Macular Ganglion Cell Complex Measurement Using Spectral Domain Optical Coherence Tomography in Glaucoma

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Abstract

Background: Glaucoma is a progressive optic neuropathy primarily damaging the ganglion cell complex and causing a gradual loss of ganglion cell axons. The FD-OCT offers comprehensive glaucoma evaluation by providing assessment of RNFL thickness, optic disc morphology, and Ganglion Cell Complex (GCC) thickness, which is defined as the combination of nerve fiber, ganglion cell, and inner plexiform layers. In this study, we studied the diagnostic value of macular GCC thickness measurement in glaucoma suspects and in early to moderate glaucoma cases.

Methods: A total of 91 eyes were included in the study. The eyes of participants were classified into 3 groups: The control group (30 eyes), the glaucoma suspects group (31 eyes) and the early to moderate glaucoma group (30 eyes). All subjects underwent complete ophthalmic examination, gonioscopy, Goldmann applanation tonometry, corneal pachymetry, Visual field examination using standard automated perimetry performed with a Humphrey Field Analyzer using the Swedish Interactive Threshold Algorithm (SITA) standard strategy, program central 24-2 and imaging using FD-OCT; the RTVue-100 glaucoma protocol.

Results: GCC parameters significantly differentiated between controls and suspects and between controls and early glaucoma cases.

Conclusions: Macular GCC thickness is promising for detection of early and moderate glaucoma. However, further clinical evidence is needed to assess GCC role in detecting early glaucomatous cases.

Key Words: Glaucoma – Ganglion cell complex – Macula – FD OCT.

Introduction

GLAUCOMA is a progressive optic neuropathy primarily damaging the ganglion cell complex and causing a gradual loss of ganglion cell axons. Structural damage precedes detectable visual field loss measured with the standard automatic perimetry. Early detection is therefore essential to stop or delay progressive loss of visual function. In recent years, new technologies for the early detection of structural damage have been developed [1].

Optical coherence tomography (OCT) provides real-time, objective, and reproducible measurements. The FD-OCT offers comprehensive glaucoma evaluation by providing assessment of RNFL thickness, optic disc morphology, and Ganglion Cell Complex (GCC) thickness, which is defined as the combination of nerve fiber, ganglion cell, and inner plexiform layers [2].

Reduced macular thickness was initially described by Zeimer et al., using the slit-scanning Retinal Thickness Analyzer hypothesizing that macular thickness could be a measure of glaucoma damage [3].

Ishikawa et al., developed a macular segmentation algorithm to measure sublayer thickness for glaucoma diagnosis. They showed that macular inner retinal complex (ganglion cell layer, inner plexiform layer, inner nuclear layer) was thinner in eyes with perimetric glaucoma [4].

The RTVue directly measures the thickness of the inner three retinal layers. By targeting cells directly affected by glaucoma in the area of their highest concentration, it is believed to detect glaucoma earlier [5].

Macular GCC parameters have a theoretical advantage over peripapillary RNFL parameters in diagnosis, because RGC loss occurs early in the pathogenesis of glaucoma. Further, early RGC loss
typically gives rise to isolated damage in the para-
central areas. The macular GCC scan is centered
on the fovea, covers a 7 X 7-mm grid on the central
macula, and readily detects early GCC loss [5].

The aim of this work is to evaluate the capability
of macular GCC thickness measurement of detec-
tion of structural damage in glaucoma suspects
and in patients with mild to moderate glaucoma.

Material and Methods

This study, carried out from March 2012 to June
2013 in Kasr Al-Ainy Hospital, Cairo University to
evaluate the diagnostic value of macular ganglion
cell complex measurement in glaucoma using spectral
domain OCT.

Study design:
Cross sectional case control study.

Population of the study and disease condition:
A total of 91 eyes were included in the study.

The eyes of participants were classified into 3
groups:
- The control group (30 eyes) had: Intraocular
  pressure (IOP) of 21mmHg or less, a normal
  Humphrey SITA 24-2 standard visual field; a
  central corneal thickness >500 µm; Normal ONH,
  defined as intact neuroretinal rim without peri-
papillary hemorrhages, notches, localized pallor,
or RNFL defects; an open anterior chamber angle;
and no history of chronic ocular or systemic
corticosteroid use.
- The glaucoma suspects group (31 eyes) had: IOP
  >21mmHg or ONH changes, such as an optic rim
  notch, vertical cup/disc diameter ratio asymmetry,
  and reliable Humphrey SITA central 24-2 standard
  visual field that is normal or showing changes
  not fulfilling the minimal criteria for glaucoma
diagnosis.
- The glaucoma group (30 eyes) had: Early to
  moderate glaucoma according to Hodapp-Anderson-
Parrish grading scale based on MD of visual
  fields, glaucomatous optic disc with typical loss
  of neural rim and changes as inter eye asymmetry
  more than 0.2, RNFL defects, with or without
  increase in Intraocular Pressure (IOP) to more
  than 21 mmHg.

Background and demographic characteristics:

Patients between 25 and 80 years old with no
sex predilection.

Inclusion criteria:
- Normal open anterior chamber angle.
- No media opacities.
- Refractive errors in the spherical equivalent not
  exceeding –6 or +3 dipters, and cilindrical
  correction within 3.0 dipters.
- In addition, the subjects has to be familiar with
  SAP and have a reliable Humphrey visual field
  with SITA 24-2 standard tests (fixation loss <20%,
  false-positive and false-negative rates <33%).

Exclusion criteria:
- Age <25 or >80 years.
- Spherical equivalent refractive error <–6.00
  dipters to eliminate errors arising from macular
  atrophy in high myopes.
- Diabetic retinopathy or other diseases that could
  cause visual field loss or optic disc abnormalities.
- Previous intraocular surgery.
- Presence of other intraocular eye diseases or
  other diseases affecting the visual fields (e.g.,
  pituitary lesions, diabetic retinopathy).
- Treatment with miotics, known to affect visual
  field sensitivity.
- Unreliable visual field tests.
- Scans with motion artifacts, segmentation errors,
  and images with poor signal strength.

Interventions: All subjects underwent:
- Complete ophthalmic examination.
- Gonioscopy.
- Goldmann applanation tonometry.
- Corneal pachymetry.
- Visual field examination using standard automated
  perimetry performed with a Humphrey Field
  Analyzer using the Swedish interactive threshold
  algorithm (SITA) standard strategy, program
  central 24-2.
- Imaging using FD-OCT; the RTVue-100 glaucoma
  protocol.

Statistics:

Data were statistically described in terms of
mean ± standard deviation (±SD), median and
range, or frequencies (number of cases) and per-
centages when appropriate. Comparison of numer-
cal variables between the study groups was done
using one way analysis of variance (ANOVA) test.
with Benferroni post-hoc multiple 2-group comparisons. For comparing categorical data, Chi square ($\chi^2$) test was performed. Fisher’s exact test was used instead when the expected frequency is less than 5. Binary logistic regression was used to study the relation of different perimetry and OCT parameters to prediction of glaucoma patients and the predictive ability of these parameters was analyzed using Receiver operating Characteristics (ROC) Curve. $p$-values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15. ROC curves were developed using MedCalc biomedical statistics software version 12.2.1 (MedCalc Software bvba, Ostend, Belgium).

**Results**

**Subjects’ characteristics:**

A total of 98 eyes were examined. Four eyes were excluded because of poor OCT images. In addition, three eyes were excluded because of unreliable VFs. Finally, a total of 91 eyes (total participants, $n=91$; normal controls, $n=30$; glaucoma suspects, $n=31$; patients with early to moderate glaucoma, $n=30$) were included.

The mean ages of the controls, glaucoma suspects and cases were $43.93 \pm 8.55$, $46.03 \pm 14.24$, and $45.53 \pm 12.08$ years respectively ($p$-value=0.77) Fig. (1). 60.4% of the participants were females and 39.6% were males. This difference was not found to be statistically significant ($\chi^2=2.159$, $p=0.34$).

Family history of glaucoma was positive in 15% of the eyes.

The mean IOPs were $12.63 \pm 1.30$, $16 \pm 3.37$, $17.03 \pm 4$mmHg for the controls, suspects and cases respectively. The difference between the control group and the two other groups was found to be statistically significant ($p$-value <0.001).

**OCT measurements:**

**Ganglion cell complex measurements:**

The mean average GCC thickness was $103.52 \pm 5.73$, $95.35 \pm 7.29$ and $95.40 \pm 6.9$ micrometres for the controls, suspects and cases respectively. The difference between the control group and the two other groups was found to be statistically significant ($p$-value <0.001). The mean superior GCC thickness was $103.52 \pm 5.7$, $94.76\pm 7.84$ and $95.48 \pm 7.37$ micrometres while the mean inferior GCC thickness was $103.49 \pm 6.17$, $95.96 \pm 7.19$ and $95.29 \pm 6.95$ micrometres for the controls, suspects and cases respectively.

Mean FLV was $0.16 \pm 0.18, 0.97 \pm 1.27$ and $0.93 \pm 1.32\%$ for the controls, suspects and cases respectively and the mean GLV was $0.71 \pm 0.94, 6.04 \pm 4.86$ and $5.75 \pm 4.87$ for the same groups respectively.

ANOVA test showed highly significant difference in the average, superior average and inferior average thickness, FLV and GLV between the 3 groups. Bonferroni post-hoc test showed highly significant difference between controls and suspects and between controls and cases and no difference between suspects and cases for the 3 parameters and GLV. FLV showed significant difference between controls and suspects and between controls and cases and no difference between suspects and cases.

83.9% of the suspects and 73.3% of the cases showed GCC defect. The difference between the groups was highly significant ($\chi^2=50.637$, $p<0.001$) (Table 1).

70% of the suspects and 55% of the cases showed focal GCC affection despite having GCC parameters within normal values Fig. (3).

**ROC curve analysis:**

The diagnostic value of mean GCC thickness was assessed with ROC curve. Sensitivity, specificity, area under the curve (AUC) and cutoff point were determined (Table 2).

**Table (1): GCC defect distribution between the groups of subjects in the study.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls</th>
<th>Suspect</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCC defect:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>16.1%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>83.9%</td>
<td>73.3%</td>
</tr>
</tbody>
</table>

**Table (2): Sensitivity, specificity, area under the curve (AUC) and cutoff point of average GCC.**

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cut-off point</th>
<th>AUC</th>
<th>Confidence interval</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average GCC</td>
<td>66.7</td>
<td>65.6</td>
<td>&lt;=96.72</td>
<td>0.637</td>
<td>0.515-0.760</td>
</tr>
</tbody>
</table>
Discussion

Glaucoma management involves visual field testing and morphologic assessment of ONH and the RNFL [1].

In this regard, it has been proved by Li et al., that RTVue-OCT may provide objective, quantitative, and reproducible images of the ONH and RNFL thickness in glaucoma [6].

The changes in the macular structures in the glaucomatous eyes are not visible during routine clinical examinations. The development of more sensitive measurement technology has increased interest in investigating this area for glaucoma diagnosis [4].

The study was performed on 91 participants, including 30 controls, 31 glaucoma suspects and 30 early to moderate glaucoma cases.

In this study, we found that GCC parameters significantly differentiated between controls and suspects and between controls and glaucoma cases.

83.9% of the suspects had GCC defect despite their normal visual fields.

These results are consistent with the idea that structural changes precede visual function changes, and visual function changes are less apparent in the early stages of structural damage [7].

70% of the suspects and 55% of the cases showed focal GCC affection despite having GCC
parameters within normal values. This highlights the importance of checking for focal affection even with parameters within normal values.

The RTVue directly measures the thickness of the inner three retinal layers. By targeting cells directly affected by glaucoma in the area of their highest concentration, it is believed to detect glaucoma earlier [5].

The result of the present study is consistent with that of many other studies.

A study by Takagi and colleagues showed that GCC analysis significantly detected GCC thinning in eyes with visual field defects in one hemisphere and significantly correlated with the severity of visual field loss, it concluded that in addition to ppRNFL thickness, the mGCC thickness could be a structural parameter for detecting preperimetric glaucoma [8].

In the study by Mwanza and colleagues it was found the ability of macular GCC parameters to discriminate normal eyes and eyes with early glaucoma was high and comparable to that of the best peripapillary RNFL and ONH parameters [9].

This study also detected sensitivity and specificity of average GCC which were 66.7 and 65.6 respectively.

Our study also developed cutoff points for average GCC (<=96.72). Moreno et al., also developed cutoff values for average GCC and RNFL which were 89.9 and 111.8 micrometers respectively [10].

The present study included controls, suspects and glaucoma patients, comprising the full spectrum of glaucomatous damage including suspected glaucoma.

There were several limitations to this study, including a relatively small sample size. This cross-sectional study cannot provide longitudinal structural and functional data associated with GCC parameters.

Only caucasian participants were included in the study; the role of race in determining structure-function relationships is not known.

Conclusion:
Macular GCC thickness is comparable to RNFL thickness for detection of early and moderate glaucoma. However, further clinical evidence is needed to assess GCC role in detecting early glaucomatous damage.

References
الملخص العربي

مقدمة: يعتبر مرض الجلوكوما من الأمراض التي تؤثر على البصر إذا اتُعالمت التشخيص والعلاج، يعد التشخيص على فحص مجال الاستجابة وقياس ضغط العين، دراسة خلايا العصب البصري، والآليات العصبية للشبكة، وتوفر جهاز الامسج المقطعي الضوئي الطيفي تعليمات في تقييم ومتداينة مرضى الجلوكوما عن طريق دراسة سdek الآليات العصبية وقياس مركب الخلايا العقدية بالمقولة.

الهدف من البحث: يهدف إلى دراسة وتقدير أهمية قياس مركب الخلايا العقدية باستخدام الجهاز المقطعي الضوئي الطيفي في مرضى الجلوكوما.

خطوات البحث: تم في قسم طب وجراحة العيون، كلية طب، جامعة القاهرة في الفترة من مارس 2012 إلى يونيه 2013 وشمل البحث 91 حالة مقسمة إلى ثلاث مجموعات.

المجموعة الأولى: تعاني من مرض الجلوكوما المبكرة والمتوسطة.
المجموعة الثانية: تعاني من احتمال وجود جلوكوما.
المجموعة الثالثة: لا تعاني مرض بالعين.

نتائج البحث: أظهرت الدراسة أن قياس مركب الخلايا العقدية بالمقولة لها أهمية تشخيصية على وتواقيت النتائج مع نتائج الإيجابيات الأخرى.

الاستنتاج: يوصى البحث باستغلال هذه الطريقة الأساسية في تشخيص مرضى الجلوكوما بالإضافة إلى الطرق الحالية في التشخيص.