. (p<0.056). Similar to what was described by Foster et al. (4) and by Brand et al. (5). Gordon et al. (20) reported a thinning of 10 um per decade and 6.3 um per decade in corneas, respectively.

4.4 CCT and ethnicity

The average central corneal thickness of our study was 538.91 μm. Concerning ethnicity, La Rosa et al. (6) reported that the average CCT in whites (approximately 556 um) is more than the average CCT in African Americans (approximately 518-534 μm), similar to what was reported by Wang et al. in a multiethnic population study (30) where Blacks had 537.3 μm, SD 39.9 and the thickest corneas were reported in Whites 558.5 μm, SD 40.3, and corneas of intermediate thickness among Asians and Hispanic. Foster et al. (4) reported a CCT in Mongolians of 495 and 514 uμm in the right and left eye, respectively. Additionally, people from Japan (517-532 μm) (10) (14)(15) and India (511 μm) (16) have thinner corneas when compared with Caucasians (542-558μm) (6)(11)(17), Chinese 542 μm (8), Korean 554 μm (18) and Hispanic 547 μm patients (19).

4.5 CCT and IOP

Patients with IOP lower than 15 mmHg had thinner corneas than patients with IOP between 15 - 21 mmHg and higher than 21 mmHg; 536.92 μm, 543.41 μm, 559.50 μm, respectively (p: 0000). The Chenai Glaucoma Study, an Indian study based population (16), a Japanese based population study (14) and the Angeles Eye Latino Study Group (25) also described a higher IOP range associated with a significantly greater CCT.

This study, to our knowledge, is the first population-based study to describe the Central Corneal Thickness distribution among patients diagnosed with Systemic Hypertension and Diabetes Mellitus in patients over 50 years of age in Colombia.

Our study included two essential vascular risk factors for glaucoma. The implementation of standardized protocols for conducting the study makes the information collected from the six participating cities comparable, increasing the quality of the information. Furthermore, the sociodemographic and risk factors surveys were performed before the ophthalmologic evaluation, which would reduce a differential information bias between patients diagnosed with suspicious or confirmed POAG compared with healthy subjects.

Due to our study's cross-sectional design, it is impossible to establish causal associations conclusively. However, these findings represent a starting point for further studies that evaluate the biological association between Central Corneal thickness in patients with SH and DM.

5 Conclusion

In summary, CCT is thicker in males compared to females. Glaucoma patients had thinner corneas than glaucoma suspects and non-glaucoma patients. Older patients (>80 years) had thinner corneas than younger patients. Mestizo subjects had thicker corneas than white (caucasian) and African - descendants. Patients with lower Intraocular Pressure (IOP) had thinner corneas than patients with higher IOP mmHg.

Compliance with ethical standards

Acknowledgments

We also want to thank all the participants of the Colombian Glaucoma Study: Erica Cantor E, Andres Castillo, Alexander Martinez, Lile Newball L., Juan Carlos Rueda, Alejandro Valencia, Sandra Belalcazar, Tulio Cabal, Oscar Albis - Donado, Fabian Mendez.

Disclosure of conflict of interest

The authors declared no conflict of interest.

Statement of ethical approval

The Universidad del Valle Review Board approved this study (Approval Code 030-014), and all participants signed informed consent. This research was conducted according to the Declaration of Helsinki.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Funding

The authors would like to thank Tecnoquimicas S.A. for supporting this study financially. The funder had no role in the design, data collection, analysis, and interpretation of the data or the writing of the study

References

[1] Goldmann H, Schmidt Th. Über Applanationstonometrie. Ophthalmologica [Internet]. 1957 [cited 2022 Oct 9], 134(4):221–42. Available from: https://www.karger.com/Article/FullText/303213

[2] Central Corneal Thickness in the European Glaucoma Prevention Study. Ophthalmology [Internet]. 2007 Mar [cited 2022 Oct 4], 114(3):454–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642006011225

[3] Sng C, Barton K, Kim H, Yuan S, Budenz DL. Central Corneal Thickness and its Associations With Ocular and Systemic Factors in an Urban West African Population. Am J Ophthalmol [Internet]. 2016 Sep [cited 2022 Oct 7], 169:268–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939416303336

[4] Foster P. Central corneal thickness and intraocular pressure in a Mongolian population. Ophthalmology [Internet]. 1998 Jun 1 [cited 2022 Oct 7], 105(6):969–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642098960213

[5] Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the ocular hypertension treatment study (OHTS). Ophthalmology [Internet]. 2001 Oct [cited 2022 Oct 7], 108(10):1779–88. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642001007606

[6] La Rosa FA, Gross RL, Orengo-Nania S. Central corneal thickness of Caucasians and African Americans in glaucomatous and nonglaucomatous populations. Arch Ophthalmol Chic Ill 1960. 2001 Jan, 119(1):23–7.

[7] Budenz DL, Barton K, Whiteside-de Vos J, Schiffman J, Bandi J, Nolan W, et al. Prevalence of Glaucoma in an Urban West African Population: The Tema Eye Survey. JAMA Ophthalmol [Internet]. 2013 May 1 [cited 2022 Oct 7], 131(5):651. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/jamaophthalmol.2013.1686

[8] Shimmyo M, Ross AJ, Moy A, Mostafavi R. Intraocular pressure, Goldmann applanation tension, corneal thickness, and corneal curvature in Caucasians, Asians, Hispanics, and African Americans. Am J Ophthalmol [Internet]. 2003 Oct [cited 2022 Oct 7], 136(4):603–13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939403004240

[9] Mercieca K, Odogu V, Fiebai B, Arowolo O, Chukwuka F. Comparing Central Corneal Thickness in a Sub-Saharan Cohort to African Americans and Afro-Caribbeans. Cornea [Internet]. 2007 Jun [cited 2022 Oct 7], 26(5):557–60. Available from: https://journals.lww.com/00003226-200706000-00010

[10] Aghaian E, Choe JE, Lin S, Stamper RL. Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology [Internet]. 2004 Dec [cited 2022 Oct 7], 111(12):2211–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642004009583

[11] Nemesure B. Corneal Thickness and Intraocular Pressure in the Barbados Eye Studies. Arch Ophthalmol [Internet]. 2003 Feb 1 [cited 2022 Oct 7], 121(2):240. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/archopht.121.2.240

[12] Kniestedt C, Lin S, Choe J, Nee M, Bostrom A, St??rmer J, et al. Correlation Between Intraocular Pressure, Central Corneal Thickness, Stage of Glaucoma, and Demographic Patient Data: Prospective Analysis of Biophysical Parameters in Tertiary Glaucoma Practice Populations. J Glaucoma [Internet]. 2006 Apr [cited 2022 Oct 7], 15(2):91–7. Available from: http://journals.lww.com/00061198-200604000-00003

[13] Dohadwala AA, Munger R, Damji KF. Positive correlation between Tono-pen intraocular pressure and central corneal thickness. Ophthalmology [Internet]. 1998 Oct [cited 2022 Oct 7], 105(10):1849–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642098910296

[14] Suzuki S, Suzuki Y, Iwase A, Araie M. Corneal Thickness in an Ophthalmologically Normal Japanese Population. Ophthalmology [Internet]. 2005 Aug [cited 2022 Oct 7], 112(8):1327–36. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642005004835

[15] Tomidokoro A, Araie M, Iwase A. Corneal Thickness and Relating Factors in a Population-Based Study in Japan: The Tajimi Study. Am J Ophthalmol [Internet]. 2007 Jul [cited 2022 Oct 7], 144(1):152–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939407001973

[16] Vijaya L, George R, Arvind H, Ve Ramesh S, Baskaran M, Raju P, et al. Central Corneal Thickness in Adult South Indians. Ophthalmology [Internet]. 2010 Apr [cited 2022 Oct 7], 117(4):700–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642009010902

[17] Eysteinsson T, Jonasson F, Sasaki H, Arnarsson A, Sverrisson T, Sasaki K, et al. Central corneal thickness, radius of the corneal curvature and intraocular pressure in normal subjects using non-contact techniques: Reykjavik Eye Study. Acta Ophthalmol Scand [Internet]. 2002, 80(1):11–5. Available from: https://dx.doi.org/10.1034/j.1600-0420.2002.800103.x

[18] Lee ES, Kim CY, Ha SJ, Seong GJ, Hong YJ. Central Corneal Thickness of Korean Patients with Glaucoma. Ophthalmology [Internet]. 2007 May [cited 2022 Oct 7], 114(5):927–30. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642006014837

[19] Hahn S, Azen S, Ying-Lai M, Varma R. Central Corneal Thickness in Latinos. Investig Opthalmology Vis Sci [Internet]. 2003 Apr 1 [cited 2022 Oct 7], 44(4):1508. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.02-0641

[20] Gordon MO. The Ocular Hypertension Treatment Study. Arch Ophthalmol [Internet]. 2002, 120(6):714. Available from: https://dx.doi.org/10.1001/archopht.120.6.714

[21] Results of the European Glaucoma Prevention Study. Ophthalmology [Internet]. 2005 Mar [cited 2022 Oct 7], 112(3):366–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642004017865

[22] Miglior S, Torri V, Zeyen T, Pfeiffer N, Vaz JC, Adamsons I. Intercurrent Factors Associated with the Development of Open-Angle Glaucoma in the European Glaucoma Prevention Study. Am J Ophthalmol [Internet]. 2007 Aug [cited 2022 Oct 7], 144(2):266-275.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939407004102

[23] Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of Long-term Progression in the Early Manifest Glaucoma Trial. Ophthalmology [Internet]. 2007 Nov [cited 2022 Oct 7], 114(11):1965–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642007002412

[24] Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B. Risk Factors for Incident Open-angle Glaucoma. Ophthalmology [Internet]. 2008 Jan [cited 2022 Oct 7], 115(1):85–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642007002424

[25] Francis BA, Varma R, Chopra V, Lai MY, Shtir C, Azen SP. Intraocular Pressure, Central Corneal Thickness, and Prevalence of Open-Angle Glaucoma: The Los Angeles Latino Eye Study. Am J Ophthalmol [Internet]. 2008, 146(5):741–6. Available from: https://dx.doi.org/10.1016/j.ajo.2008.05.048

[26] Su DHW, Wong TY, Foster PJ, Tay WT, Saw SM, Aung T. Central Corneal Thickness and its Associations With Ocular and Systemic Factors: The Singapore Malay Eye Study. Am J Ophthalmol [Internet]. 2009 Apr [cited 2022 Oct 7], 147(4):709-716.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S000293940800809X

[27] Wang D, Huang W, Li Y, Zheng Y, Foster PJ, Congdon N, et al. Intraocular Pressure, Central Corneal Thickness, and Glaucoma in Chinese Adults: The Liwan Eye Study. Am J Ophthalmol [Internet]. 2011 Sep [cited 2022 Oct 7], 152(3):454-462.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002939411002327

[28] Nishitsuka K, Kawasaki R, Kanno M, Tanabe Y, Saito K, Honma K, et al. Determinants and Risk Factors for Central Corneal Thickness in Japanese Persons: The Funagata Study. Ophthalmic Epidemiol [Internet]. 2011 Oct [cited 2022 Oct 7], 18(5):244–9. Available from: http://www.tandfonline.com/doi/full/10.3109/09286586.2011.594206

[29] Chen YC, Kasuga T, Lee HJ, Lee SH, Lin SY. Correlation between central corneal thickness and myopia in Taiwan. Kaohsiung J Med Sci [Internet]. 2014 Jan [cited 2022 Nov 6], 30(1):20–4. Available from: http://doi.wiley.com/10.1016/j.kjms.2013.08.008

[30] Wang SY, Melles R, Lin SC. The Impact of Central Corneal Thickness on the Risk for Glaucoma in a Large Multiethnic Population. J Glaucoma [Internet]. 2014, 23(9):606–12. Available from: https://dx.doi.org/10.1097/ijg.0000000000000088

[31] Rivera CE, Cantor E, Castillo A, Martinez A, Newball L, Rueda JC, et al. Prevalence of Primary Open Angle Glaucoma among Patients with Diagnosis of Systemic Hypertension and Diabetes Mellitus: The Colombian Glaucoma Study. Open J Ophthalmol. 2020, 10(02):99-114.

[32] American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010, 33(Supplement_1):S62-9.

[33] Narkiewicz K, Redon J. 2013 ESH/ESC Guidelines for the management of arterial hypertension. :72.

[34] Foster PJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. Feb of 2002, 86(2):238-42

(1993) Molecular analysis of Hurler syndrome in Druze and Muslim Arab patients in Israel: multiple allelic mutations of the *IDUA* gene in a small geographic area. Am J Hum Genet 53:330–338

Flint J, Harding RM, Clegg JB, Boyce AJ (1993) Why are some genetic diseases common? distinguishing selection from other processes by molecular analysis of globin gene variants. Hum Genet 91:91–117

Heinisch U, Zlotogora J, Kafert S, Gieselmann V (1995) Multiple mutations are responsible for the high frequency of metachromatic leukodystrophy in a small geographic area. Am J Hum Genet 56:51–57

Jaber L, Bailey-Wilson JE, Haj-Yehia M, Hernandez J, Sohat M (1994) Consanguineous matings in an Israeli-Arab community. Arch Pediatr Adolesc Med 148:412–415

Motulsky AG (1995) Jewish diseases and origins. Nat Genet 9:99–100

Richard I, Broux O, Allamand V, Fougerousse, Chiannikulchai N, Bourg N, Brenguier L, et al (1995) Mutations in the proteolytic enzyme calpain 3 cause limb-girdle muscular dystrophy type 2A. Cell 81:27–40

Rund D, Cohen T, Filon D, Dowling CE, Warren TC, Barak I, Rachmilewitz EA, et al (1991) Evolution of a genetic disease in an ethnic isolate: beta-thalassemia in the Jews of Kurdistan. Proc Natl Acad Sci USA 88:310–314

Address for correspondence and reprints: Dr. Joël Zlotogora, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel.

0002-9297/96/5801-0029$02.00

Am. J. Hum. Genet. 58:243–244, 1996

The Distinction Between Juvenile and Adult-Onset Primary Open-Angle Glaucoma

To the Editor:

Because of the significant differences between the juvenile and adult forms of open-angle glaucoma, especially with regard to inheritance, prevalence, severity, and age of onset, we read with interest the recent publication by Morissette et al. (1995), describing a pedigree with a phenotype that overlaps the distinctive features of juvenile-onset open-angle glaucoma (JOAG) and adult-onset primary open-angle glaucoma (usually abbreviated as POAG or COAG). These authors conclude that a gene mapped to human chromosome 1q21-q31 (GLC1A) can be responsible for both juvenile and adult forms of open-angle glaucoma. The implications of such a result could be extremely important, in light of the high prevalence of the adult form of the disease. However, while the data presented in this report suggest that variable expressivity of the GLC1A gene may lead to a broader range of onset for this form of juvenile glaucoma, these data do not identify the GLC1A gene as an important cause of POAG. To prevent misleading interpretations of this and similar studies, we wish to clarify the distinction between the juvenile and adult forms of open-angle glaucoma.

Glaucoma is a term used to describe a disease process that results in a loss of retinal ganglion cells, causing a characteristic degeneration of the optic nerve. Typically the deterioration of the optic nerve is associated with an elevation of intraocular pressure that is probably related to the pathogenesis of the disorder. The ocular structures comprising the fluid pathways that contribute to the variation in intraocular pressure are located in the "angle" created by the junction of the cornea with the iris. Clinical descriptions of the various types of glaucoma often refer to the appearance of the angle; in particular, glaucoma is frequently divided into the open-angle and closed-angle subtypes. Closed-angle glaucoma is very rare and is usually caused by anatomical abnormalities. Open-angle glaucoma is much more common and is likely to result from a number of different, and as yet undefined, physiological and biochemical abnormalities. Although glaucoma eventually causes a complete loss of sight, the destructive process is usually very slowly progressive, and most patients are unaware of a loss of vision, or any other symptom, until quite late in the course of the disease. Of the many different types of glaucoma, the most common is POAG, which affects individuals in the later decades of life, with an onset usually after the age of 50 years (Armaly 1962, 1969). A rare form of glaucoma that has been recently well studied is the primary open-angle glaucoma of juvenile-onset (JOAG). Unlike the adult-onset disease, the juvenile type almost always develops before the age of 40 years and is an unusually severe form of the disease, frequently causing substantial visual impairment in affected individuals (Wiggs et al. 1995). While the adult form of the disease is likely to be inherited as a complex trait, without an obvious segregation pattern, the juvenile form is inherited as an autosomal dominant Mendelian trait with high penetrance. One locus for JOAG has been mapped to human chromosome 1q21-q31 (Sheffield et al. 1993; Richards et al. 1994; Wiggs et al. 1994). The clinical phenotype of the pedigrees shown to be linked to the 1q21-q31 region is remarkably uniform (Johnson et al. 1994; Wiggs et al. 1995).

In the recent publication by Morissette et al. (1995), a common haplotype derived from microsatellite markers located in the 1q21-q31 region segregates with the disease phenotype in 40 individuals included in this study. Of these 40, 36 were documented to develop the disease before the age of 40 years and consequently were designated as JOAG. The remaining four were first diagnosed at ages 44, 47, 53, and 62 years. Because the disease

was diagnosed after the age of 40 years, these individuals were felt to have clinical features more in line with the adult form of the disease (POAG or COAG). Hence, the authors conclude that the gene located in the 1q21-q31 region can be responsible for both the juvenile and adult forms of the disease. We contend that onset before age 40 years is an arbitrarily defined distinction between the two forms of the disease. The severity of the glaucoma afflicting the majority of the affected members of this pedigree and the demonstration of simple Mendelian inheritance suggest that the phenotype described in this report is an example of variable expression of the JOAG phenotype rather than true POAG. Moreover, because of the insidious character of the glaucoma disease process, clinically pinpointing the actual onset of the disease is quite difficult. The possibility exists that these four individuals had developed the disease prior to age 40 years. The data presented in this report suggest that the age at onset of the form of juvenile glaucoma caused by GLC1A may occasionally extend beyond the age of 40 years. However, one should not conclude from these data that the GLC1A gene is commonly responsible for the very prevalent adult-onset form of the disease.

JANEY L. WIGGS,[1,2] KARIM F. DAMJI,[4] JONATHAN L. HAINES,[3] MARGARET A. PERICAK-VANCE,[5] AND R. RAND ALLINGHAM[4]

[1]*Department of Ophthalmology, Tufts University School of Medicine,* [2]*Genetics Division, Tufts University, Sackler School of Graduate Biomedical Sciences, and* [3]*Molecular Neurogenetics Unit, Massachusetts General Hospital, Boston; and* [4]*Department of Ophthalmology and* [5]*Division of Neurology, Department of Medicine, Duke University Medical Center, Durham*

References

Armaly MF (1962) The Des Moines population study of glaucoma. Invest Ophthalmol Vis Sci 1:618

——— (1969) Ocular pressure and visual fields: a ten-year follow-up study. Arch Ophthalmol 81:25

Johnson AT, Drack AV, Kwite AE, Cannon RL, Stone EM, Alward WLM (1993) Clinical features and linkage analysis of a family with autosomal dominant juvenile glaucoma. Ophthalmology 100:524–529

Morissette J, Côté G, Anctil J-L, Plante M, Amyot M, Héon E, Trope GE, et al (1995) A common gene for juvenile and adult-onset primary open-angle glaucomas confined on chromosome 1q. Am J Hum Genet 56:1431–1442

Richards JE, Lichter PR, Boehnke M, Uro JLA, Torrez D, Wong D, Johnson AT (1994) Mapping of a gene for autosomal dominant juvenile-onset open-angle glaucoma to chromosome 1q. Am J Hum Genet 54:62–70

Sheffield, VC, Stone EM, Alward WLM, Drack AV, Johnson AT, Streb LM, Nichols BE (1993) Genetic linkage of familial open-angle glaucoma to chromosome 1q21-q31. Nat Genet 4:47–50

Wiggs JL, Del Bono EA, Schuman JS, Hutchinson BT, Walton DS (1995) Clinical features of five pedigrees genetically linked to the juvenile glaucoma locus on chromosome 1q21-q31. Ophthalmology 102:1782–1789

Wiggs JL, Haines JL, Paglinauan C, Fine A, Sporn C, Lou D (1994) Genetic linkage of autosomal dominant juvenile glaucoma to 1q21-q31 in three affected pedigrees. Genomics 21:299–303

Address for correspondence and reprints: Dr. Janey L. Wiggs, Molecular Genetics Unit, Department of Ophthalmology, New England Medical Center, 750 Washington Street, Box 450, Boston, MA 02114. E-mail: jwiggs_gla@opal.tufts.edu

0002-9297/96/5801-0030$02.00